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| [Brain Mets/Palliative/Oligo/Immuno](https://bit.ly/PalliativeRoR)| [Breast](https://bit.ly/BreastRoR) | [CNS/Peds](http://bit.ly/CNSandPeds) | [Constraints](https://bit.ly/RoRConstraints) | [GI](https://bit.ly/RoRGI) | [GU](https://bit.ly/GURoR) | [Gyn](https://bit.ly/RoRGyn) | [H&N/Skin](https://bit.ly/HNRoR) | [Heme](https://bit.ly/RoRHeme) | [Sarcoma](https://bit.ly/RoRSarcoma) | [Thorax](https://bit.ly/RoRThorax) | [Rad Phys/Bio](https://bit.ly/RORPhysBio)  [**www.RadOncReview.org**](http://www.radoncreview.org)  For best navigation, click on the Table of Contents (ToC) to navigate and click on a subheader or header to return to the ToC. Otherwise, use the Document Outline feature or control-F to search for a clinical trial or type ASCO '20 to see what's new. Best held horizontally on mobile.  **This document is a collaborative resource. All comments, corrections, and additions are welcome! Editing tips [**[**here**](https://docs.google.com/document/d/163jAwVLz8Wnno7jttJnDIM-4kTxkSSmj9XLP1W5pPJs/edit)**].**  Patterns of recurrence data found in the Follow Up section for most disease sites. Ongoing Trials are found in Future Directions.  **2020 Gold Star sections: [**[**Central and Ultracentral Lung**](#4q1lwlblkw4q)**] and [**[**SCLC Systemic Therapy**](#_1z7stjs4ecr2)**].** |

See NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)].

# **Thorax**

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| [**Thorax**](#_6sfwza45y5km)  [Screening](#_g85gu4x5x0u0)  [Workup](#_3741ekhp6g64)  [Mediastinal sampling](#_m9mlrdiu8lc0)  [Lymph node Levels](#_6jx2f37knu1t)  [Toxicity](#_k70amn44ux20)  [**Early Stage NSCLC**](#_opxxqv56465m)  [Principles of Surgery](#_mzlcyebp13ga)  [Determining Resectability](#_l1upef32bg54)  [RFA](#_juvtmxe2el27)  [SABR](#_p20pk5rzxumi)  [Treating without a biopsy](#_canzrk46c7jc)  [SABR vs. older techniques](#_dbzp3svougkc)  [SABR vs. Lobectomy](#_d87gioouw4cz)  [Central and Ultra-central tumors](#_x8xiuqy6pz44)  [SBRT for tumors > 5 cm](#_31j3vr6mrwkq)  [Toxicity](#_m3ugsmf72kwx)  [SBRT Treatment Planning](#_xemdc7nwlnr2)  [Follow up after SABR](#_rcvd3544vxc7)  [**Locally Advanced NSCLC**](#_lx2epxcmsg6)  [Unresectable / Medically inoperable](#_u2qcktecac9d)  [RT Dose escalation](#_1zk2d6pobdtm)  [SCRT](#_16zvai86raju)  [CCRT](#_t13rsjlyvgp)  [Resectable Stage III NSCLC](#_164x49br3mq1)  [Surgery→ Chemo ± RT](#_appsakxjrxyt)  [PORT](#_hm73vr2km2pa)  [NAC](#_c7xchspoicn)  [CCRT first (or alone)](#_1h35734g6pse)  [Elective Nodal Irradiation](#_1u6t437wyiec)  [PCI and NSCLC](#_4g2cyvv94kv6)  [Reirradiation](#_biqaee7jirzq)  [Toxicity](#_w15kt2maghny)  [Conventional Treatment planning](#_6aijvzbkbcqt)  [Intact](#_fh58ftr0o2dx)  [PORT](#_g10gqc6wm2cu)  [Palliation](#_vb8n5yg6vww0)  [Follow up](#_12dcu6uefto4) | [**Oligo and Metastatic NSCLC**](#_4f6vjyau5afh)  [**Systemic therapy for NSCLC**](#_wp55nx1rut9o)  [Targeted therapy](#_iwtyyd6s6gm9)  [Targeted Therapy: EGFR](#_kgqozkr7mums)  [Targeted therapy: ALK](#_u04kjdwoxshp)  [Concurrent Chemotherapy](#_8fm890uhgxjw)  [Adjuvant Systemic Therapy](#_lb6jpbt88b0h)  [Immunotherapy](#_v3h6cj546hkq)  [**NSCLC: Future Directions**](#_m5aoyuk8s5l5)  [Curative Intent](#_bzte211ncx4).  [Non-curative Intent](#_g18j10rquitr)  [**Small Cell Lung Cancer**](#_nruipiivq02s)  [Systemic Therapy](#_1z7stjs4ecr2)  [Limited Stage](#_x7eot2pqwmlq)  [PCI in Limited Stage](#_6a2wqadfkp6a)  [Extensive Stage](#_mr2dodxoiote)  [Role of RT in ES](#_ym48hrkd7ijr)  [Oligometastatic SCLC](#_jw31k4zcm6jc)  [PCI in Extensive Stage](#_fqykplq2bckm)  [Treatment planning](#_73v1nhuzo9vt)  [Follow up](#_rapv6j5t9wie)  [Future Directions](#_kcsj058yvbh4)  [**Thymoma, Thymic Carcinoma**](#_smffiejkpron)  [Treatment planning](#_t6pdtyx0snn)  [Follow up](#_2o6yepuivfcf)  [Future Directions](#_wx3ni5l3fmen)  [**Pleural Mesothelioma**](#_5m4o063lxb43)  [Toxicity](#_81dz6yp57mff)  [Treatment planning](#_nsfzu5bs88w7)  [Future Directions](#_cpbqoifbflcb)  [**Benign**](#_jpfa84tktu44)  [Ventricular Tachycardia](#_xvtpgq20iha1)  [Coronary Restenosis](#_hy4g0ffp4b5w) |

[**StatPearls: Bronchoalveolar**](https://www.ncbi.nlm.nih.gov/books/NBK513281/)*Last update: 11/12/2019.*

[**StatPearls: Cardiac**](https://www.ncbi.nlm.nih.gov/books/NBK537144/) *Last update: 11/12/2019.*

[**StatPearls: Lung**](https://www.ncbi.nlm.nih.gov/books/NBK482357/)*Last update: 3/14/2019.*

[**StatPearls: Lung Adenocarcinoma**](https://www.ncbi.nlm.nih.gov/books/NBK519578/) *Last update: 1/11/2019.*

[**StatPearls: Lung Cancer Screening**](https://www.ncbi.nlm.nih.gov/books/NBK537283/)*Last update: 2/21/2019.*

[**StatPearls: Lung Carcinoid Tumors**](https://www.ncbi.nlm.nih.gov/books/NBK537080/)*Last update: 11/12/2019.*

[**StatPearls: Lung Small Cell (Oat Cell)**](https://www.ncbi.nlm.nih.gov/books/NBK482458/)*Last update: 2/14/2019.*

[**StatPearls: Malignant Mesothelioma**](https://www.ncbi.nlm.nih.gov/books/NBK519530/) *Last update: 3/12/2019.*

[**StatPearls: Mucoepidermoid Lung Tumor**](https://www.ncbi.nlm.nih.gov/books/NBK537277/) *Last update: 9/23/2019.*

[**StatPearls: Mediastinal Cancer**](https://www.ncbi.nlm.nih.gov/books/NBK513231/) *Last update: 9/11/2019.*

[**StatPearls: Pancoast Syndrome**](https://www.ncbi.nlm.nih.gov/books/NBK482155/)*Last update: 3/3/2019.*

[**StatPearls: Papillary Fibroelastoma**](https://www.ncbi.nlm.nih.gov/books/NBK549829/)*Last update: 12/5/2019*

[**StatPearls: Pleuropulmonary Blastoma**](https://www.ncbi.nlm.nih.gov/books/NBK534211/)*Last update: 12/2/2019.*

[**StatPearls: Radiation Therapy for Early Stage NSCLC**](https://www.ncbi.nlm.nih.gov/books/NBK459385/)*Last update:12/16/2019 .*

[**StatPearls: Trachea**](https://www.ncbi.nlm.nih.gov/books/NBK538437/)*Last update: 12/3/2019.*

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| **ASCO Guidelines for Surveillance after Definitive Curative-Intent therapy** [[Schneider JCO '19](https://www.ncbi.nlm.nih.gov/pubmed/31829901)]: TBL [QS](http://www.quadshotnews.com/2019/12/still-too-hot.html): PET shouldn’t be used for routine surveillance of locally-advanced lung cancer.   * Imaging surveillance should be performed q6m x2y, then annually. PET/CT should not be used for surveillance. * Surveillance should not be offered for patients unwilling to accept further treatment. * Brain MRI should not be used for routine surveillance in NSCLC, but may be used q3 mo for the first year and q6 mos in for the second year in patients with stage I-III SCLC who have undergone curative-intent treatment. |

Introduction to lung cancer [[www.aboutcancer.com](http://www.aboutcancer.com/lung_intro.htm)]

* The leading cause of cancer deaths in the USA (second most common cancer) and overall most common cancer worldwide.
* 225k cases per year, 160k deaths [[Siegel Cancer Statistics '19](https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551)].
  + 20% early stage, 15% IIIA. Of those cT1-3cN0-1, 25% can be N2. ~40% not amenable to surgery, 40% w mets.
    - #2 cancer in the USA behind prostate and breast. Still, #1 cause of death.
    - Lung cancer kills more people than the next five most common combined cancers (CRC, breast, pancreas, prostate, leukemia) in the world.
  + 15-20% SCC (2/3 are extensive), 3% large cell neuroendocrine (M:F 17:1, >50py). Small decrease in the last 30y.
    - Brain mets in 10-15% at Dx→ 80% autopsy. Up to 30% w BM after chemo! (depends on timing of MRI).
      * 2y incidence of brain mets after CRT of 50-80%.
  + Smoking is responsible for 80% of cases in men, while 50% for women.
  + **Secondary lung cancer** [[Johnson JNCI '98](https://www.ncbi.nlm.nih.gov/pubmed/9747865)]: Annual incidence for NSCLC / SCLC of 1-2→ 6%.
* Chemo will have around 15% response rate in the brain (40-60% for targeted) vs. 50% for SCLC.
  + Alectinib [QS](http://www.quadshotnews.com/2017/10/battle-of-brains.html) (Alk) or Osimertinib [QS](http://www.quadshotnews.com/2018/09/new-age-aura.html) (EGFR, now first line even if T790M negative) for best CNS penetration.
* **Paraneoplastic syndromes**

[Statpearls: Paraneoplastic syndromes](https://www.ncbi.nlm.nih.gov/books/NBK507890/) *Last update June 3, 2019*

* + **SCLC**: 7-16% have SIADH.
    - ADH, ANP and ACTH can all be secreted by SCLC: Treat SIADH with fluid restriction, saline.
  + 10% of all NSLC patients will have paraneoplastic syndromes.
    - Hypercalcemia: PTHrP in primary **SqCC**.
    - LEMS, cerebellar ataxia, retinopathy in SCLC, with ~3% of SCLC demonstrating LEMS.
      * Pre-synaptic Ca++ channels, prox weakness improves with reps, dry mouth, paresthesias.
    - Hypertrophic osteoarthropathy: bilateral clubbing, most commonly AC.
    - Hypercoagulable: AC.
    - Dermato/polymyositis: AC.
    - Gynecomastia: Large cell.
    - VIP diarrhea: Seen in carcinoid. Treat with somatostatin.
* **Pathology**
  + AC 40% > 30% SqCC > Large cell = SCLC 15-20% [[Wahbah ADP '07](https://www.sciencedirect.com/science/article/pii/S1092913406000530?via%3Dihub)].
    - AC can transform to SCLC 5% of the time.
    - Targetable mutations in nearly 20%, the vast majority in AC.
  + **Location**
    - Peripheral: AC, Large cell.
    - Central: SqCC.
  + TTF-1: AC, non-mucinous AIS, and neuroendocrine tumors. Rarely SqCC.
* **Subtypes**
  + **Atypical adenomatous hyperplasia**: VDT ~1000d. Small < 5 mm pure GGO.
  + **Adenocarcinoma in situ** (**AIS**/**BAC**): VDT ~600d. **Lepidic spread**: Spreads along alveolar structure, does not invade stroma, pleura, or lymphatic spaces. Tends to be pure GGO.

[StatPearls: Bronchoalveolar](https://www.ncbi.nlm.nih.gov/books/NBK513281/) *Last update: 11/12/2019.*

* + - Subtypes: Mucinous, non-mucinous, mixed. Diffuse, multifocal w high rate of EGFR/ALK (may have good response to TKIs).
    - R0 5y DFS 100%.
  + **Adenocarcinoma**: **TTF-1**, **CK7**, **Napsin A**. Least associated with smoking.

[StatPearls: Lung Adenocarcinoma](https://www.ncbi.nlm.nih.gov/books/NBK519578/) *Last update: 1/11/2019.*

* + - Napsin in 80% of lung AC but only 10% of thyroid AC.
    - **Acinar**
    - **Papillary**: Micropapillary (no microvascular core) and solid two of the worst subtypes.
      * Solid and micropapillary may benefit from chemo.
      * If micropap AC ≥ 5% and ≤ 2cm then 67% LRR of those that relapse. Want ≥ 1 cm margin.
  + **SqCC**: p40. VDT ~100d. Well differentiated keratin pearls. EGFR 90% (compared to ~33% for AC).
  + **Large cell**:
    - **Giant cell** behaves like SCLC with high propensity for brain mets.
    - Clear cell.
  + **SCLC**: Limited stage ~1/3, Extensive stage ~2/3.

LS-SCLC: one tolerable port. Controversial SVC, contralateral LAD, pleural effusion.   
[StatPearls: Lung Small Cell (Oat Cell)](https://www.ncbi.nlm.nih.gov/books/NBK482458/) *Last update: 2/14/2019.*

* + - **Neuroendocrine**: **CD56**, **chromogranin A**, **synaptophysin**, TTF-1.
  + **Carcinoid tumors**: Rare, most commonly GIT. But, 25% are in the lung and usually endobronchial. Most are **typical** carcinoids, which rarely metastasize and are not associated with smoking. **Atypical** carcinoids are associated with smoking, tend to metastasize and have a poorer prognosis. Only 10-15% have carcinoid syndrome, but up to 2/3 eventually develop symptoms.  
    [StatPearls: Lung Carcinoid Tumors](https://www.ncbi.nlm.nih.gov/books/NBK537080/) *Last update: 11/12/2019.*

See the [[Neuroendocrine](https://docs.google.com/document/d/13NEZCS6s13MVLixabbO2vjY73zHxJ37qE16gBbApSdY/edit#heading=h.pk4st76y39sf)] section in the GI section for more.

* + - Subtypes: Typical, atypical, large cell neuroendocrine.
    - Mediastinal nodal evaluation only if cN+. Octreotide scan if secreting.
    - Can observe if grade I, up to stage IIIA.
    - No evidence for CCRT in unresectable for typical, add EPP for atypical.
    - 5y OS 90% for typical, 70% atypical.
  + **Mesothelioma**: **WT-1**, **calretinin**, **CK5/6**, **D2-40**. *Not TTF-1 or CEA like adenocarcinoma.*

[StatPearls: Malignant Mesothelioma](https://www.ncbi.nlm.nih.gov/books/NBK519530/)*Last update: 3/12/2019.*

* **Mutations**
  + Targetable mutations in nearly 20%, vast majority in AC.
  + Molecular testing for EGFR, KRAS, ALK, ROS-1, BRAF, PD-L1.
    - Liquid biopsy for T790M mutations (EGFR TKI resistance).
  + **Frequency**: KRAS (20-25%) > EGFR (15%) > ALK (5%) > ROS1(1-2%).
    - **Prognosis**:EGFR ≅ ALK > KRAS > Wild type.
  + **KRAS** (20-25%): Associated with lack of sensitivity for EGFR inhibitors.

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| As of 4/19/2018, **Osimertinib** FDA approved and **now** **NCCN first line preferred Cat 1 for EGFRm**!   * Osimertinib has the best penetration into the brain, though appears to be best if rec'd prior RT within 6 mo. * TBL [QS](http://www.quadshotnews.com/2018/09/new-age-aura.html): Osimertinib has more intracranial activity and lower rates of intracranial progression than other EGFR-TKIs such as gefitinib and erlotinib. |

* + **EGFR** (10-15%): **Erlotinib/Gefitinib→ Afatinib/Dacomitinib→** **osimertinib** (if T790M) before non-targeted tx.
    - EGFR 90% exon 19/21. Exon 19 best px. Exon 21 L858R missense mutation.
      * **Exon 20 = T790M** (Osimertinib).
    - Most pts progress within the first 2y. Of those, 50% are T790M mutations (rociletinib, osimertinib). They are 10x more likely to develop T790M than progress to SCLC (6%).
    - Erlotinib→ gefitinib, afatinib→ osimertinib (if T790M) before non-targeted therapy.
  + **Alk** (2-7%): **Crizotinib**→ **ceritinib, alectinib, brigatinib** or before non-targeted tx.
    - ~33% present w brain mets, and >50% will develop brain mets.
    - If progression on first generation (crizotinib), no bx necessary and switch to second generation.
    - If progression on second generation, recommend bx to look for **G1202R** mutation.
    - Alk typically 5%, but subset for invasive, solid, micropapillary, acinar, minimally invasive from 15% down to 2.5% for minimally invasive. Then pap predominant, lepidocrocite, ACIS ≤ 2%.
    - **Alectinib**: 25% CR in **CNS**, 50% PR in CNS, 25% SD in CNS. **Now first line!** [QS](http://www.quadshotnews.com/2017/10/battle-of-brains.html)
      * Overall, CNS control 80-85% in Alk-naive, 65% in Alk-pretreated.
    - **Lorlatinib** (ALK/ROS) overcomes **G1202R** mutation. It is selectively brain-penetrant.

Approved in Nov 2018 for second/third line treatment.

* + - * Phase 1 trial promising [[Shaw Lanc Onc '17](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30680-0/fulltext)], waiting phase III [NCT03052608](https://clinicaltrials.gov/ct2/show/NCT03052608) to demonstrate superiority over alectinib.
  + **ROS1** (1-2%): **crizotinib**, **ceritinib** second line
  + **MET** (3-4%) testing is now recommended. Crizotinib.
    - **VISION** [[Paik NEJM '20](https://www.nejm.org/doi/full/10.1056/NEJMoa2004407)]: Phase II. **Tepotinib**.

TBL [QS](http://www.quadshotnews.com/2020/06/meet-met.html): Almost half achieved a response by RECIST criteria and two-thirds a deep (14%) or complete (53%) molecular response to the highly-selective MET-inhibitor tepotinib.

* + - * 99 patients. Advanced or metastatic NSCLC. Confirmed MET exon 14 skipping mutation.
      * ORR 46% with median DOR 11 mo in the combined-biopsy group.
      * ORR 48% in liquid-biopsy group (n=66) and ORR 50% in the tissue-biopsy group (n=60). Only 27 patients had positive results according to both methods.
      * ORR was 56% regardless of previous therapy received for advanced or metastatic disease.
      * Molecular response as measured by circulating free DNA was observed in 67% of patients with matched liquid-biopsy samples at baseline and during treatment.
      * G3+ AE 28%, including peripheral edema in 7%. AE leading to permanent discontinuation in 11%.

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| **ASCO Guideline:** [**The role of CT screening for Lung Cancer in clinical practice**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/10211) *June 13, 2012*   * NLST lung cancer mortality RR 0.80, all-cause mortality RR 0.93. * **On average, false positive rates req further imaging / subsequent invasive procedures 20→ 1%**. * ASCO recommendations for screening:   + Ages 55-74, ≥ 30 py, current smoker or quit < 15y ago.   + Pts with < 30 py, either younger than 55 and older than 74, quit smoking > 15y ago, or pts with severe comorbidities that would preclude potentially curative tx and/or limit life expectancy should forego LDCT. |

## [Screening](#_6sfwza45y5km)

See the Summary Box above.

[StatPearls: Lung Cancer Screening](https://www.ncbi.nlm.nih.gov/books/NBK537283/)*Last update: 2/21/2019.*

* 6 large RCTs for lung cancer screening with CXR ± sputum did not show mortality benefit.

* **NLST - US National Lung Screening Trial** [[Aberle NEJM '11]](https://www.nejm.org/doi/full/10.1056/nejmoa1102873): **CXR vs. LDCT** **q1y x3y**.  
  LDCT improves overall survival. **20% RRR in CSM** and **6.7% RRR in *all-*cause****mortality**.

Rate of positive result with CXR less than 10%, while LDCT was around 25%.

On average, false positive rates req further imaging / subsequent invasive procedures 20→ 1%.

* + 53k patients. 55-74y, 30py current smoker or quit < 15y ago.
  + Rate of positive result 7→ 24%. False positives ~95% in each group.
  + Each year of smoking abstinence = 9% decrease in risk of CSM, OM decreased by 3% per 5 pack years.
    - Deaths from lung cancer per 100,000 person-years of 309→ 247.
  + NNS to prevent one lung cancer death 320.
  + Subsequent publication: ICER = $81k QALY (ICER for crizotinib is $250k QALY).
* **NELSON** [[de Koning NEJM '20](https://www.ncbi.nlm.nih.gov/pubmed/31995683)]: **Observation vs. CT at baseline, 1y, 3y and 5.5y**.

TBL [QS](http://www.quadshotnews.com/2020/02/willie-nelson.html): Non-con volumetric CT screening for lung cancer decreases lung cancer deaths without a heavy undue burden of working-up false positives.

LDCT improves CSS. **There is a 24% RRR in CSM** at 10 years.

* + 13k men, 2.5k women. 50-74y. MFU 10y.
    - Current/former smoker (quit ≤ 10y ago) who smoked > 15 cigs/d for > 25y or >10 cigs/d for >30y.
  + Average adherence of 90%.
  + On average, 9% of screened participants underwent at least one additional CT scan (if initially indeterminate).
  + The overall referral rate for suspicious nodules was 2%.
  + 10y cumulative rate ratio for death from lung cancer of 0.76.
  + Among women, the 10y rate ratio for death from lung cancer was 0.67.
* **I-ELCAP -** International Early Lung Cancer Action Program [[Yip Eur J Cancer Prev '15](https://www.ncbi.nlm.nih.gov/pubmed/25089376)]: **CXR (NLST) vs. low-dose CT**.
  + Size 2.3→ 1.7 cm.
  + Stage I 67→ 82%.
  + Surgery 76→ 86%.
  + 5y OS 67→ 83%.
* **I-ELCAP** [[Buckstein IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/30677471)]: **SABR in screened populations**.
  + Among 83k baseline and 109k annual repeat screenings, 853 patients were diagnosed with stage I NSCLC, of whom 4% (n=31) were treated by definitive RT and 82% (n=702) were treated by surgery alone. CSS was 90% for both surgery and RT.
* **Recommendations**: **Annual LDCT for high risk** (1.5 mSv/scan)
  + Age 55-74, 30 py history, current smoker or quit < 15y ago.
    - Also screen if Age ≥ 50y, ≥ 20 pack years and one additional risk factor (e.g. Radon exposure, Occupational exposure, cancer history, COPD/pulmonary fibrosis).
  + Follow up recommendations based on 1% chance of being cancer.
  + **Solid nodules**:
    - < 6 mm→ repeat LDCT in one year.
    - ≤ 7 mm→ LDCT in 6 mo.
    - < 15 mm→ LDCT in 3 mo or immediate PET/CT→ bx if high suspicion.
    - ≥ 15 mm→ Chest CT and/or PET/CT→ bx if high suspicion.
  + **Part-solid**: < 6 mm→ repeat LDCT in q1y x5y.
  + **Non-solid nodules** (ground glass):
    - ≤ 19mm→ Annual LDCT→ if growing LDCT in 6mo.
    - ≥ 20mm→ LDCT in 6mo→ if growing consider bx.
  + **Segmentectomy or wedge** for peripheral nodule < 2 cm that is 1) AIS, 2) >50% GG, 3) TD >400d.

## [Workup](#_6sfwza45y5km)

* **H&P:** Cough, smoking, PS, weight loss, abdominal pain (2/2/ hypercalcemia, also hypotonia, hyporeflexia).
* CXR: Prior chest imaging for comparison!
* Labs: CBC, CMP, calcium, LDH.
  + Sputum cytology x3: Large central tumor 80% yield, peripheral < 3 cm tumor < 20% yield.
* Smoking cessation.
* Early palliative care.
* **CT chest** and upper abdomen (liver, adrenals) with IV contrast.  
  Sensitivity for N2 ~60%, ~80% specific. Around 10% FNR for peripheral disease [[Detterbeck Chest '07](https://www.ncbi.nlm.nih.gov/pubmed/17873169)].
  + Approximate 10-20% false negative rate for CT depending on T stage and size.
* **PET/CT** to evaluate liver, adrenals. Bone scan if there is no PET.  
  **Sensitivity for N2 ~80%**. Around 5% FNR for peripheral disease [[Detterbeck Chest '07](https://www.ncbi.nlm.nih.gov/pubmed/17873169)], while 24-83% FNR if central.

False positives are not uncommon, and confirmatory EBUS is encouraged if PET/CT is suggestive of N2 disease.

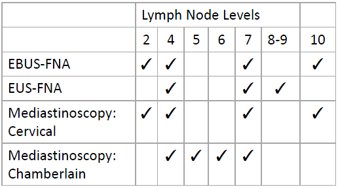
False negatives are higher for central tumors and PET positive hilum, but still may not warrant EBUS if frail/elderly.

The [[ASTER trial](#uvpyhpg46hix)] suggests a false negative rate of 15% for patients staged with PET/CT and EBUS.

* + PET/CT can avoid unnecessary surgery in ~10-20%.
  + **False positive rates for N2 can approach 25%**, therefore EBUS may be warranted [[Rwigema JTD '15](http://jtd.amegroups.com/article/view/6201/html)].
  + Cochrane Review [['14](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009519.pub2/full)]: PET w 77% Sn and 90% Sp for N2, great heterogeneity between studies.
  + Al-Sarraf [[EJCTS '08]](https://academic.oup.com/ejcts/article/33/1/104/350111): After a negative PET, 16% will have occult N2 disease.
    - On MVA, central tumors, RUL tumors and PET+ hilum are more suggestive of N2 involvement.
  + For central tumors, invasive mediastinal LN staging is still warranted with a negative PET/CT (e.g., even with small nodes < 1 cm).
* **MRI**: Stage II+, consider for IB for AC (Cat 2B - it doesn't happen more often, but can happen in earlier stage dz).

* Tissue
  + Biopsy the site that can both diagnose and stage.
  + Bronchoscopy for central lesions, CT-guided for peripheral lesions.
  + Core biopsy preferred over FNA/cytology.
  + **Primary lung adenocarcinoma**: TTF-1, CK7, Napsin A.
  + **Neuroendocrine**: CD56, chromogranin A, synaptophysin, TTF-1.
  + **Mesothelioma**: WT-1, calretinin, CK5/6, D2-40. Not TTF-1 or CEA like adenocarcinoma.
  + Molecular testing: EGFR, KRAS, ALK, ROS-1, BRAF, PDL-1 status.
  + Liquid biopsy: Emerging area of diagnosis such as T790M mutation for EGFR TKI resistance.

## [Mediastinal sampling](#_6sfwza45y5km)

* Only 72% of pts believed to be stage I are pathologically stage I [[D'cunha](https://www.sciencedirect.com/science/article/pii/S0169500204005756?via%3Dihub)]. Upstaging occurs in ~25-33% of pts.
* PET/CT has a ~5% FNR for peripheral disease, while upwards of 25% for central disease.
  + Peripheral tumors with negative PET/CT in N2 may not require EBUS if frail or elderly.
  + Peripheral tumors with positive PET/CT in N2 are encouraged to have EBUS for confirmation given false positives.
  + Central tumors with negative PET/CT in N2 or hilar positivity are encouraged to have confirmatory EBUS.
* **General recommendations**:
  + EBUS/FNA or surgical. If EBUS/FNA negative, do surgical if imaging positive, otherwise forego.
    - Only time NO mediastinal sample = ≤ 2 cm with negative PET and peripheral.
  + Sample at least 3 stations.
  + Sample all abnormal LN.
* **Needle approach**:
  + EUS: 4, 7, 8-9.
  + EBUS: 2, 4, 7, 10.
* **Surgical approach**:
  + **Cervical mediastinoscopy**: Gold standard (Sn 44-92%, Sp 100%) but risk of complication and operator dependent. Incision 1 cm above suprasternal notch. All superior sulcus, or T3 or central T1-2 lesions: superior mediastinal nodes 1-4R, ± 7, 10.
  + **Anterior/parasternal (Chamberlain) mediastinotomy**: Incision at left 2nd ICS. 5, 6 ± 4L, 7.

* **ASTER** [[Annema JAMA '10](https://jamanetwork.com/journals/jama/fullarticle/186959)]: **Surgical staging vs. EUS-EBUS→ Surgical staging**. Thoracotomy for all if negative.

The negative predictive value of EUS-EBUS alone is only 85%. However, EBUS can avoid morbid thoracotomies.

* + 241 pts. 2007-2009. Mediastinal staging indicated by CT or PET.
    - Mediastinal staging indicated if nodes ≥ 1 cm SAD, PET positive mediastinal nodes, or central.
  + Nodal metastases of ~35→ 46% (p=0.11). *Almost half of EUS-EBUS had N2 disease and avoided surgery.*
  + Sn for N2/3 disease of 80→ 94%. *N2 disease found in 9% of pts after negative EBUS, 8% had complications.*
  + NPV of ~86→ 93% (p=0.18).
  + Sn for surgical staging alone / EUS-EBUS without surgical staging of ~79→ 85%, NPV ~85%.
  + Unnecessary thoracotomies 18→ 7%.
  + EUS-TBNA with similar sensitivity as mediastinoscopy ~80% with complications 6→ 1%.

|  |  |  |  |
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| [**Lymph node Levels**](#_6sfwza45y5km) | Sup | Inf | Notes |
| **1R/L** (Low cervical, SCV, Sternal notch) | Lower cricoid | Manubrium | Sagittal for 1st rib/thoracic inlet.  Midline trachea. |
| **2R/L** (Upper paratracheal) | Apex of lung, manubrium | R: **Caudal** **innominate**  L: **Cranial AA** | Left lat trachea |
| **3A** (Prevasculars) | Apex of chest | Carina | Posterior borders:  R: Ant SVC L: Ant LCa |
| **3P** (Retrotracheals) | Apex of chest | Carina |  |
| **4R/L** (Lower paratracheal) | R: Caudal innominate  L: Cranial AA | R: **Caudal** **azygos**  L: **Cranial LMPa** | Left lat trachea |
| **5** (Subaortic/AP window) | Inf AA | Cranial LMPa | Lat to LA |
| **6** (Para Aortics) | Sup AA | Inf AA |  |
| **7** (Subcarinal) | Carina | R: Caudal RML bronch  L: Cranial LLL bronch |  |
| **8** (Paraesophageal) | R: Caudal RML bronch  L: Cranial LLL bronch | Diaphragm |  |
| **9** (Pulmonary ligament) | Inf pulm vein | Diaphragm |  |
| **10R/L** (Hilar) | R: Caudal azygos  L: Cranial LMPa | Interlobar regions | **Region ant to tracheal bifurcation is N2** |
| [**General nodal tidbits**](#_6jx2f37knu1t)  See [[Radiology Assistant](https://radiologyassistant.nl/chest/mediastinum-lymph-node-map)]. Zaorsky: [[LN stations in lungs](https://twitter.com/NicholasZaorsky/status/1211640873634664453)].  AVARO [[Normal Thorax Anatomy](http://econtour.org/cases/89)], [[Thoracic nodal levels](http://econtour.org/cases/88)].  CT-based definition of thoracic LN stations: An atlas from the University of Michigan [[Chapet IJROBP '05](https://www.ncbi.nlm.nih.gov/pubmed/16111586)]  Mediastinal nodes in the single digits increase from cranial to caudal.  Subcarina is level 7.  Interlobar nodal stations are in the double digits, while hilar lymph nodes are level 10.  N1 is double digit nodes (IIB, IIIA): Resectable.  N2 is ipsilateral mediastinal nodes (IIIA-IIIB/large primary): Resectable.  N3 is contralateral or SCV nodes (IIIB-IIIC): Unresectable. | | | |

## [Toxicity](#_6sfwza45y5km)

Cardiac Contouring Atlas (Supplement) [[Duane RTO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5356506/)]

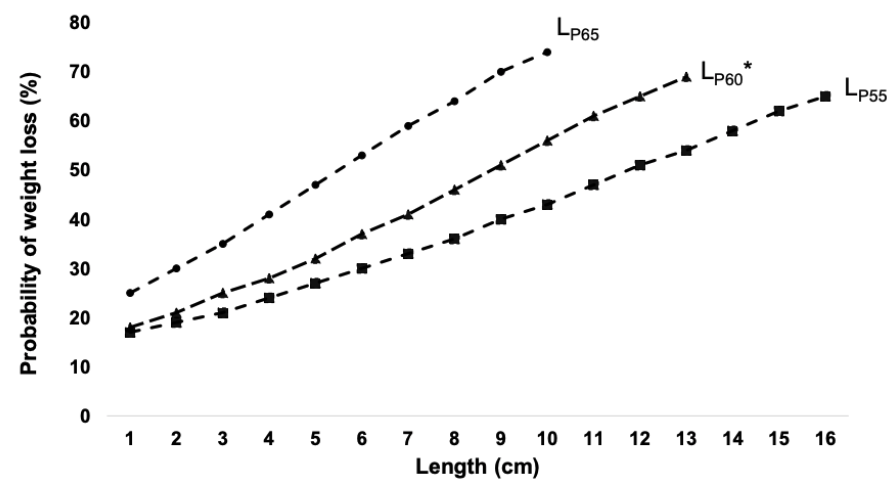
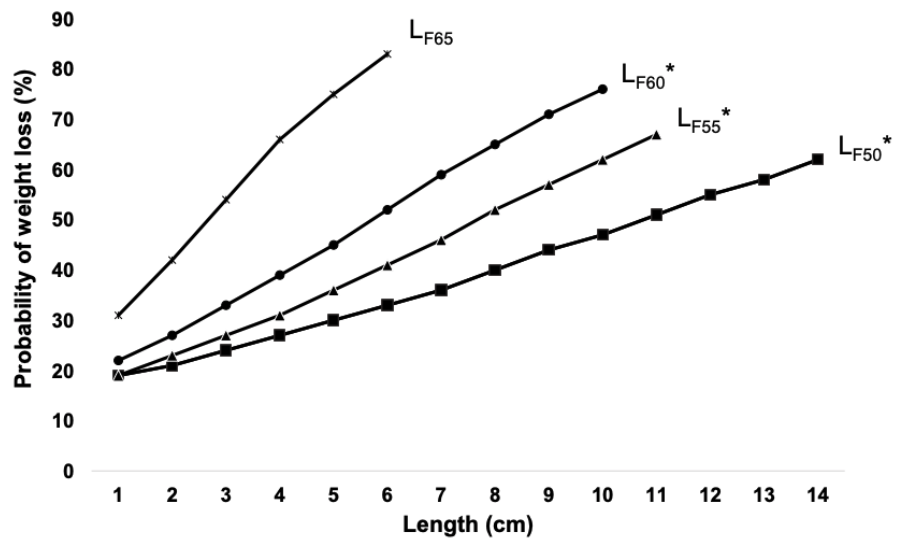
* **Heart**: **MHD ≤ 20 Gy, V50 ≤ 25%**
  + **Cardiac morbidity: Pooled analysis of 6 dose escalation trials for stage III NSCLC** [[Wang JCO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5455462/)]

Mean heart dose should be limited to less than 20 Gy if at all possible.

* + - 127 patients. UNC. Dose escalated RT 70-90 Gy. Prospective phase I-II trials 1996-2009.
      * All received induction, most received CCRT.
    - 2y cardiac events for < 10 Gy / 10-20 Gy / >20 Gy MHD of 4→ 7→ 21%.
  + **Heart V50 independently predicts for decreased OS** [[Speirs JTO '17](https://www.jto.org/article/S1556-0864(16)31144-3/fulltext)]: 66 Gy (50-84.9 Gy).

Heart V50 < 25% should be standard.

* + - 416 pts. Single institute. 333 plans re-contoured per 06-17. LA-NSCLC.
    - 1y OS for Heart V50 ± 25% of 47→ 70%. 2y OS 27→ 46%.
  + Dess [[JCO '17](https://www.ncbi.nlm.nih.gov/pubmed/28301264)]: Prospective trials. **CCRT**.
    - 125 stage II-III NSCLC pts. 2004-2013. 85% CCRT. 27% pre-existing cardiac disease. MFU 4y.
    - 19 pts had a G3+ cardiac event at a median of 11 mo. 2y cumulative incidence 11%.
    - On MVA, pre-existing cardiac disease and mean heart dose were associated with G3+ cardiac events.
    - Among patients with baseline cardiac disease, 2y G3+ cardiac events for MHD of 5 / 12 Gy of 10→ 15%.
    - Among patients with healthy hearts, 2y G3+ cardiac events for MHD of 23 / 29 Gy of 10→ 15%.
* **Esophagus**: **Mean < 34 Gy**, **Max 105% Rx**, **V60 ≤ 17%**, V55 < 33%
  + Palma paper: eval V5-V70 for esophagus, and V50-V60 predicted G2 and G3 events.
  + Management: Sucralfate, MMW, ranitidine, fluconazole.
  + Grade 3 esophagitis: >24h IVF or TPN.
  + Grade 4 esophagitis: Life threatening.

[](https://www.practicalradonc.org/article/S1879-8500(20)30062-X/fulltext)

* **Exploring the relationship of RT dose and length of esophagus to weight loss in lung cancer** [[Han PRO '20](https://www.practicalradonc.org/article/S1879-8500(20)30062-X/fulltext)]: Retro.

Exposing a large portion of the near-circumferential esophagus to 50 Gy appears to be tolerable, while less so for 60-65 Gy. Although this study is for lung cancer, it also highlights the difficulty in dose escalation to 60 Gy for esophageal cancer (TL;DR: 50 Gy vs. 64 Gy Rx for esophageal cancer while 60 Gy vs. 74 Gy Rx for lung cancer. Each has a 14 Gy gap, the lower end or a maximum of 6 Gy above the lower end is generally acceptable for boards and in clinic if isotoxic dose escalation based on OARs. Also, one key difference in esophageal cancer is the importance of ENI in esophageal cancer based on location of tumor. Don’t mention ENI in lung cancer, but that’s another conversation for another day). [RoR](#_1u6t437wyiec)

TBL [QS](http://www.quadshotnews.com/2020/03/the-lengths-some-people-go-to.html): The length of esophagus receiving a near-circumferential dose of 60 Gy appears to be a strong predictor of weight loss during lung cancer radiation.

* + 214 pts. 2010-2018. Median RT dose 63 Gy. 88% received CCRT.
    - LF = Length of near-circumferential (> 90% of the slice). LP= Partial-circumferential (> 50% of the slice).
  + One quarter of patients had > 5% weight loss by the end of treatment.
  + The length of the esophagus receiving a near-circumferential (> 90% of the slice) dose between 50-60 Gy is associated with weight loss on MVA.
* **RP for combined V20** [[Graham IJROBP '99]](https://www.sciencedirect.com/science/article/pii/S0360301699001832?via%3Dihub): Retro. Less than half received concurrent chemo.   
  QUANTEC V20 < 30% for < 20% risk of RP. Recall: CCRT may increase risk of RP per [[STRIPE](#m38qrqqzr43q)].

Goal: Keep V20 < 37% for ~10% risk of RP.

* + 99 inoperable patients.
  + V20 ≤ 22% with 0% RP.
  + V20 ≤ 31% with < 10% RP.
  + V20 ≤ 40% with < 15% RP.
  + V20 > 40% with nearly 40%.

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# [Early Stage NSCLC](#_6sfwza45y5km)

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T2: ≤ 5 cm. Visceral pleura, no carina. Whole lung atelectasis, mainstem bronchus.

T3: ≤ 7 cm. Parietal pleura. Pericardium. Chest wall, brachial plexus, tumor in the same lobe.

T4: > 7 cm, Vertebral body, subclavian, diaphragm, mediastinum, tumor in the same lung.

M1b: Solitary extrathoracic.

Over 50% of patients present with stage IV disease.

Zaorsky: [[LN stations in lungs](https://twitter.com/NicholasZaorsky/status/1211640873634664453)], [[No Fly Zone](https://twitter.com/NicholasZaorsky/status/1211642313333772292)]

eContour [[Thoracic OARs and lobar anatomy](https://econtour.org/cases/89), [Kong IJROBP '11](https://www.ncbi.nlm.nih.gov/pubmed/20934273)], [[PORT for pN2](https://econtour.org/cases/96)].

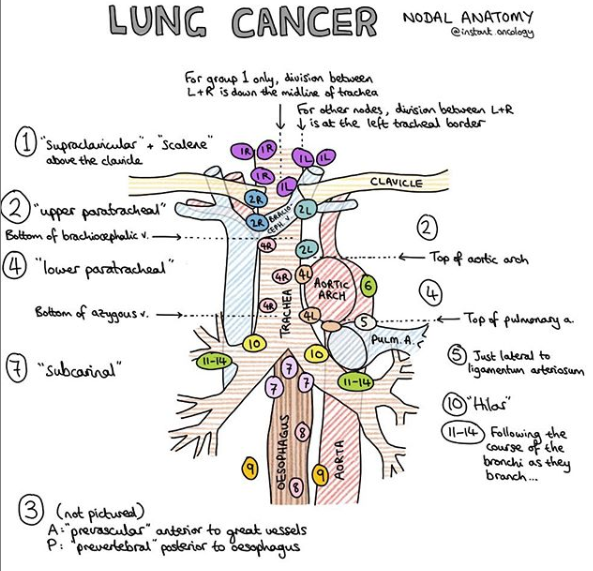
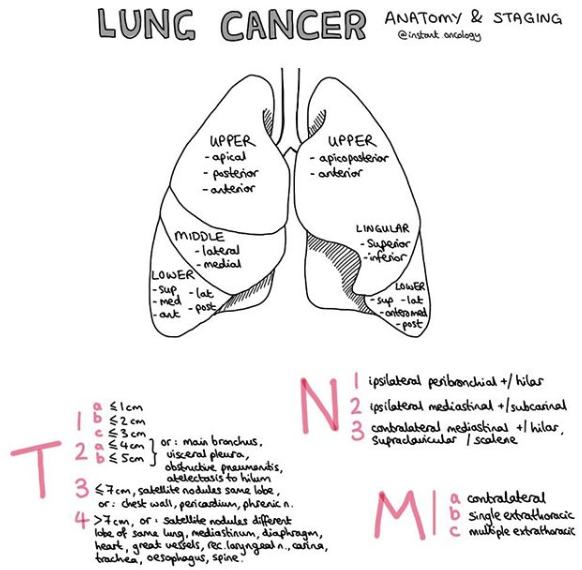
AVARO [[Normal Thorax Anatomy](http://econtour.org/cases/89)], [[Thoracic nodal levels](http://econtour.org/cases/88)]

ARRO: [[Management of CW Toxicity After SBRT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/ChestWallToxicity.pdf)], [[Central Lung Early Stage NSCLC](https://www.astro.org/ASTRO/media/ASTRO/AffiliatePages/arro/PDFs/ARROCase_SABR_Lung_EarlyStage.pdf)], [[NSCLC](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/NSCLCIIIB.pdf)], [[Resectable LA-NSCLC](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/Resectablelung.pdf)].

RTOG 1106 OARs [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-lung)]: PET-Guided therapy for stage III NSCLC. [RoR](#p1qgl9x43th3)

[**StatPearls: Lung**](https://www.ncbi.nlm.nih.gov/books/NBK482357/)*Last update: 3/14/2019.*

[**StatPearls: Lung Adenocarcinoma**](https://www.ncbi.nlm.nih.gov/books/NBK519578/) *Last update: 1/11/2019.*

[](https://www.instagram.com/p/B-3xOU-ARPm/?utm_source=ig_web_copy_link)[](https://www.instagram.com/p/B-1vBf2gLtz/?utm_source=ig_web_copy_link)

## [Principles of Surgery](#_opxxqv56465m)

* Lobectomy (preferred) + MLND (≥ 3 N2 stations).
* **Variability in surgical expertise** [[von Meyenfeldt JTO '12](https://www.jto.org/article/S1556-0864(15)33295-0/fulltext)]: Meta of 19 studies.  
  General surgeons (who perform 25% of surgeries) have 20% higher periop mortality rates than cardiothoracic surgeons.
  + General surgeons have higher mortality risks than general thoracic or cardiothoracic surgeons, OR 0.80.
  + A minimal annual volume of resections for lung cancer could not be identified.
  + 30 day mortality ranges from 0-29% and is worse in elderly.
* **30-90d mortality after surgery typically 0-10%** for early stage [[Senthi & Senan EJC '14](https://www.ejcancer.com/article/S0959-8049(13)01014-9/fulltext)], while < 1% for SBRT.
  + It is not uncommon for 90 day mortality to be double that of 30 day mortality.
  + Generally speaking, 30d mortality for lobectomy is around 1-3% while 90 day mortality is around 6%.
  + Generally speaking, pneumonectomy mortality after CCRT can range from 0% [[Eberhardt](#92lqqnk97mp3)] to around 10% [[Albain](#fe2c038zyqzk)].
* Wedge resection = "scraping the mold off the cheese".
* **Segmentectomy (preferred) or wedge** appear appropriate for < 2 cm peripheral nodules that are 1) AIS, 2) > 50% GG, 3) TD > 400d (NCCN 2020).
* **VATS vs. open thoracotomy lobectomy** [[Paul JTCVS '10](https://www.sciencedirect.com/science/article/pii/S0022522309010800?via%3Dihub)]: **Consider minimally invasive VATS lobectomy**.

There is no improvement in overall survival with VATS.

* + No difference in operative mortality for propensity matched cohorts.
  + Lower incidence of complications and shorter length of hospital stay with VATS.
  + No improvement in long-term survival.
* **LCSG 821** [[Ginsberg ATS '95]](https://www.sciencedirect.com/science/article/pii/000349759500537U?via%3Dihub): **Lobectomy vs. wedge** with 2 cm normal lung margin.  
  Improved LC with lobectomy with a trend to increased overall death and cancer death with wedge.

Wedge may be appropriate for small tumors, such as ≤ 1 cm with 2 cm surgical margins.

* + 247 pts with peripheral T1N0. 25% SqCC, 75% non-SqCC.
  + LRF 6→ 17%. Non-local failure ~13%.
  + 6y OS ~67→ 48% (p=0.09 one-tailed).
* [[Sienel Eur J CTS '07](https://academic.oup.com/ejcts/article/31/3/522/511985)]: Retro. **Segmentectomy vs. Lobectomy**.
  + 199 patients. 1987-2002. T1N0 ≤ 2 cm. 49 segmentectomies, 150 lobectomies. MFU 4.5y.
  + Local recurrence 16→ 5%.
  + CRD 33→ 17%.
  + Local recurrence for S1-3 / S4-10 of ~23→ 5% (p=0.08)
  + Resection margin ± 1.0 cm of ~23→ 0% (p=0.06).
* **JCOG 0802** [[Suzuki JTCVS '19](https://www.jtcvs.org/article/S0022-5223(19)30776-7/abstract)]: Non-inferiority. **Segmentectomy vs. lobectomy**.

Segmentectomy was associated with significantly more air leaks.

* + 1,106 pts. 2009-2014. T1N0 ≤ 2 cm.
  + LR 12→ 2%.
* **SEER** [[Cao ATS '18](https://www.sciencedirect.com/science/article/pii/S0003497518301474?via%3Dihub)]: **Wedge vs. Segmentectomy vs. Lobectomy for stage IA NSCLC**.
  + For tumors ≤ 1 cm, no differences in OS. *Wedge may be adequate for small tumors.*
  + For tumors 1.1-2 cm, OS improved with non-wedge surgeries.
  + For tumors 2.1-3 cm, OS improved with lobectomy.
* **CALGB 140503** [[NCT00499330](https://clinicaltrials.gov/ct2/show/NCT00499330)]: **Lobectomy vs. segmentectomy/wedge**.  
  This trial is looking at appropriateness for wedge treatment of T1 peripheral lung lesions.
  + 697 pts. Peripheral ≤ 2 cm presumed to be lung cancer. Center of tumor in outer third of lung. Tumor location suitable for lobar or sublobar resection.
  + 61% randomized, as not cancer in 16% or N+ in 7%.
* **Brachy in sublobar resection**:
  + [Colonias](https://www.sciencedirect.com/science/article/pii/S0360301609034221?via%3Dihub) from Allegheny: 145 pts treated with I-125 mesh. Stage I NSCLC. COPDers. LF 4%, LRR, 6%, DM 17%. This compares favorably with LF rates from [LCSG 821](https://www.sciencedirect.com/science/article/pii/000349759500537U?via%3Dihub) of 18%.
  + [**ACOSOG Z4032** [Fernando JCO '14]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4121503/): **Sublobar resection ± I-125 mesh**.
    - 224 COPDers. NSCLC ≤ 3 cm.
    - 5y LR ~8%. 3y OS ~71%.
    - Appears to be no benefit for BT when compromised margins.
    - 90d Respiratory G3+ ~20%.
    - 90d any G3+ ~30%.
* There is only a 20% pCR after Ipi + Nivo [[NEOSTAR](#9bx2771urd5r)].

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| **Treatment paradigm**   * **Unresectable**: CCRT→ Durvalumab (Cat 1). * **Resectable**   + Incidental stage III at surgery→ Chemo ± RT for N2 or SM+.     - Consider adjuvant chemo for ≥ 4 cm, give for N1 disease (e.g. CE 100 q2w x4c).   + Known stage III: NAC/CCRT→ Surgery ± PORT (if not received neoadjuvantly) for N2 or SM+. * Resectability should be determined upfront (prior to initiation of CCRT). * Order of treatment: Chemo→ RT unless positive margin. CCRT→ chemo for positive margin. For positive margin but no concurrent, R2 gets 66 Gy while R1 gets 60 Gy. |

## [Determining Resectability](#_opxxqv56465m)

See [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1211642313333772292)] diagram which points out the importance of FEV1 > 50%.

* Carefully select pts that can be completed resected: T3N1, or T4 disease due to multiple tumor nodules in one lung.
* **Unresectable**: T4 (great vessel encasement, VB invasion, carina/trachea), N3, multilevel or bulky N2, ECE, malignant effusion, progression of disease during or after induction chemotherapy.
  + Tumor beyond hemithorax (including SCV node).
  + cN2 patients may be candidates if single station < 3 cm with planned lobectomy.
* **Relative C/I to surgery**: brachial plexopathy, recurrent laryngeal nerve paralysis, subclavian artery, vertebral body, esophagus, mediastinal lymph nodes, DM.

* **Medically inoperable**: Varied definition.
  + **High risk generally FEV1 ≤ 50%** (FEV < 1.2L) or **DLCO ≤ 50%** predicted.
    - Desire FEV1 ≥ 1.2-2L or > 75% predicted, DLCO > 60%, and predicted post-op FEV1 > 0.8 L.
  + **Inoperable generally** **FEV1 ≤ 40%** (or < 30% postop) or **FEV < 1L** for lobectomy (**< 2L** for pneumonectomy), DLCO ≤ 50%, FVC < 70% but less restrictive if wedge/segmentectomy is planned.
    - If FEV1 ≤ 40%. ~LC 89% w SABR. 30 day mortality 0 for SABR and 10% for surgery.
* **Resectable**: Pre-op CCRT→ surgery 2-4 weeks afterwards→ Chemo.
* Let's assume surgery first… Then what?
  + Many trials support adjuvant chemo for > 4 cm or LN+ tumors.
  + Recall: There is a **5%** 5y OS benefit with chemo in II/III disease [LACE].

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| **COPD prognosis**:   * **5y OS for FEV1 < 1 L = 50%** [Source: Toronto Notes '14]. * **5y OS for FEV1 < 0.75 L = 33%** [Source: Toronto Notes '14]. |

## RFA

* [**ACCP and STS RFA Consensus Statement** [Chest '12]](https://www.sciencedirect.com/science/article/pii/S0012369212606990?via%3Dihub): American College of Chest Physicians (ACCP) and the Society of Thoracic Surgeons (STS) report recommends RFA as reasonable treatment option only for those high-risk patients with peripheral lesions who are not candidates for SBRT or sublobar resection, or have failed prior SBRT.
* Japan [[Hiraki Radiology '06]](https://pubs.rsna.org/doi/10.1148/radiol.2431060088?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed): 224 RFAs in 142 pts. 50% PTX, with 10% of those receiving chest tubes. 19% pleural effusions.
* Simon [[Radiology '07](https://pubs.rsna.org/doi/10.1148/radiol.2431060088)]: RFA Procedure-specific mortality rate of 2.6%.

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| **ASCO/ASTRO Guideline:** [**Stereotactic Body Radiotherapy for Early-Stage NSCLC**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/28316) *November 6, 2017*  See [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1211642313333772292)] diagram which points out the importance of FEV1 > 50% for [[surgical candidacy](#3e7lasvskpqm)].   * SBRT is standard of care for medically inoperable NSCLC (T1-2). * Any patient being considered for SBRT should be evaluated by a thoracic surgeon to reduce specialty bias. * Local control for BED10 ≥ 100 (e.g. 60/8, 50/5, 48/4) is over 90% at 5 years.   + RTOG 02-36: 5y LR 7%, 5y involved lobar recurrence 20%, 5y DM ~30%, 5y LRR ~40%, 5y OS 40%.  5y values to quote: The "~10, 20, 30, 40%" rule as above. 5y DFS only 26%. * SBRT for operable candidates on clinical trial only. * Lobectomy standard of care, though sublobar resection may be considered in select cases. * SBRT is an appropriate option for tumors > 5 cm in diameter with an acceptable therapeutic ratio.   **ESTRO/ACROP consensus guidelines for SBRT of peripherally located Early-Stage NSCLC** [[Guckenberger RTO '17](https://www.ncbi.nlm.nih.gov/pubmed/28687397)]   * 45/3 favored for peripherally located lesions while 48/4 favored with broad chest wall contact. * PTV D95-99; Dmax < 125 - 150%. * For patients free from severe comorbidities and favorable OS expectancy, 54/3 should be considered. *Although this was used in RTOG 0236, this is above the range that [*[*HyTEC*](#g64ukngzwack)*] recommends.* |

## 

## [SABR](#_opxxqv56465m)

See Summary Box above.

* Radiation alone is inferior to surgery. 5y OS poor at 10-15%, 30% die from DM. LC ~50-60% [[Sibley Cancer '98](https://www.ncbi.nlm.nih.gov/pubmed/9452258)]
* Older radiation plans: LC rates as high as 66%, BED ~80. We now want at least 100 BED [[Onishi](#4elbijb8sf9m)].
* Older radiation plans: Rx 60 Gy to center of tumor, Rx to 95% (57 Gy)→ LC 50-60%, MS 15-17 mo, CCRT 5y OS 13-16%.
* **CALGB 39904** [[Bogart JCO '10]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2815709/): **70 Gy in 29 to 17 fractions** (2.41 Gy to 4.11 Gy).  
  This trial may provide useful dose options for palliation.
  + 39 pts. Stage I. ≤ 4 cm. Central allowed. High risk COPD: FEV1 < 40%, predicted DLCO < 50%, predicted PCO2 > 45 mmHg, VO2 max < 15 mL (kg/min), or on oxygen.
  + 4y LC 92.3% (n=3), 4y DM 18% (n=7).
  + No late G3 or G4, but two acute G3 dyspnea and pain.
* **Synchronous early stage NSCLC treated definitively have favorable outcomes** [[Ayoub IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32044413)]: Retro.
  + 912 patients, 82 (9%) of whom presented with synchronous tumors. MFU nearly 5y.
  + 5y Involved lobar recurrences of 20%, 5y DM of 30%, 5y OS of 50%, which is similar to [[RTOG 02-36](#a7j9wvgpo9h0)].
  + Ipsilateral synchronous disease was associated with greater regional and distant failure
* SABR plans: 60 Gy to periphery and Rx to 80% (75 Gy in the middle). RTOG protocols even Rx to 60% IDL (100 Gy center).
  + 3D: Japan always prescribed 100% to isocenter: LC only 86%! Instead Rx to 69% IDL, for example.
  + Heterogeneity corrections! If not utilized, then the planning system will weight air pockets in lung as normal tissue and there is in reality less dose buildup and therefore less overall dose is delivered to tumor. This is the reason by RTOG 02-36 was actually 54 Gy/3 even though it was planned to 60 Gy/3 [[Xiao IJROBP '09](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2911132/)].

* **SBRT Nomogram: Predicting 5y PFS and OS for NSCLC** [[Kang IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/31586665)]:  
  Significant predictors for OS and PFS includes age, gender, Charlson comorbidity index, DLCO, systemic-immune inflammation index (SII), and tumor size. ECOG predicted for OS as well.

PTV D95 BED10 < 113 Gy and tumor size > 2.45 cm were predictive of time to progression.

Patients with plans who do not meet these criteria may benefit from systemic therapy, as there is ~30% chance of DM in these groups.

* + 715 early stage NSCLC pts (T1-T3N0). 2004-2015. Median 2 cm (85% ≤ 3 cm). Only 7 pts > 5 cm. MFU 5y.
    - SII = (Plt X PMN) / Lymphocytes. Independently associated with OS in the past.
  + MS 57 mo. OS at 1 / 3 / 5y of 90→ 65→ 49%.
  + MPFS 40 mo. PFS at 1 / 3 / 5y of 79→ 53→ 30%.
  + MTTP 14 mo.
  + Concordance indexes for OS / PFS / TTP of 0.72→ 0.66→ 0.59. Therefore, TTP is more likely due to random chance as it is closer to 0.5 than to 1. Models generally considered good when exceeding 0.7, excellent if exceeding 0.8.
  + Optimal values for predicting progression: tumor size < 2.45 cm and PTV D95 BED10 of 113 Gy.
  + 2y LR for tumors ± 2.45 cm of 6→ 11%. 5y LR for tumors ± 2.45 cm of 10→ 15%.
  + 2y DM for tumors ± 2.45 cm of 12→ 19%. 5y DM for tumors ± 2.45 cm of 19→ 27%.
  + 2y LR for PTV D95 BED10 ± 113 Gy of 5→ 9%. 5y LR for PTV D95 BED10 ± 113 Gy of 8→ 13%.
  + 2y DM for PTV D95 BED10 ± 113 Gy of 12→ 20%. 5y DM for PTV D95 BED10 ± 113 Gy of 19→ 28%.

* **RTOG 0236** [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?study=0236), [Timmerman JCO '10,](https://jamanetwork.com/journals/jama/fullarticle/185547) ['14](https://www.sciencedirect.com/science/article/pii/S036030161400786X?via%3Dihub), ['18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6117101/)]: Phase II. Equivalent of **54/3 biw**.  
  1st time SABR done! No EBUS req'd. Sobering trial: 5y DFS only 26%, with intralobar 20% and LRR 40%, DM in 30%.

Grade 3+ toxicity of 30%, twice as high as RTOG 06-18 likely due to non-operable candidates in this study.

* + 55 pts. ≤ 5 cm, > 2 cm from PBT. PET/CT utilized for screening and staging.
    - GTV = CTV. PTV = at most 0.5 cm axial and 1 cm sup/inf, while 0.5 cm isometric if 4D/ITV.
    - RT given BIW w at least 40h separation. Dex 4 mg prior to each treatment.
  + 3y OS > 50% with most ppl dying of other comorbidities. MS 48 mo.
  + **3y LC 98%**, involved lobar control 91%.
  + 3y LR 2%, 3y involved lobar recurrence 9%, 3y DM 22%, 3y LRR 13%, 3y OS 56%.
  + 5y DFS only 26%.
  + **5y LR 7%**, **5y involved lobar recurrence 20%**, **5y DM ~30%, 5y LRR 40%**, **5y OS 40%**. *"10, 20, 30, 40s"*
  + G3/4 Toxicity 31%; G3 27% (n=15), G4 4% (n=2).
    - 10% something bothersome like CW pain or SOB. Only 2.3% incidence of RP req steroids.

* **RTOG 0618** [[Protocol](http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4650), [Timmerman JCO '13](http://ascopubs.org/doi/abs/10.1200/jco.2013.31.15_suppl.7523), ['18](https://jamanetwork.com/journals/jamaoncology/fullarticle/2682582)]: Phase II. **54/3** **biw**.

Operable patients.

SBRT has high tumor control and low toxicity.  
G3 toxicity in 15%, twice as low as RTOG 02-36 likely due to healthier, operable patients without as many COPD issues.

* + 33 pts, 26 evaluable. Bx proven peripheral T1-T3 (≤ 5 cm). Medically operable. MFU 2y.
  + 2y LF 8%. 2y lobar failure 20%, 2y LRF 32%, 2y DM 15%.   
    Only 26 pts evaluable, therefore there are estimated 2y rates.
    - Of two local failures, only one was eligible for and underwent salvage lobectomy.
  + 4y LF 4%. No patients with lobar failure. 4y LRF 12%. 4y DM 12%. 4y DF and OS > 50%.
  + G3 AE in 15% (n=4) with 0 G4/5.

* **MISSILE** [[Palma JAMA Onc '19](https://jamanetwork.com/journals/jamaoncology/article-abstract/2725402)]: Phase II. **SBRT→ lobectomy or sublobar resection** after 10 weeks.  
  pCR rate was lower than expected, but this trial only allowed 10 weeks until surgery.
  + 40 pts. T1-2N0M0. Operable NSCLC.
  + pCR 60%.
  + 2y OS 77%, LC 100%, RC 53%, DM 24%.
  + G3-4 toxicity in 18%.

* **RTOG 0915** [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?study=0915&mode=bro%20adcasts&ptid=387), [Videtic IJROBP '15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4744654/), ['17](https://www.redjournal.org/article/S0360-3016(17)31102-1/abstract), ['19](https://www.sciencedirect.com/science/article/pii/S0360301618340483?via%3Dihub)]: Phase II. **34/1** (BED 150) **vs 48/4** (BED 105).  
  All things considered, there appears to be increased late toxicity with 48/4 compared to 34/1.
  + 84 pts. ≤ 5 cm NSCLC, > 2 cm from TBT. Powered to detect AE > 17%. MFU ~5y.
  + 2y LC ~97→ 93% [NS]. 5y LC ~89→ 93% [NS].
  + 2y OS ~61→ 78% [NS]. 5y OS ~30→ 41% [NS]. MS ~4.1→ 4.6y [NS]
  + 2y DFS ~56→ 71% [NS].
  + G3+ ~13% . One death in each arm, but not definitively due to SBRT.
    - ~33% died from other causes. ~33% died from unknown causes.
  + Late G3+ 3→ 11%.
  + Second primary 15%.
* **Roswell Park** [[Singh IJROBP '19](https://www.redjournal.org/article/S0360-3016(19)33653-3/abstract)]: Phase II. **30/1 vs. 60/3**.   
  TBL [QS](http://www.quadshotnews.com/2019/08/one-shot-is-all-i-need.html#more): Within the confines of another phase 2 trial, there appear to be no major differences in toxicity or disease outcomes for 1 fraction versus 3 fractions of lung SBRT.
  + 98 patients. 2008-2015. T1-2N0M0 NSCLC. MFU 4.5y.
    - GTV = CTV. Add 5 mm for PTV if 4D.
  + G3+ ~15%. No G4+ toxicity.
  + 2y LC ~95%. No differences in overall survival.

### [Treating without a biopsy](#_p20pk5rzxumi)

* ATS Surgical guidelines: **If cancer probability is > 65%, surgeons can proceed with oncologic surgery *without* bx**.
* Three models for calculating probability of malignancy: Download the Pulmonary Nodule Risk smartphone app.
  + Probability following PET/CT: [[Herder]](http://spn.azurewebsites.net/Herder).
  + Probability following CT: Brock and [[Mayo](https://reference.medscape.com/calculator/solitary-pulmonary-nodule-risk)].
* **When Is Bx-Proven Dx Necessary Before SBRT for Lung Cancer? A Decision Analysis** [[Louie Chest '14](https://www.sciencedirect.com/science/article/pii/S001236921550069X?via%3Dihub)]:
  + 3 approaches to nodules ≥ 1 cm: Survey, PET(+)→ bx vs. SABR.
  + **If probability is > 85%, SABR**. 17-85%, bx if PET+. If probability < 17%, observation.
* **RT for Lung Ca Collaborative Group for SBRT without path** [[Berman TLCR '19](http://tlcr.amegroups.com/article/view/26375/19723)]:
  + Obtain PET/CT for lesions > 3 cm. Treat if positive.
    - MRI brain for lesions 3-5 cm (6% risk if cN0). *If PET and pN0, may omit unless > 5cm.*
  + For lesions ≤ 3 cm, calculate probability with [[Mayo](https://reference.medscape.com/calculator/solitary-pulmonary-nodule-risk)]. If 65-85%, get PET/CT. If > 85%, treat.
    - If SUV ≥ 2, then empiric SBRT is reasonable.
    - If non-avid, scan in three months and calculate projected VDT:

If projected VDT < 400 days, or new solid component in previously non-solid nodule, then the argument for SBRT strengthened.

#### 

### [SABR vs. older techniques](#_p20pk5rzxumi)

* Several population based studies suggest SABR has a better OS.
* **SPACE** (Sweden) [[Nyman RTO '16](https://www.sciencedirect.com/science/article/pii/S0167814016342797?via%3Dihub)]: Phase II. **70/35** (2 cm margin) **vs. 66/3** (0.5-1 cm margin to *isocenter*).  
  Even long courses have good LC! No difference in OS or PFS, despite larger tumors in the SBRT arm. Toxicity is higher with conventional, again, despite larger tumors in the SBRT arm.
  + 102 pts. T1-2aN0M0, medically inop, Bx proven or growing on CT with positive PET. MFU 3y.
    - RT dose to isocenter, therefore 45/3 to PTV was given.
    - T2 tumors 25→ 50%. *SABR is more likely T2, AC, COPD, therefore no difference in OS.*
  + 3y PFS ~60%. Similar OS.
  + 3y LF 15%, 3y NF 8%, 3y DM 25%.
  + Esophagitis (any grade) 30→ 8%.
  + Pneumonitis (any grade) 34→ 19%.

* **CHISEL / TROG 09.02** (Australia) [[Protocol (Supplement) Ball Lanc Onc '19]](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30896-9/fulltext): 1:2. **Conventional RT vs. SBRT**.

TBL [QS](http://www.quadshotnews.com/2019/02/chisel-ed.html): SBRT has chiseled out a role in peripheral early-stage NSCLC by improving local control when compared to conventional radiation, translating to longer survival when the treated cancer is a patient’s biggest problem

* + 101 pts. > 2 cm from bifurcation of lobar bronchus. Primary endpoint = LF. MFU at least 2y.
    - RT:(66/33 or 50/20) vs. (54/3 or 48/4).
  + 2y LC 69→ 86% (HR 0.32), 2y OS 59→ 77% (HR 0.51), MS 3→ 5y.
  + Toxicity: G3 in 2→ 9 pts (6→ 14%), G4 in 0→ 1 pt (0→ 1.5%).

* **LUSTRE** (Canada) [[Swaminath Clin Lung Cancer '17]](https://www.sciencedirect.com/science/article/pii/S1525730416302248?via%3Dihub): **60/15** (BED = 84) **vs. SBRT** 48/4 or 60/8 (for central).

Protocol in Treatment Interventions and Table 1.

* + 324 pts expected to detect 3y LC improvement from 75% with CRT to 87.5% with SBRT.
  + Pending results.

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### [SABR vs. Lobectomy](#_p20pk5rzxumi)

* SABR vs. Lobectomy: Randomized trials below - both closed to inadequate accrual.
* High risk patients: severe COPD. FEV 1 ≤ 40% has 10% mortality with surgery, 0% with SABR.
* **STARS**: Peripheral IA. Primary endpoint: 2 and 5 year LRC, QOL and Tx costs
  + Central: 50/4.
  + STARS included brachial plexus and VB as well.
* **ROSEL**: IA or T2 if < 4 cm. Primary endpoint: 3 year OS.
  + Central: 60/8.
  + PROs [[Louie RTO '15](https://www.ncbi.nlm.nih.gov/pubmed/26492839)]: HR-QoL and indirect costs are significantly favorable and cheaper with SABR.

* **STARS-ROSEL pooled** [[Chang Lanc Onc '15](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)70168-3/fulltext)]: **Lobectomy and MLND vs. 54/3** (If central: 50/4, 60/8).   
  Superior OS with SABR vs. lobectomy highly controversial, ~5x less G3 toxicity with SABR!
  + 58 pts. < 4 cm. Medically operable. MFU 3.5y.
  + 3y OS 79→ 95%. G3-4 toxicity 44→ 10%.
  + 3y RFS ~80%, but why is there no RFS benefit but OS benefit is present?
    - May be due to more involved lobar failures because the rest of the lobe was not resected.
* Many other studies demonstrate rough equivalence between lobectomy and SBRT after stage / age matching.
  + [[Zheng IJROBP '14](https://www.redjournal.org/article/S0360-3016(14)00706-8/abstract), [Chen IJROBP '18](https://www.redjournal.org/article/S0360-3016(18)30178-0/abstract)]
  + [[Stokes JCO '18](http://ascopubs.org/doi/abs/10.1200/JCO.2017.75.6536)]: Short term mortality for wedge resection and SBRT at 90d of ~3%.
* Pending trials
  + **STABLE-MATES** [[NCT02468024](https://clinicaltrials.gov/ct2/show/NCT02468024)]: Timmerman. **54/3 vs. sublobar resection**.
    - Peripheral NSCLC ≤ 4 cm, "high" surgical risk.
  + **VALOR** [[NCT02984761](https://clinicaltrials.gov/ct2/show/NCT02984761)]: Moghanki. **Surgery** (pN0-3) **vs. SBRT** (pNx) w adjuvant tx when indicated.
    - Operable. T1-2N0M0 ≤ 5 cm fit for lobectomy.
    - Surgery with adjuvant treatment when indicated.
    - Primary 5y OS, secondary endpoints QoL, respiratory function, tumor control and LCSM.
  + **RTOG 3502** [[NCT01753414](https://clinicaltrials.gov/ct2/show/NCT01753414)]: Kong. **Sublobar resection vs. SBRT.**
    - T1N0M0 ≤ 3 cm fit for lobectomy.

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| [**Treatment of Central and Ultracentral tumors**](#_p20pk5rzxumi)  See the [[Constraints and Toxicity](https://docs.google.com/document/d/1DnTzXxvgAsnW9eR7Br-W7ajBAFXL2IIZhvoRNcLYTK0/edit#heading=h.32fci3qg0zf)] section for more.  TL;DR - Of course, never limit tumor coverage, but try to intelligently plan and limit the PBT to 80-95% of your BED10 ~ 100 Gy prescription scheme (e.g. 65/10, 60/8, 50/5) - not 105%. Still, it's quite nice that 08-13 is essentially an "insurance policy" to be able to push your PBT doses higher. [[LungTECH](https://www.birpublications.org/doi/10.1259/bjr.20150036)] and [[British Columbia](#ju4kfce49bih)] actually limit the PBT to below 80% of the BED10 = 100 Gy prescription dose (Canadians and pre-[[SUNSET](#2btlcyn3xrm9)] Europeans aren't quite as ballsy as RTOG was in 08-13). Sure, we're talking about late tissue side effects, so a lower alpha beta should be used (i.e., BED3 to PBT should be [[< 180 Gy](#iuao5xsxaskw)]). Ultracentral lesions should use algorithm-based VMAT to plan, and consider sacrifice of PTV coverage immediately adjacent to organs at risk so long as ITV coverage is maintained instead of lowering overall PTV coverage. Grade 5 toxicity for ultracentral lesions is a [[real thing](#iuao5xsxaskw)] (insert [[Corradetti NEJM '12](https://www.nejm.org/doi/full/10.1056/NEJMc1203770)] quote) - consent your patients on the risk of death with treatment. Boards answer for ultracentral lesions (and commonly the clinic) = Conventional CCRT.   * **Central** = 2 cm around carina, hilum, or touching mediastinum.   + Older definitions included within 2 cm of VB, brachial plexus. * **Ultracentral** = GTV or PTV abutting PBT (< 2 cm from the carina), or PTV touching mediastinal structure such as esophagus or great vessels. * [[Timmermann](#ycmpv6pzu51d)] demonstrated nearly 50% G3+ toxicity for central tumors, establishing a "no fly zone" within 2 cm of PBT to segmental bronchi. Around half of G3+ toxicities will occur from 1-2y, with half within the first year. Ensure studies have at least 2 years of follow up when reporting toxicities. In the modern era, G3+ toxicity of 10-25% is more commonly reported [[MDACC 2018](#g3o06wmhcj70), [RTOG 08-13](#vmah88n82ask)]. * [[RTOG 08-13](#vmah88n82ask)] was a dose-escalation trial for central lesions. Above 50/5, there were deaths due to toxicity ranging from 3-7% (normally < 1% with SABR), whereas the risk of death from pneumonectomy at a high volume center is ~8% and after lobectomy is 1-3% (double this at 90 days). Review of a multitude of studies, including 5 and 8 fractions, demonstrate SBRT to ultra-central lesions to appear to have a mortality rate between that of lobectomies and pneumonectomies. Most patients will die of fatal pulmonary hemorrhage. No matter how "safe" your plan is, be sure to consent your patients on the risk of death as a result of your treatment for lesions with a PTV abutting the PBT. * Dmax < 105% recommended for proximal bronchial tree (PBT) on 08-13, although [[Cleveland Clinic data](#pp0f11325dsw)] suggests a Dmax closer to 95% may be wiser. Keep in mind most discussions of five fraction regimens do not comment on these suggested constraints when recommending 8 or 10 fractions, instead commonly "ensuring no hot spots" or using < 105% as per RTOG 08-13 to the PBT. It is becoming more common to see constraints suggesting 95% of a tumoricidal BED10 ≅ 100 Gy prescription dose should be allowed to the PBT (e.g. BED10 ≅ 100 Gy regimens of 65/10, 60/8, and 50/5. For 10 fraction regimens, MDACC suggests PBT dmax of 60 Gy, or ~93% of BED10 = 100, [[Manyam](#vpyexbt32q11)] 0813 data for 50/5 which suggests limiting the PBT to ~95% of the Rx dose, and the design of [[HILUS](#dldhobpv14xl)] which essentially limits the PBT to 93% of the 60/8 prescription dose by lowering overall dose prescription to 56/8). * Use extreme caution: Consider [[UK/AAPM](https://www.sciencedirect.com/science/article/pii/S093665551730434X)] constraints from 2018, although these are much more tight than 08-13.   + The ongoing [[LungTECH](https://www.birpublications.org/doi/10.1259/bjr.20150036)] trial for 60/8 to central tumors recommends ~78% of and ~ 72% of the 60/8 dose to be delivered to the PBT and esophagus, respectively.   + [[SUNSET](#2btlcyn3xrm9)] and [[RTOG 08-13](#vmah88n82ask)] push constraints the most. * **Be wary of lesions ≤ 1 cm from mainstem bronchus**: 14% G5 mortality on [[HILUS](#dldhobpv14xl)] which uses 56/8 and has a BED10 of 95 (93% of 60/8, which should be "safe" based on commentary above). *The leaves (are different from the branches) are different from the trunk [*[*Chaudhuri Lung Ca '15]*](#ctkqot8uicm)*, [*[*HILUS*](#dldhobpv14xl)*].* * Therefore, for lesions ≤ 1 cm from the mainstem bronchus, it may be reasonable to consider 60/15 [[NCIC](#j7hoeajh3wsc)], which has a BED10 of 84 (Compare to 50/5 or 60/8, which have a BED10 of 100 while 70/10 has a BED10 of 119). Dose escalation to ITV above BED10 of 100 appears quite reasonable to maximize local control. See [[SBRT Treatment Planning](#_g75vmdnm0cmm)]. * Keep in mind that lesions abutting the mainstem bronchus were not candidates on the [[NCIC](#j7hoeajh3wsc)] 60/15 regimen. If there is not direct invasion, 60/15 to primary and 40-45/15 to potentially involved mediastinal lymph nodes appears reasonable. For lesions directly invading the mainstem PBT, any form of treatment may lead to a fistula between normal parenchyma and the PBT. Therefore, death may be certain regardless of fractionation. * There is no evidence for 8 or 10 fraction regimens being superior to 5 fraction regimens. * It's not just the prescription dose, but how it is prescribed. Consider the sacrifice of PTV coverage so long as ITV coverage is maintained [[Shaverdian BJR '16](#xrsc2jfubvx4), [MDACC Chang RTO '18](#g3o06wmhcj70)].   **Safety and Effectiveness of SABR for ultra-central lung lesions** [Chen JTO '19]   * 10 studies met inclusion, totaling 250 ultra-central lung lesions. All retrospective. * Median G3+ toxicity 10%. * Median G5 toxicity 5%, with over half due to pulmonary hemorrhage.   + **For endobronchial lesions, treatment related toxicity is ~20%** (range 17-33%). * Highest risk for SABR-related mortality: gross endobronchial disease, BED3 ≥ 180 (e.g. 36/3, 45/5, 55/8, 60/10), peri-SBRT bevacizumab use, and antiplatelet/anticoagulant use. * Median LC at 1y / 2y of 96→ 92%.   **LungTech** / **EORTC 22113-08113** [[Adebahr ARO '15](https://www.birpublications.org/doi/10.1259/bjr.20150036)]: Phase II. **60/8 for central lesions**.   * Tumors that are "too central", e.g. T4 tumors or abutting esophagus are excluded. * See Table 1 for an excellent review of severe radiation induced toxicity for lung cancers. * The ongoing [[LungTECH](https://www.birpublications.org/doi/10.1259/bjr.20150036)] trial for 60/8 fractions recommends ~78% of and ~ 72% of the 60/8 dose to be delivered to the PBT and esophagus, respectively. This is very similar to the retrospective [[British Columbia](#ju4kfce49bih)] study. * These constraints are in stark contrast to the 105% allowable to the PBT in 0813.   **SUNSET** [[NCT03306680](https://clinicaltrials.gov/ct2/show/NCT03306680), [Giuliani Clin Lung Cancer '18](https://www.ncbi.nlm.nih.gov/pubmed/29759332)]: Phase I dose escalation. **60**/(**15-10-8-6-5**).  Excellent resource for dose constraints (Table 2). See [[Constraints and Toxicity](https://docs.google.com/document/d/1DnTzXxvgAsnW9eR7Br-W7ajBAFXL2IIZhvoRNcLYTK0/edit#)] for more, constraints are ballsy like RTOG 08-15.   * cT1-3N0M0 NSCLC. Tumor size < 6 cm. Ultracentral: PTV touches/overlaps central bronchial tree, esophagus, pulmonary vein, or pulmonary artery. * Patients with hilar or mediastinal nodes < 1 cm and no abnormal uptake on PET are considered N0. Patients with > 1cm hilar or mediastinal lymph nodes on CT or suspicious uptake on PET may be eligible if biopsies are negative. * Predicted risk of G3-5 toxicity of 30% or less at two years. * PTV D95% = 100%. PTV D99% = 90%. * Prescription IDL must be 60-90% of normalization dose, with a maximum dose of 120% allowed within the ITV. |

### [Central and Ultra-central tumors](#_p20pk5rzxumi)

See the Treatment of Central and Ultracentral summary box above. See the [[Constraints and Toxicity](https://docs.google.com/document/d/1DnTzXxvgAsnW9eR7Br-W7ajBAFXL2IIZhvoRNcLYTK0/edit#heading=h.32fci3qg0zf)] section for more.

* **Indiana Central Toxicity** [[Timmerman JCO '06]](http://ascopubs.org/doi/abs/10.1200/JCO.2006.07.5937?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **60-66/3**. **BED = 180-211**.   
  Nearly 50% G3+ toxicity with central tumors helped establish a "no-fly-zone" of 2 cm around the proximal bronchial tree.  
  Unexpectedly high toxicity with central tumors - G3 toxicity nearly 50%!
  + 70 medically inoperable pts. T1-3N0 (**≤ 7 cm**), including central tumors.
  + 3y LC 88%, 3y CSS 82%, 3y OS 43%, LRF 9%, DM 13%.
  + G3+ toxicity 20% overall, or for peripheral / central 17→ 46%.
  + There were six deaths attributed to late toxicity.

* **HILUS trial** [[Lindberg JTO abstract '17](https://www.jto.org/article/S1556-0864(16)31610-0/pdf)]: Phase II. **56/8**.  
  Central = ≤ 1 cm from the proximal bronchial tree.  
  RT prescribed to the 65-70% IDL.

Very intelligently designed dosimetric constraints: 56 Gy to ipsi mainstem is 93% of the Rx dose for 60/8.

Aim for ≤ 90-95% of Rx dose to the PBT as contoured by 08-13, not ≤ 105% to the PBT (e.g. 90-95% of 60/8, 50/5, 48/4)

**This trial resulted in a 14% Grade 5 toxicity rate for tumors ≤ 1 cm from the mainstem bronchus** when allowing 56 Gy (93% of Rx) to the mainstem. Treatment of tumors close to lobar bronchi appears more safe than tumors close to the mainstem bronchi.

For tumors ≤ 1 cm from the mainstem bronchus, 60/15 appears reasonable per [[NCIC](#j7hoeajh3wsc)], despite the fact that BED10 is 84 Gy.

* + 74 patients. NSCLC or progressive mets from another solid tumor. Max diameter 5 cm.
    - Arm A (n=42): Tumors close (≤ 1 cm) to the main bronchus.
    - Arm B (n=31): Tumors close (≤ 1 cm) to lobar bronchus.
  + Rx: 65-70% IDL. Max PBT < 48.8 Gy to contralateral mainstem, < 56 Gy to ipsi mainstem.
  + G3+ toxicity 28%.
  + G4+ toxicity for Arm A (main) / B (lobar) of 19→ 3%.
  + G5 toxicity 10%, n=6 (14%) in Arm A and n=1 (3%) in Arm B. All but one died of lethal hemoptysis.

* **Stanford** [[Chaudhuri Lung Ca '15](https://www.ncbi.nlm.nih.gov/pubmed/25997421)]: Retro. **50**/(**4-5**).

Central and ultracentral lung tumors have similar outcomes as to patients with peripheral lung tumors.

Ultracentral: Tumors whose GTV directly abuts the PBT or trachea. GTV abutting esophagus were excluded.

See Fig 3 for an excellent breakdown of the PBT. Only 1 patient had GTV abutting mainstem bronchus (see HILUS above).

*This paper suggests PBT doses may not matter, however, most tumors were near subsegmental bronchi. Does exceeding the dose to the subsegmental bronchi matter? A hot spot in the subsegmental bronchi is very different from a hot spot in the mainstem or the trachea. The leaves (are different from the branches) are different from the trunk. Issue: RTOG 08-13 accounts for all of these structures as one unit. Dose to mainstem and trachea need to be reported separately!!! (see G5 toxicity in HILUS Arm A above).*

* + 34 central (7 ultracentral), 34 peripheral per 08-13. 2007-2011. MFU 1.5y (all) or 2y (ultracentral).
    - PTV = ITV + 0.5 cm.
    - Ultracentral: only 1 abutted mainstem bronchus, 6 abutting remainder of PBT. None touched trachea.
  + 2y LC ~90%. Death within follow up in 30%.
  + Symptomatic G2+ toxicity ~20%.
  + 2y G3+ toxicity < 10%.

* **RTOG 0813** [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=9067), [Bezjak IJROBP '16](https://www.redjournal.org/article/S0360-3016(16)30361-3/fulltext), [JCO '19](https://ascopubs.org/doi/full/10.1200/JCO.18.00622)]: Phase I/II. **Dose escalation for medically inoperable central lesions**.   
  Central = 2 cm from TBT or PTV touching mediastinal/pericardial pleura.   
  RT prescribed to the 60-90% IDL.  
  Even 60/5 seems reasonable for centrally located lung tumors, although deaths exceed that of lobectomy.

Dose limiting toxicity of 7% as defined as G3+ toxicity within the first year after SBRT.

Of the 11 patients not evaluable for DLT, 10 patients were not evaluable due to death within 1 year "without DLT".

Timmerman demonstrated year 1-2 = same amount of toxicities as year 0-1. *2y toxicity reporting remains important!* [RoR](#ycmpv6pzu51d)

New school: Many patients are living longer and longer, even with metastatic disease ([www.brainmetgpa.com](http://www.brainmetgpa.com)).

* + 120 pts, < 5 cm. 65% T1. MFU 38 mo.  
    Contouring the PBT: includes distal 2 cm of trachea down to the sub-segmental bronchi. Subtract out the portion of the PBT which is included in the GTV from the PBT contour.
    - RT given BIW w at least 40h separation. Steroids at the discretion of treating rad onc.
    - Only 60% of 12 Gy arms used IMRT. The rest were 3D!
    - Lung constraints:
      * **V20 < 10%**, < 15% minor deviation.
      * V12.5 (2.5 Gy/fx) < 1500 cc.
      * V13.5 (2.7 Gy/fx) < 1000 cc.
    - PBT constraints:
      * D4cc < 18 Gy.
      * Dmax < 105%. *Manyam data below suggests Dmax closer to 90-95% may be more wise.*

* + - * [[Manyam IJROBP '18](https://www.redjournal.org/article/S0360-3016(18)31118-0/fulltext)] suggests PBT D0.33cc < 46.5 Gy should be added to constraints.
      * [[Manyam IJROBP '19](#vpyexbt32q11)] confirmed 0813 constraints limiting the PBT to 105% of the Rx dose have a low sensitivity to detect non-pulmonary grade 3 toxicity.
    - Brachial plexus: V30 < 3 cc.   
      Per Joe Chang: limit brachial plexus to 25-35 Gy in 4-5 fx.
  + **Starts at 50/5, all the way up to 60/5!** (lowest could have been 40/5). Dose limiting toxicity goal ≤ 20%.
  + Overall, G5 toxicity was 6.7% (Only 2.2% within year 1).
  + For the 57.5-60 Gy (11.5-12 Gy) cohort (n=71):
    - 2y LC 88% (includes involved lobe failures), 2y OS 70%, 2y PFS 53%. Distant failure ~20%.
    - G3+ toxicity 21%.
    - G5 toxicity 5.6% (n=4), while for the 57.5 Gy cohort G5 toxicity was 7.8%. 3 died of lethal hemoptysis.
  + For the 52.5-55 Gy (10.5-11 Gy) cohort (n=21):
    - G3+ toxicity 24%.
    - G5 toxicity 9.5% (n=2).

* **MDACC** [[Chang IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301614000960?via%3Dihub): **50/4** (BED10=112) **vs. 70/10** (BED10=119).Central tumors treated with either 4 or 10 fractions have 100% LC at 17 mo.

MDACC is now favoring 5 fraction regimens.

* + 100 pts. ≤ 2 cm from central structures. MFU 31 mo.
    - Includes TBT, major vessels, esophagus, heart, pericardium, brachial plexus, or VB.
    - RT: 88 pts 50/4, 18 pts 70/10 if unable to meet 4 fx constraints.
    - Prescription: Cover ITV + 5mm to at least 95% of the Rx dose, while ITV requires 100% of Rx dose.
  + 3y LC 97% (nearly **100%**!). 3y RC 88%. 3y DM 23%.
  + MS 56 mo, 3y OS 70%.
  + G3 pneumonitis 1%, no G4/5 toxicity. G2 CW pain 13%.

* **MDACC** [[Chang RTO '18](https://www.thegreenjournal.com/article/S0167-8140(18)33380-2/abstract)]: Retro. **Central vs. Ultracentral tumors**. All treated with 5 fractions.  
  Central: ≤ 2 cm of PBT (but not abutting) or ≤ 2 cm from mediastinal structures (including abutment).

Ultracentral: Tumors abutting the PBT.

* + 107 patients. 2009-2015. Primary and metastatic lung tumors. 20% had lymph nodes covered. MFU 15 mo.
    - PTV = ITV + 0.5 cm. All IMRT or VMAT. 80% received 50/5.
    - ITV V100% > 99%, PTV V95% > 99%, PTV Dmax < 120%.
    - Constraints as per RTOG 08-13.
  + 2y OS 57→ 50% (p=0.10). MS 27 mo.
  + 2y LF ~4%.
  + 2y G3+ toxicity 4→ 9% (p=0.23).
  + 2y G5 toxicity ~3%.
* **Israel** [[Korzets ceder Rad Onc '18]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5918762/): Single institution. 60% (40 pts) got **60/5** (12 Gy). **BED10 = 132**.
  + 70 pts. Majority recurrence and oligomets. < 2 cm from the carina. Some 60/8 (10 pts), 54/3 (6 pts), 48/4 (4 pts).
    - PTV = ITV + 3-4 mm, priority given to OAR over PTV.
  + 1.5y LC 93%.
  + 10 pts had G1-2 pneumonitis.
  + One pt developed fatal bronchial bleeding, but had prior surgery and RT.

* **Canadian NCIC CTG BR.25** [[Cheung JNCI '14]](https://academic.oup.com/jnci/article/106/8/dju164/910382): Phase II. **60/15** (4 Gy). **BED10 = 84**.
  + 80 pts. Technically "peripheral" < 5 cm but defined as not involving mainstem bronchus. MFU 4y.
    - 3D conformal, no inhomogeneity correction. PTV = GTV + 1-1.5 cm.
  + G3+ toxicity 40% (n=32), G3 toxicity 5% (n=4), G5 toxicity 1% (n=1, fatal hemoptysis).
  + 2y LC 87%, 3y LC 83%. 2y regional relapse 9%, distant relapse 22%. 2y OS 69%.
* **VUMC** [[Tekatli RTO '15]](https://www.sciencedirect.com/science/article/pii/S0167814015005101?via%3Dihub): **60/8** (7.5 Gy). **BED = 105**.
  + 80 pts. PTV < 2 cm from PBT.
    - PTV = ITV + 3 mm isotropic + 5 mm modifiable.
  + 3y LC > 90%. 3y OS 53% (similar to peripheral).
  + G3+ toxicity 14%, or 5/78 pts with G3 toxicity, none with G4 toxicity.
  + G5 toxicity 3-5%! Possible in 3 pts and likely in 3 pts.
    - ~70% exceeded RTOG 08-13 point dose limits for ≥ 1 OAR. >50% of these in heart.

* **MSKCC** [QS](http://www.quadshotnews.com/2018/10/not-so-fast.html)[[Wang IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618311192)]: Retro. 60/8 (n=14), 50/5 (n=25), 45/5 (n=25).  
  G5 toxicity > 10%! Consider PBT Dmax < 46.5 for PBT, as Dmax < 105% to PBT did these pts no justice.
  + 65 pts. **Ultracentral** = **touching PBT or esophagus** (n=8). MFU 3y.
    - No mention of priority given to OAR over PTV.
  + G3+ 19% with G5 11% (n=7).
    - 3 pts had fatal pulmonary hemorrhage, w max point dose to PBT ≥ 50 Gy. 2 had bev close to RT.
      * [[Manyam IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618311180)] suggests PBT D0.33cc < 46.5 Gy should be added to constraints. Other PBT constraints: D4cc < 18 Gy, Dmax < 105%.
  + LC at 2/4y of 85→ 71%.

* **BC** [[Zhao Rad Onc ‘20](https://www.ncbi.nlm.nih.gov/pubmed/32106868)]: Retro. **60/8**.

SBRT when prioritizing OARs appears safe and effective. Note: This study did not mention how close tumors were to the mainstem bronchus.

* + 35 **ultracentral** patients with PTV touching PBT. 2013-2017. MFU nearly 2y.
    - PTV sacrifice with ITV coverage prioritized in 30%. ITV coverage sacrificed in 16%.
    - PTV = ITV + 5 mm isotropic expansion.
    - PBT D0.035cc < 46.3 Gy (< 80% of BED10 = 100, i.e., 60/8). Very similar to [[LungTECH](https://www.birpublications.org/doi/10.1259/bjr.20150036)].
  + 2y LC > 90%!
  + G3 AE in 5%. There were no grade 4 or 5 events.
* **SBRT for ultra-central tumors: Good Idea, or Ultra-Risky?** [[Palma IJROBP '19](https://www.redjournal.org/article/S0360-3016(18)33859-8/fulltext)]
  + Suggests 60/8 best, but does not account for the new [[Manyam PBT constraints](#vpyexbt32q11)] for 50/5 in 2020. Both 8 fractions and 5 fractions are likely legit, but most oncologists tend to hedge and favor 8 fractions despite lack of data demonstrating superiority by way of local control or safety.

### [SBRT for tumors > 5 cm](#_p20pk5rzxumi)

ASTRO/ASCO Guidelines: SBRT is an appropriate option for tumors > 5 cm in diameter with an acceptable therapeutic ratio.

* Stage II disease (T2bN0 - 4-5 cm; T3N0 - 5-7 cm).
  + ~10% of pts at diagnosis.
  + N1, > 4 cm, or invading pleura, chest wall, diaphragm, phrenic nerve, pericardium, tumor in the same lobe.
  + Adjuvant RT only in R1/2 resections.
  + Given the 30% risk of DM and 40% LRR on [[RTOG 02-36](#a7j9wvgpo9h0)], four new trials are looking at immuno for early NSCLC: SWOG/NRG S1914, UCLA, PACIFIC 4, and NRG-LU004. See the NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)] and [[Future Directions](#_m5aoyuk8s5l5)] section for more.
* Concurrent nivolumab [[appears safe](#kix.yc9oslrzybud)] with conventionally fractionated radiation therapy.
* Peterson [[Clinical Lung Cancer '17](https://www.clinical-lung-cancer.com/article/S1525-7304(16)30374-6/abstract)]: Retro. Rx 25-60/3-5 fractions.
  + 41 patients. Median size 5.6 cm (5-12.2 cm). MFU 16 mo.
  + 1.5y LF 5%, 1.5y DF 32%.
  + G3 toxicity 5%.
* Verma [[IJROBP '17](https://www.sciencedirect.com/science/article/pii/S0360301616332473?via%3Dihub)]: NCDB. Median **50/4**.
  + 201 pts. NSCLC > 5 cm treated with SBRT.
  + 15% received chemotherapy, which was associated with improved OS.
* Verma [[Cancer '17](https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.30375)]: Retro. Median **50/5**.
  + 92 pts. Pooled multi-institutional analysis. Median size 5.4 cm (5-7.5 cm). MFU 12 mo.
  + 2y LC 73%, 2y DFS 54%, 2y DM 33%, 2y OS 46%.
  + G3+ toxicity 5%.

## [Toxicity](#_opxxqv56465m)

* Rengan [[NEJM '12](https://www.nejm.org/doi/10.1056/NEJMc1203770)] demonstrating central airway necrosis after SBRT.
* Patients with interstitial lung disease may have higher rates of toxicity.
* **A Primer on Interstitial Lung Disease and Thoracic RT** [[Goodman JTO’ 20](https://www.ncbi.nlm.nih.gov/pubmed/32105810)]:
  + ILD-GAP index: Mortality risk prediction for patients with ILD. Patients with a score of 0-1 have a 3y mortality of 10%, while scores > 5 are associated with a predicted 3y mortality of 75%.
  + Aim for Lung V20 ≤ 6.5% and MLD ≤ 4.5 Gy with SBRT, although G5 mortality when meeting either metric is still 11%. Issue: Does not report different types of ILD individually [[Chen IJROBP ‘17](https://www.ncbi.nlm.nih.gov/pubmed/28581404)].
  + Aim for Lung V20 < 25% with conventional fractionation [[Kobayashi JCO ’18](https://www.ncbi.nlm.nih.gov/pubmed/29896291), [Higo Jpn JCO ‘19](https://www.ncbi.nlm.nih.gov/pubmed/30793176)].

* **ASPIRE-ILD Protocol** [[Palma BMC Cancer '19](https://www.ncbi.nlm.nih.gov/pubmed/31829203)]: Phase II, single arm. **Dose de-escalation for patients with ILD**.
  + T1-2N0M0 NSCLC with co-existing ILD who are not candidates for surgical excision.
  + Starting dose 50/5 (BED10 100 Gy) with de-escalation to 50/10 (BED10 75 Gy) or 45/15 (BED10 58 Gy).

* **Validation of RTOG 0813 PBT constraints for non-pneumonitis toxicity (NPT)** [[Manyam IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31987965)]:

Manyam data suggests Dmax closer to 95% may be more wise than RTOG 08-13 limiting the PBT to 105% of 50/5.

* + 132 pts. 2009-2016. MFU over 2y.
    - RTOG 0813 constraints: D4cc ≤ 18 Gy, D0.03cc ≤ 52.5 Gy.
  + G2+ NPT predicted by D0.03cc ≤ 50 Gy (Sn 88%, Sp 77%).
  + G3+ NPT predicted by D0.33cc ≤ 47.1 Gy (Sn 100%, Sp 86%).
  + Applying RTOG constraints for G2+ NPT had Sn ~33% and Sp ~92%.
  + A PBT dosimetric correlation for pneumonitis toxicity could not be identified.

* **Lung SBRT and Concurrent Immunotherapy** [[Tian IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31982496)]: **SBRT ± ICI**.

Concurrent SBRT + ICI is safe, but there is a clinically meaningful risk of pneumonitis, especially with dual-ICI.

* + 117 pts, 54 of whom received concurrent ICI. MFU 9 mo.
  + Treatment related AE at 30 days (acute) and 180 days (subacute) were evaluated.
  + G3 pneumonitis 0→ 11%, while any grade RP was similar ~30%.
  + Subacute (90d) G3 pneumonitis in 3→ 27%.
  + Any-grade pneumonitis for ICI monotherapy vs. dual-ICI of 30→ 63%.
  + Receipt of ICI, PTV volume, and lobes involved by WBRT were linked to pneumonitis.
  + Immune checkpoint inhibition and PTV volume above 138 cc were most important.
  + Mean lung dose and V20 did not predict for RP, but they used low cut-offs with MLD of 2.7 Gy and V20 of 6.5%.

* **OARs in Lung SBRT: What is safe for lung parenchyma?** [[Kong IJROBP '19](https://www.sciencedirect.com/science/article/pii/S0360301618340148)]: **AAPM Reporting Guidelines for RP**.
  + Recommend V20 < 10%, with 15% being an acceptable deviation.
  + Suggests Mean Lung Dose limit of 8 Gy, though other high quality studies have suggested 6 Gy [[1](https://www.sciencedirect.com/science/article/pii/S0360301614000960),[2](https://www.sciencedirect.com/science/article/pii/S0169500213003899),[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604921/),[4](http://bit.ly/MLDinSBRT)].
    - All four studies subtract GTV from lungs and report dose fractionations with a BED around 100.
  + This paper is the first to suggest homogenous reporting of radiation pneumonitis!
  + Steroid administration is automatically RTOG Grade 3 toxicity, whereas for CTCAE v3.0/4.0, steroid administration can be either G2 or G3.
  + Trials very rarely report RTOG toxicity, with nearly 100% of studies using CTCAE reporting.

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| **Chest wall toxicity**  Who cares about rib toxicity? Most heal on their own without intervention[[Park J GE Hepatol '20](https://www.ncbi.nlm.nih.gov/pubmed/32052884)]  ARRO: [[Management of Chest Wall Toxicity After SBRT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/ChestWallToxicity.pdf)]   * V30 < 70cc for CW 2cm. *Contour CW as 2 cm tissue rind on the lung.* * Should not compromise tumor coverage to limit chest wall dose. * Consider increased fractionation of 4-5 fractions with high volume chest wall overlap with PTV. |

* **Rib** [[Pettersson RTO '09]](https://www.sciencedirect.com/science/article/pii/S0167814009001467?via%3Dihub): Retro. **45/3**.

Keep D2cc(rib) < 27 Gy if possible.

* + 33 patients. 1998-2005. MFU 2.5y.
  + 13 rib fractures in 7 patients.
  + Rib D2cc of 27 / 50 Gy with 5→ 50% rib fractures.
  + RTOG 0915 D1cc (rib) < 32 Gy for 4 fx.
  + D2cc 21 Gy ~0% rib fx.
* **Chest wall**: V30 < 70cc for CW 2cm.
  + [Dunlap [IJROBP '10]](https://www.sciencedirect.com/science/article/pii/S0360301609002521?via%3Dihub): V30 < 30cc for CW 3 cm, but only 15% of pts in MSKCC series met this unrealistic goal.
  + [Mutter [IJROBP '12]](https://www.sciencedirect.com/science/article/pii/S0360301611005190?via%3Dihub): 126 pts. 3-5 fx SBRT of 40-60 Gy. 2y G2+ CW pain for ± V30 < 70cc CW 2 cm 22→ 54%.
* **Brachial plexopathy** [[Forquer RTO '09](https://www.thegreenjournal.com/article/S0167-8140(09)00193-5/fulltext)]: Retro. 3-4 fraction SBRT.
  + 37 apical lesions. T1-2N0 or peripheral T3N0. 1998-2007.
  + G2-4 plexopathy in 19% (n=7). G3+ 8% (n=3). Five patients had neuropathic pain alone.
  + Median dose 30 Gy.
  + 2y risk of brachial plexopathy for Dmax of ± 26 Gy of 8→ 46%.
* **Pretreatment Immune Parameters** [[Shaverdian CLC '16](https://www.clinical-lung-cancer.com/article/S1525-7304(15)00187-4/fulltext)]:
  + 118 pts. SBRT.
  + Higher neutrophil to lymphocyte ratio (NLR) predicted for poor 3y OS.
    - Surgical series also corroborate that patients with lower lymphocyte counts do worse.
  + Higher neutrophils are protective of symptomatic radiation pneumonitis. Theory: more active immune system.
  + Higher albumin predicted for symptomatic RP.
  + Higher NLR is protective of any symptomatic toxicity, specifically G2+ RP.
  + Systemic-immune index (SII): Independently associated with OS. (Platelets X PMN) / Lymphocytes [[Nomogram](#862515115833)].
* **Pretreatment anemia may predict for overall survival** [[Shaverdian JTO '16](https://www.jto.org/article/S1556-0864(16)30462-2/fulltext)]: **SBRT and Hgb < 12.2 with worse DFS**.

Patients who receive SBRT are typically non-surgical candidates. It is important to be able to identify patients who may do worse when treated with SBRT. Hgb < 12.2 portends to poor regional control, poor DFS, and poor OS.

* + 147 cases. MFU 2.5y.
  + 3y LC / RC / DC of 95→ 87→ 89%.
  + 3y OS / DFS of 75→ 83%. *Survival rates for the whole cohort are comparable to surgery.*
  + 3y DFS for Hgb ± 12.2 g/dL of 70→ 94%. All non-local increase in failures, no less LC for anemic pts.
  + Lower pretreatment Hgb predicted for poor LRC, DFS, and OS.

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| **Treatment planning for SBRT**  **BED10 and local control**  Tumor size < 2.45 cm and PTV D95 BED10 ≥ 113 maximizes local control [[Kang IJROBP '19](#862515115833)].  BED10 of 113 is around 54/5, which is in the range recommended by HyTEC.   * 60/3 BED10 = 180. * 54/3 BED10 = 151. * 34/1 BED10 = 150. * 60/5 BED10 = 132. * 70/10 BED10 = 119. * 65/10 BED10 = 100. * **50/4 BED10 = 112**. * 60/8 or 48/4 BED10 = 105. * 50/5 BED10 = 100. * 60/15 (NCIC) BED10 = 84... Rut roh!   **HyTEC**: **LC following SBRT for Stage I NSCLC** [[Lee IJROBP '19](https://www.redjournal.org/article/S0360-3016(19)30572-3/pdf)]:   * 160 studies looked at, only 47 high quality studies included. α/β ratio believed to be around 20. * **Maximum LC for Rx to PTV periphery for combined T1 and T2 tumors**: **43/3, 47/4 or 50/5** ± 1 Gy at each level.   + **T1**: **42/3, 46/4, 48/5** to PTV, ± 1 Gy at each level.   + **T2**: **45/3, 50/4, 53/5** to PTV, ± 1 Gy at each level.   **Consider PTV sacrifice if concern for DLT** [[Shaverdian BJR '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4986505/)]. Hypothesis-generating. **Ensure 100% coverage of ITV**   * UCLA. 120 definitive SABR cases. 54/3 to (PTV + 6 mm CC and 3 mm axial margin) vs. full ITV coverage w no margin. * Goal to cover PTV to 95% and ITV to 100%. * 3y LC 100% in both groups, 3y OS ~76%. * Goal V20 < 10% (15% acceptable), although reports of G3+ radiation pneumonitis are common if baseline pulmonary fibrosis or if receiving immunotherapy. * There appears to be a direct correlation with mean lung dose > 6 Gy and G3+ RTOG radiation pneumonitis. |

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  Zaorsky: [[LN stations in lungs](https://twitter.com/NicholasZaorsky/status/1211640873634664453)].  ARRO: [[Management of Chest Wall Toxicity After SBRT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/ChestWallToxicity.pdf)], [[Central Lung Early Stage NSCLC](https://www.astro.org/ASTRO/media/ASTRO/AffiliatePages/arro/PDFs/ARROCase_SABR_Lung_EarlyStage.pdf)].  Contouring   * eContour [[Thoracic OARs and lobar anatomy](https://econtour.org/cases/89), [Kong IJROBP '11](https://www.ncbi.nlm.nih.gov/pubmed/20934273)] * Cardiac Contouring Atlas (Supplement) [[Duane RTO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5356506/)] * RTOG 1106 OARs [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-lung)]: PET-Guided therapy for stage III NSCLC. [RoR](#p1qgl9x43th3) * EORTC guidelines for planning and delivery of high-dose, high precision RT for lung cancer [[De Ruysscher RTO '17](https://www.ncbi.nlm.nih.gov/pubmed/28666551)] * CT-based definition of thoracic LN stations: An atlas from the University of Michigan [[Chapet IJROBP '05](https://www.ncbi.nlm.nih.gov/pubmed/16111586)] [RoR](#_6jx2f37knu1t)   Review Articles   * RT for Lung Cancer Collaborative Group for SBRT without pathology [[Berman TLCR '19](http://tlcr.amegroups.com/article/view/26375/19723)]. [RoR](#_canzrk46c7jc) * Differential Relapse Patterns for NSCLC Subtypes [[McAleese Clin Onc '19](https://www.ncbi.nlm.nih.gov/pubmed/31351746)]: Retro. AC vs. SqCC. [RoR](#_12dcu6uefto4) * What is the role of RT for ES-SCLC in the immunotherapy era? [QS](http://www.quadshotnews.com/2019/07/chest-bump.html) [[Nesbit TLCR '19](http://tlcr.amegroups.com/article/view/28932)]. [RoR](#snu066265ta7) * Oligo Review of NSCLC Oligometastases [Giulani IJROBP '20]. [RoR](https://docs.google.com/document/d/1CfbqB4YnaPB8U3r2LykLv2v3bRLJyYQV0tvX4Js2Mog/edit#heading=h.sfi9w935mota) * 4π VMAT RT [[Dong IJROBP '13](https://www.redjournal.org/article/S0360-3016(12)03636-X/fulltext)]: Extensive non-coplanar beams. "Poor man's proton therapy". [RoR](#fisjtvppfzs8) * Onishi [JTO '07]: Goal BED ≥ 100 Gy (dose to iso, though), comparable OS to Ginsberg which was only stage IA. [RoR](#4elbijb8sf9m) * Tumor size < 2.45 cm and PTV D95 BED10 ≥ 113 Gy maximizes local control in SBRT [[Kang IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/31586665)] [RoR](#862515115833)   Society Guidelines   * ASCO/ASTRO Guideline: [Stereotactic Body Radiotherapy for Early-Stage NSCLC](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/28316) *November 6, 2017* [RoR](#r6yxnlb4f49j) * ESTRO/ACROP consensus guidelines for SBRT of peripherally located Early-Stage NSCLC [[Guckenberger RTO '17](https://www.ncbi.nlm.nih.gov/pubmed/28687397)] [RoR](#3hkmkuz2stjz) * [ACCP and STS RFA Consensus Statement [Chest '12]](https://www.sciencedirect.com/science/article/pii/S0012369212606990?via%3Dihub) * HyTEC: LC following SBRT for Stage I NSCLC [[Lee IJROBP '19](https://www.redjournal.org/article/S0360-3016(19)30572-3/pdf)] [RoR](#g64ukngzwack) * UK/AAPM Consensus on Normal Tissue Dose constraints for SBRT [[Hanna CO '18](https://www.sciencedirect.com/science/article/pii/S093665551730434X)] [RoR](https://docs.google.com/document/d/1DnTzXxvgAsnW9eR7Br-W7ajBAFXL2IIZhvoRNcLYTK0/edit#heading=h.hjf4rn360avr) * ASCO Guidelines for Surveillance after Definitive Curative-Intent therapy [[Schneider JCO '19](https://www.ncbi.nlm.nih.gov/pubmed/31829901)] [RoR](#x0pt4mmhjq2i)   Relevant Accessible Radiation Protocols   * RTOG 0236 [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?study=0236)]: Phase II. Equivalent of 54/3 biw in medically inoperable early NSCLC. [RoR](#a7j9wvgpo9h0) * RTOG 0618 [[Protocol](http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4650)]: Phase II. 54/3 biw in medically *operable* early NSCLC. [RoR](#a3yfypawrt4n) * RTOG 0813 [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=9067)]: Phase I/II. Dose escalation for medically inoperable central NSCLC lesions. [RoR](#vmah88n82ask) * SUNSET (Table 2) [[NCT03306680](https://clinicaltrials.gov/ct2/show/NCT03306680), [Giuliani Clin Lung Cancer '18](https://www.ncbi.nlm.nih.gov/pubmed/29759332)]: Phase I Central dose escalation. 60/(15-10-8-6-5). [RoR](#2btlcyn3xrm9) * RTOG 0915 [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?study=0915&mode=bro%20adcasts&ptid=387)]: Phase II. 34/1 (BED 150) vs 48/4 (BED 105) medically inoperable peripheral NSCLC. [RoR](#yy4w2zafo8vx) * CHISEL (Australia) [[Protocol (Supplement) Ball Lanc Onc '19]](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30896-9/fulltext): 1:2. Conventional RT vs. SBRT stage I NSCLC. [RoR](#2jnczabvubqg) * LUSTRE (Canada) [[(Treatment and Interventions, Table 1)](https://www.sciencedirect.com/science/article/pii/S1525730416302248?via%3Dihub): 60/15 vs. SBRT 48/4 or 60/8 (for central). [RoR](#ina2v8rfz7lo) * ASPIRE-ILD Protocol [[Palma BMC Cancer '19](https://www.ncbi.nlm.nih.gov/pubmed/31829203)]: Phase II, single arm. Dose de-escalation for patients with ILD. [RoR](#kix.o1he394ouy3r) * Consider PTV sacrifice if concern for DLT [[Shaverdian BJR '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4986505/)]. Hypothesis-generating. Ensure 100% coverage of ITV [RoR](#xrsc2jfubvx4)   Quality of Life/Toxicity   * VATS vs. open thoracotomy lobectomy [[Paul JTCVS '10](https://www.sciencedirect.com/science/article/pii/S0022522309010800?via%3Dihub)]: Consider minimally invasive VATS lobectomy. * Safety and Effectiveness of SABR for ultra-central lung lesions [Chen JTO '19] [RoR](#iuao5xsxaskw) * LungTECH summary of RILTs for Central SBRT to the Lung (Table 3) [[Adebahr BJR '15](https://www.birpublications.org/doi/10.1259/bjr.20150036)]. [RoR](#kix.hsgc4mx4om77) * Stanford [[Chaudhuri Lung Ca '15](https://www.ncbi.nlm.nih.gov/pubmed/25997421)]: Retro. Central and Ultracentral. 50/(4-5). [RoR](#ctkqot8uicm) * HILUS trial [[Lindberg JTO abstract '17](https://www.jto.org/article/S1556-0864(16)31610-0/pdf)]: Phase II. Central tumors. 56/8. Lesions < 1 cm from mainstem very high risk. [RoR](#dldhobpv14xl) * MSKCC [QS](http://www.quadshotnews.com/2018/10/not-so-fast.html) [[Wang IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618311192)]: Retro. Central and Ultracentral. 60/8 (n=14), 50/5 (n=25), 45/5 (n=25). [RoR](#o1jeelwgulz6) * ROSEL PRO SABR vs surgery [[Louie RTO '15](https://www.ncbi.nlm.nih.gov/pubmed/26492839)] [RoR](#rx1mp1g7p9vd) * RTOG 0813(Table 3) [[Bezjak JCO '19](https://ascopubs.org/doi/full/10.1200/JCO.18.00622)]: Phase I/II. Dose escalation for medically inoperable central NSCLC lesions. [RoR](#vmah88n82ask) * Validation of RTOG 0813 PBT constraints for non-pneumonitis toxicity (NPT) [[Manyam IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31987965)]. [RoR](#vpyexbt32q11) * Lung SBRT and Concurrent Immunotherapy [[Tian IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31982496)]: SBRT ± ICI. [RoR](#70uud96bc7wd) * OARs in Lung SBRT: What is safe for lung parenchyma? [[Kong IJROBP '19](https://www.sciencedirect.com/science/article/pii/S0360301618340148)]: AAPM Reporting Guidelines for RP. [RoR](#sz9jsyj0jga4) * RTOG 0236(Table 4/5) [[Timmerman JCO '10](https://jamanetwork.com/journals/jama/fullarticle/185547)]: Phase II. Equivalent of 54/3 biw in medically inoperable early NSCLC. [RoR](#a7j9wvgpo9h0) * Rib fracture rates analysis for 3 fractions [[Pettersson RTO '09](https://www.ncbi.nlm.nih.gov/pubmed/19410314/)]. [RoR](#xqqctftfgb5b)   + Who cares about rib toxicity? Most heal on their own without intervention[[Park J GE Hepatol '20](https://www.ncbi.nlm.nih.gov/pubmed/32052884)] * Brachial plexopathy [[Forquer RTO '09](https://www.thegreenjournal.com/article/S0167-8140(09)00193-5/fulltext)]: Retro. 3-4 fraction SBRT. |

## 

## [SBRT Treatment Planning](#_opxxqv56465m)

* CT with ≤ 1.5-2 mm slices, 4DCT, no fiducials necessary.
* MIP may be best to guide target delineation, but it is important to go through all phases of the breathing cycle.
* The average CT scan is optimal for dose calculation.
* 4DCT: External surface marker signal designates which breathing phase is obtained. Tumor organ/motion reconstructed over virtual breath cycle to bin the images from 0-100%. 0% = inspiration, 50% = expiration.
* Know how to plan in 3D and IMRT. OK to say "Rapid arc with avoidance of contra lung".
  + 7-11 beams or Arc therapy.
  + Beams: 6-10 MV FFF. 7-11 non-opposing, non-coplanar fields (RTOG)
* **Movement of tumors based on real-time MRI** [[Thomas Br J Radiol '18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5965474/)]: **4DCT vs. MRI.**

The 4D CT isn't the most reliable tool to determine tumor location. Patients may have different patterns of breathing on different fractions (Figure 2a). Both inter and intra fractional breathing amplitude should be taken into account during planning, but further work is required to investigate the dosimetric effects of results.

* + Five lung tumor patients. PTV = ITV + 3-6 mm. No abdominal compression.

* **4π VMAT RT** [[Dong IJROBP '13](https://www.redjournal.org/article/S0360-3016(12)03636-X/fulltext)]: **Extensive non-coplanar beams**. **"Poor man's proton therapy"**.
  + Giving up to 200-300 beams with couch rotations and kicks.
  + 4π optimization using group sparsity takes ~5 minutes.
  + Reduces R50 by 54%.
  + Heart, esophagus, trachea, bronchus and spinal cord were reduced by 44%, 74%, 40%, 42% and 51%.

* **Onishi** [JTO '07]: **Goal BED ≥ 100 Gy** (dose to iso, though), comparable OS to Ginsberg which was only stage IA.  
  Recall this is dose to iso, which is 20% less as dose in USA in Rx to 80% IDL for LINAC-based treatments.  
  BED10 ≥ 100 Gy in SBRT results in an improved OS and LC, also with improved results over conventional RT.
  + 257 pts. Retro. Stage I NSCLC < 6 cm. MFU 3y. Median BED10 111 Gy (57-180 Gy).
  + For BED10 ± 100 Gy, 5y LF 43→ 8%, 5y OS for medically operable refusing surgery of 30→ 71%.
* **Consider PTV D95 and Mean for Optimal LC for SABR** [[Zhao and Chang IJROBP '16](https://www.redjournal.org/article/S0360-3016(16)00320-5/fulltext)]: **Aim for PTVD95 BED10 125 Gy**.  
  See Kang paper below for the most modern BED10 SBRT recommendations from 2019.
  + PTVD95 BED10 > 86 Gy and PTVmean BED10 >130 for plan optimization. *BED 130: 55/4 or 75/10.*
  + PTVD95 BED10 >124 Gy and PTVmean BED10 > 150 achieved 100% LC in lesions treated.
  + Larger tumor (e.g. >8.3 cm3) was associated with poor local/lobar control, but the difference diminished with PTVD95 BED10 >124 Gy or PTVmean BED10 >150 Gy. *BED 150: 60/4 or 82/10.*
* **Tumor size < 2.45 cm and PTV D95 BED10 ≥ 113 Gy maximizes local control** **in SBRT** [[Kang and Chang IJROBP '19](#862515115833)]
* **Correlating dose variables with local tumor control** [[Klement IJROBP '20]](https://www.ncbi.nlm.nih.gov/pubmed/32188579): **Mean ITV BED10 164 Gy**.

PTV BED10max > 201 Gy, PTV BED10ave > 164 Gy, PTV BED10min 100 Gy.

BEDave was highly correlated to the mean GTV dose, meaning the GTV may be used as a prescription target. More emphasis could be placed on achieving sufficiently high mean doses within the GTV rather than the PTV covering dose, a concept which needs further validation.

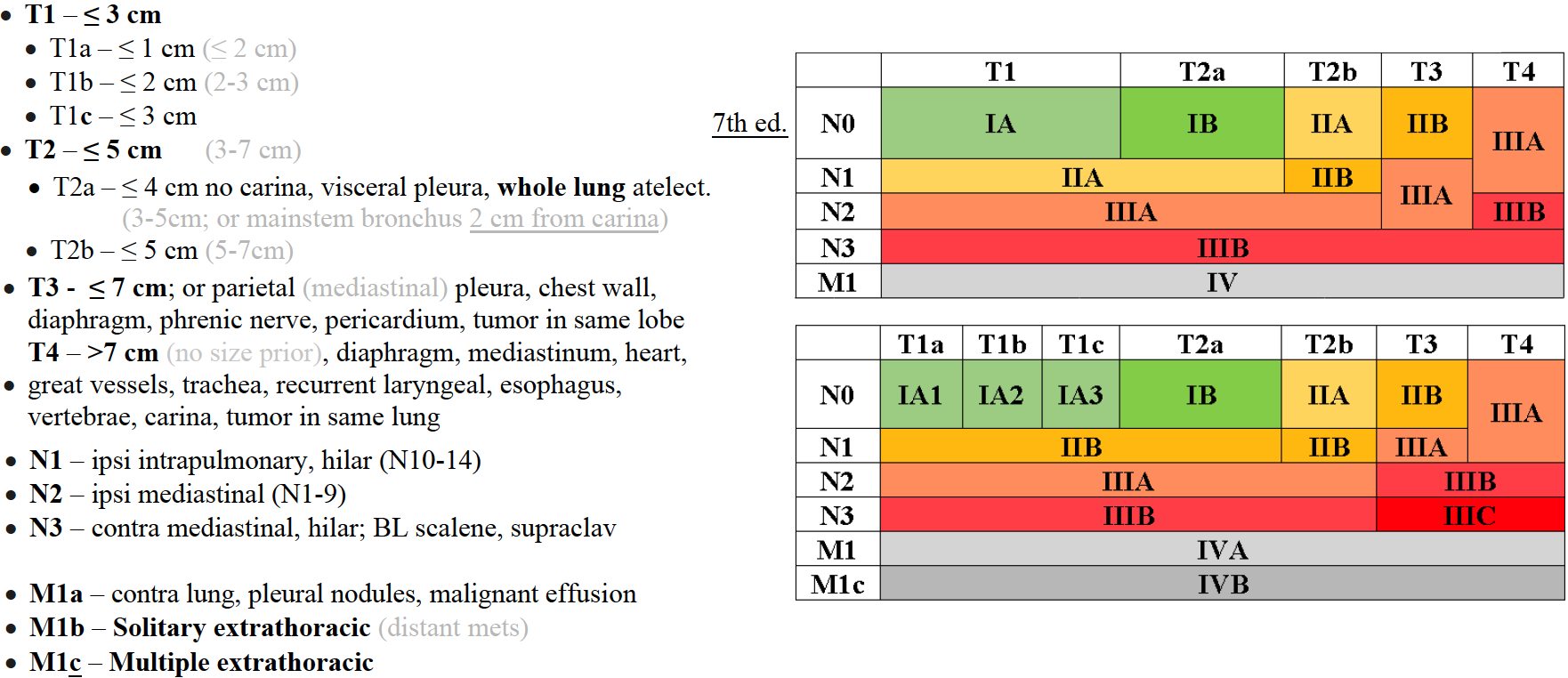
* + 1500 treatments in 1434 pts. 117 tumors recurred locally.
    - BED10min: Minimum dose prescribed to PTV periphery.
    - BED10max: Maximum dose absorbed by 1% of the PTV.
    - BED10ave: The average between the near-minimum and near-maximum doses.
  + BED10ave was the best predictor of local recurrence, while a model based on BED10min had substantially less supporting evidence. MV classification revealed BED10max as the most important predictor, followed by BED10ave.
* **Recommendations for prescribing and reporting per ICRU-91** [[de Jong RTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31767472)]
  + Minimum PTVD98% BED10 of 100 Gy.
  + Minimum GTV/ITV mean BED10 of 150 Gy.
  + D2% in the range of 60-70 Gy.
* Volumes
  + GTV on lung window.
  + ITV = 4D GTV, same concept as CTV.
  + PTV = ITV + 0.5 cm. Some use 0.3 - 0.6 mm.
    - If free breathing, use 1 cm CC and 0.5 cm radially for GTV to PTV.
* Fields: Aperture from BEV should be PTV (no extra margin for dose buildup) except for small lesions.
* Rx: to IDL covering PTV.
  + PTV V100% ≥ 95%, V90% ≥ 99%.
  + For ultracentral per MDACC: ITV V100% > 99%, PTV V95% > 99%, PTV Dmax < 120%.  
    *This suggests that ITV coverage should be maintained and PTV sacrifice is acceptable.*
  + High dose spillage: Volume outside PTV getting 105% should be < 15% of PTV
    - CI = PIV/PTV < 1.2.
  + Low dose spillage: R50 = 50% Rx.
    - R50 = Volume 50% IDL / Volume PTV.
      * Usually depends on PTV, usually < 3.5-6 (5 fx) or < 3-4 (3 fx).
    - IDL/PTV < 3.5-6 for 5 fx.
  + D2cm is max dose (in %) at 2 cm from PTV in any direction.
    - Usually depends on PTV, usu < 50-60% (5 fx) or < 30-40% (3 fx).

## 

## [Follow up after SABR](#_opxxqv56465m)

* CT chest q6 mo x2y, then annually. PET/CT should not be used as a surveillance tool [[ASCO Guidelines '19](#x0pt4mmhjq2i)]
* 5y LR 7%, 5y lobar recurrence 20%, 5y DM ~30%, 5y OS ~40% per [[RTOG 02-36](#a7j9wvgpo9h0)].
* **Patterns of Recurrence** [[Senthi Lancet '12](https://www.thelancet.com/journals/lancet/article/PIIS1470-2045(12)70242-5/fulltext)]. SABR plans: 5y LC 90%, DC 80%.  
  BED10 ≥ 100 to maximize LC; BED3 ≤ 240 to keep risk of fatal toxicity to 1%.
  + 676 pts. PET+ cT1-2N0 NSCLC. 65% treated without tissue.
  + 5y LR 11%, 5y LRF 13%, 5y DM 20%.
* **Kestin** [[RTO '14]](https://www.thegreenjournal.com/article/S0167-8140(14)00042-5/fulltext): Mostly **54/3**, but also 48/4, 60/5, 60/8.   
  Rx BED10 > 105, PTVmean >125 Gy improves outcomes.
  + 505 tumors in 483 pts from 1998-2010. cT1-T2N0. 5 different institutions. Mean f/u 1.6y.
    - 3D conformal. Only req'd 4D after 2006.
  + Overall, 26 cases (5%) had LR at 2y.
  + 2y LR for PTVmean BED10 ± 125 Gy 4→ 17%.
  + 2y LR for Rx BED10 ± 105 Gy 4→ 15%.
  + 2y LR for tx ± 10 days 4→ 14%. *11 days or greater may have worse local control?*
  + 2y LR for ± 2.7 cm tumors 3→ 9%.
* **Imaging changes after SBRT** [[Linda Eur J Radiol '11]](https://www.sciencedirect.com/science/article/pii/S0720048X0900610X?via%3Dihub)
  + Early CT findings: Diffuse consolidation, diffuse GGO, patchy consolidation and GGO, Patchy GGO.
  + Late CT findings: Modified conventional pattern, mass-like pattern, scar-like pattern.
* **PET persistence > 6 mo with SUV > 5 highly suspicious for LR** [[Zhang and Chang IJROBP '12]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474601/)
  + Only use PET if High risk CT features, there is no role for routine PET.
* **High risk CT features [**[Huang RTO '13]](https://www.sciencedirect.com/science/article/pii/S0167814013003344?via%3Dihub): Enlarging opacity, CC growth, sequential enlargement, enlarging opacity after 12 months, loss of linear margins, bulging margin, loss of air bronchograms.
  + For ≤ 2 high risk CT features, get PET. If SUV ≥ 5 or SUV > pretreatment, bx or resection.
  + For ≥ 3 high risk CT features, no PET necessary.

# [Locally Advanced NSCLC](#_6sfwza45y5km)



T2: ≤ 5 cm. Visceral pleura, no carina. Whole lung atelectasis, mainstem bronchus.

T3: ≤ 7 cm. Parietal pleura. Pericardium. Chest wall, brachial plexus, tumor in the same lobe.

T4: > 7 cm, Vertebral body, subclavian, diaphragm, mediastinum, tumor in the same lung.

M1b: Solitary extrathoracic.

[**StatPearls: Pancoast Syndrome**](https://www.ncbi.nlm.nih.gov/books/NBK482155/)*Last update: 3/3/2019.*

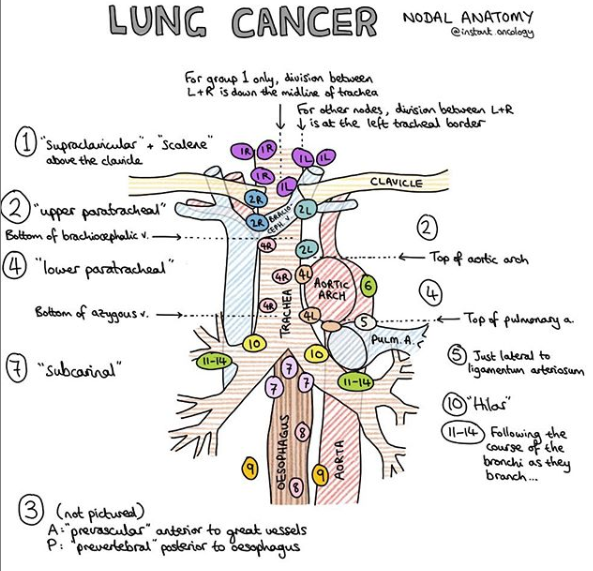
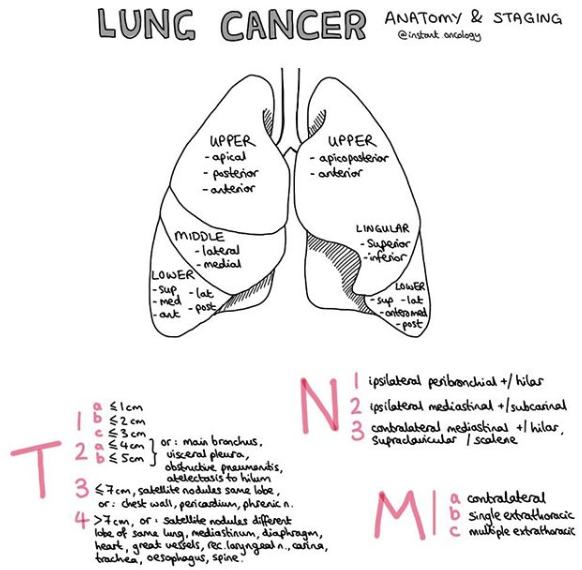
Zaorsky: [[LN stations in lungs](https://twitter.com/NicholasZaorsky/status/1211640873634664453)].

eContour [[Thoracic OARs and lobar anatomy](https://econtour.org/cases/89), [Kong IJROBP '11](https://www.ncbi.nlm.nih.gov/pubmed/20934273)], [[PORT for pN2](https://econtour.org/cases/96)].

ARRO: [[NSCLC](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/NSCLCIIIB.pdf)], [[Resectable LA-NSCLC](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/Resectablelung.pdf)].

RTOG 1106 OARs and Targets [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-lung)]: PET-Guided therapy for stage III NSCLC. [RoR](#p1qgl9x43th3)

AVARO [[Normal Thorax Anatomy](http://econtour.org/cases/89)], [[Thoracic nodal levels](http://econtour.org/cases/88)]

[](https://www.instagram.com/p/B-3xOU-ARPm/?utm_source=ig_web_copy_link)[](https://www.instagram.com/p/B-1vBf2gLtz/?utm_source=ig_web_copy_link)

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| See [[Systemic Therapy](#_wp55nx1rut9o)] for NSCLC.  **ASCO Guideline:** [**Definitive and Adjuvant RT in Locally Advanced NSCLC**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/10206) *May 5, 2015*   * CCRT improves LC and OS compared to SCRT. * Standard dose for CCRT is 60/30.   + *Doses ≥ 66 Gy based on OAR tolerances (isotoxic therapy) are reasonable [*[*PET-plan*](#qqm2ojo8sjj4)*,* [*Zhao RTO '19*](#81n83icjfhfv)*].* * No role for the routine use of induction chemo. * No clear role for consolidation treatment after CCRT unless only partial chemo delivered during RT.   + *Adjuvant durvalumab is now recommended in the [*[*PACIFIC*](#kix.8o8cpe3mdnov)*] era.* * The ideal concurrent chemo regimen and optimal management of resectable stage III disease is debated.   [**ASTRO Guideline: Definitive and Adjuvant RT in Locally Advanced NSCLC**](https://www.astro.org/Patient-Care-and-Research/Clinical-Practice-Statements/ASTRO-39;s-guideline-on-definitive-and-adjuvant-RT)*June 2015*  See ASCO Guideline above for definitive recommendations.   * R1 or N2 should receive PORT. * PORT for R0 N2 disease is controversial [[PORT Meta](#lzs6w7rjvkpn)], and is the topic of the ongoing [[Lung-ART](#jqiyx32hj0hi)] trial. * PORT for R0 N1 disease leads to a detriment in overall survival.   + *N1 should only receive PORT if not receiving chemotherapy [ANITA].* * If PORT recommended, it should be given sequentially after chemotherapy unless evidence of gross disease. * For patients receiving adjuvant PORT for R0 disease, 50-54 Gy conventional fractionation should be used. * Patients with R1 and/or microscopic ECE should receive 54-60 Gy. * Patients with R2 should receive at least 60 Gy to improve local control. * There is no level 1 evidence recommending induction RT (or CCRT) followed by surgery for resectable disease. * In patients selected for TMT, preoperatively planned lobectomy is preferred because it was associated with a survival benefit in the exploratory post-hoc [[INT 0139](#fe2c038zyqzk)] analysis. A minimum of 45 Gy should be considered based on this trial.   **ASCO Guideline:** [**Adjuvant Chemo and Adjuvant RT for Stages I-IIIA Resectable NSCLC**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/10226)*April 24, 2017*   * Adjuvant chemo is not recommended for stage IA disease. * Adjuvant cisplatin-based chemo is not routinely recommended for stage IB disease (≤ 4 cm), but should see med onc. * Adjuvant cisplatin-based chemo is recommended for pts with stage IIA-IIIA who underwent complete surgical resections. * Adjuvant RT not recommended for resected stage I-II disease.   + *Not in guidelines, but preferred by Rad Oncs: Consider PORT if no chemo for ≥ stage IIB (N1) [*[*ANITA*](#eo0e21jjvt86)*].* * Adjuvant RT is not recommended for all N2 disease.   + *Not in guidelines, but preferred by Rad Oncs: Consider PORT for N2 regardless of chemo received [*[*ANITA*](#eo0e21jjvt86)*].* |

### Stage III disease

* ~15% of pts are IIIA at diagnosis. 25% are stage III.
* Around 1/3 of NSCLC are diagnosed at stage III. MPFS ~8-10 mo with 5y OS ~15-25% prior to [[PACIFIC](#kix.8o8cpe3mdnov)].
* **IIIA**: N2, T3/4 N1 or T4.
  + Surgery first can be for T3/4 N1 but in carefully selected, limited stage III dz such as superior sulcus tumors.
* **IIIB**: N3 or T3/4 N2.
* **IIIC**: T3/4 N3.
* **French series** [[Andre JCO '00]](http://ascopubs.org/doi/full/10.1200/JCO.2000.18.16.2981): **Surgery alone for presumed N2 NSCLC**.  
  Surgery alone is not curative for even microscopic single station nodes.

If nodes are > 2 cm, then ECE is likely. Should these patients be surgerized?

* + 702 pts undergoing resection for N2 NSCLC.
  + 5y OS 34% microscopic single station N2 involvement.
  + 5y OS 11% microscopic multiple-station N2 involvement.
  + 5y OS 8% macroscopic single-station N2 involvement.
  + 5y OS 3% macroscopic multiple-station N2 involvement.

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| **Treatment paradigm**   * **Medically inoperable**:   High risk generally FEV1 ≤ 50% or DLCO ≤ 50% predicted.  Inoperable generally FEV1 ≤ 40% or FEV < 1L for lobectomy (< 2L for pneumonectomy).   * **Unresectable**: **CCRT→ Durvalumab** (Cat 1).   cN2 patients may be candidates if single station < 3 cm with planned lobectomy.  Multi-station N2, N3, ECE, malignant effusion, progression of disease during or after chemotherapy.   * **Resectable**: Pre-op CCRT→ surgery 2-4 weeks afterwards→ Chemo.   T3N1 or T4 due to multiple nodules in one lung may be completely resected.   * + **Incidental stage III at surgery→ Chemo ± RT** for N2 or SM+.     - Consider adjuvant chemo for ≥ 4 cm, give for N1 disease (e.g. CE 100 q2w x4c).     - There is a 5% OS5 benefit with adjuvant chemo in stage II/III disease [[LACE](#2yto9p97n4x1)].   + **Known stage III**: **NAC/CCRT→ Surgery ± PORT** (if not received neoadjuvantly) for N2 or SM+. * Resectability should be determined upfront (prior to initiation of CCRT). * Order of postoperative treatment: Chemo→ RT unless positive margin. CCRT→ chemo for positive margin. For positive margin but no concurrent, R2 gets 66 Gy while R1 gets 60 Gy. |

## [Unresectable / Medically inoperable](#_lx2epxcmsg6)

* No role for induction chemo but may be considered for bulky.
* CCRT→ Durvalumab (Cat 1) [[PACIFIC](#kix.8o8cpe3mdnov)].

|  |
| --- |
| **SCRT vs. CCRT**   * CCRT appears to add ~2-3 months to overall survival as compared to SCRT. * SCRT appears to add ~4 months to overall survival as compared to RT alone. * Altered fractionation is inferior to SCRT, but better than RT alone. * **MS for RT alone / SRT / CCRT of 10→ 14→ 17 mo**. 5y OS ~15%.   + [[RTOG 06-17](#rjeb8sfzf5ot)] much better for CCRT: MS 29 mo, 5y OS 30% for 60 Gy arm.  * **Meta** [[**Auperin** JCO '10]](http://ascopubs.org/doi/abs/10.1200/JCO.2009.26.2543?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **SCRT vs. CCRT**. CCRT has improved OS compared to SCRT, although with increased esophagitis.   + 1200 patients pooled from 6 trials. MFU 6y.   + **CCRT with 5y OS benefit of 4.5%**; 5y OS 10.6→ 15.1%, 3y OS 18→ 24%.   + CCRT also decreases LRP (HR 0.77) at cost of acute G3+ esophagitis 4→ 18%.   + No effect noted on distant progression. * Meta on Altered fractionation [JCO '12]: Not in the setting of chemo.   + Altered fractionation provides 2.5% benefit in 5y OS at the expense of inc esophagitis. |

### [RT Dose escalation](#_u2qcktecac9d)

RT alone up to 80 Gy seems to be reasonable and without significant toxicity.

[[RTOG 73-01](#ycxe1kbhyljf)] in 1987 established 60 Gy RT at a minimum as standard of care.

[[Dillman](#yc495w7umwkd)] in 1990 later demonstrated induction chemotherapy (SCRT) with CDDP/vinblastine to be superior to RT alone.

[[RTOG 94-10](#w7qrf21pbfei)] in 2000 later demonstrated CCRT to be superior to SCRT.

CCRT appears to be preferable to 60 Gy, while some will escalate to 66 Gy. No one escalates to 74 Gy [[RTOG 06-17](#rjeb8sfzf5ot)].

Retrospective data [[from 2019](#81n83icjfhfv)] favors at least 66 Gy based on normal tissue constraints ("iso-toxicity").

* For dose escalation in the setting of CCRT, see [[RTOG 06-17](#rjeb8sfzf5ot)].
* Up to 80 Gy RT alone seems to be without significant toxicity.
* There is a suggestion of pCR of the primary tumor not mattering if mediastinal nodal clearance is achieved.
  + Therefore, how important is dose-escalation of the tumor in absence of mediastinal nodal clearance?
  + The more important, nuanced question is which nodal levels to cover, and to what dose.

* **RTOG 7301** [[Perez Cancer '87](https://www.ncbi.nlm.nih.gov/pubmed/3032394?dopt=Abstract)]: **40 Gy split course, 40/50/60 Gy**. T4 or N3 30/10 vs. 40 Gy split vs. 40/20.  
  Established 60 Gy as standard. Shortly thereafter, [[Dillman](#yc495w7umwkd)] demonstrated benefit with induction CDDP/Vinblastine.

RT improves overall survival, 60 Gy split course has the highest rates of LC although 30% still fail locally.

* + 447 pts. Unresectable stage III (including T3N0). 1973-1978.
    - RT included tumor, mediastinal and hilar LN. Spinal cord block to block dose to cord.
  + 60/30 has the highest rates of LC of 70% without OS difference vs. 40 or 50 Gy.
  + OS < 10% at 5y for all regimens. OS 18% at 2y.
* **RTOG 9311** [[Bradley IROBP '05](https://www.sciencedirect.com/science/article/pii/S0360301604026793?via%3Dihub), ['07]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2196217/): Phase I-II. **3D RT alone dose escalation** (70.9 - 90.3 Gy).  
  Up to 77.4 Gy of radiation alone is well tolerated. Utilizes 2.15 Gy per day. Don't go up to 90 Gy!
  + 177 pts. Inoperable stage I-III NSCLC. No N3 or CCRT allowed. 14% NAC (n=25). 1995-2001.
    - RT: PTV = GTV + at least 1 cm. Fluoroscopy used to check PTV margin.
    - V20 dictates arms:
      * V20 < 25% received 70.9/33, 77.4/36, 83.8/39, 90.3/42.
      * V20 25-36% received 70.9/33 or 77.4/36.
  + 83.8/2.15 Gy well tolerated if V20 < 25%, **77.4 Gy** well tolerated if V20 = 25-36%.
    - 90.3/42 too toxic!
  + Elective nodal failure in < 10% of patients.
* **MSKCC** [[Rosenweig Cancer '05](https://doi.org/10.1002/cncr.21007)]: Phase I. **3D-RT alone 70.2 / 75.6 / 81 / 84 Gy**.   
  84 Gy deemed to be the maximum tolerated dose. There is a suggestion of improved OS with 80 Gy.
  + 104 pts. 1991-2003. 66% stage III, rest stage I-II. Induction chemo in 16%.
    - RT: 50.4 Gy to macroscopic disease, ipsi hilum and entire mediastinum. 19.8 to macroscopic tumor and lymph nodes. Protocol later modified to allow boost only to macroscopic disease.
  + Crude late pulmonary toxicity 7%.
  + OS significantly improved for patients who received ≥ 80 Gy.
* **MSKCC** [[Sura Cancer '07](https://insights.ovid.com/pubmed?pmid=17762758)]: Retro. **80 Gy RT→ Chemo**.  
  Data from 77.4 Gy alone with best local control per 93-11 above.
  + 82 inoperable pts I-IIIB. 55 pts stage I/II, 27 pts stage IIIA/B. Only 5% mediastinoscopy. 80% PET.
    - Margin 10-15 mm. 3D RT, 16% IMRT.
  + 5y LC for I-II / IIIA-B 39→ 67%. Compare to 5y LC w CCRT > 50% based on [[RTOG 06-17](#rjeb8sfzf5ot)].
  + 5y OS for I-II / IIIA-B 31→ 36%, MS for I-II/IIIA-B 32→ 41 mo.
  + Acute G3+ pneumonitis 5% (4 pts), with two deaths. Late G3+ pneumonitis 7% (5 pts).

### [SCRT](#_u2qcktecac9d)

SCRT appears to provide a 4 mo OS benefit as compared to RT alone.

* **CALGB 8433** [**Dillman** [NEJM '90](https://www.nejm.org/doi/10.1056/NEJM199010043231403?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov),['96](https://www.ncbi.nlm.nih.gov/pubmed/8780630)]: **± CDDP/Vinblastine** x2c**→ 60/30**.SCRT is superior to RT alone, adding a 4 mo OS benefit. [[RTOG 94-10](#w7qrf21pbfei)] later demonstrated CCRT to be superior to SCRT.
  + 155 pts. IIIA 60/30 ± neoadj Cis/Vinblastine x2c. 1984-1987.
  + MS 10→ 14m and 5y OS 6→ 17%. 7y OS 6→ 13%.
* **RTOG 8808** / ECOG 4588 [[Sause '00](https://www.sciencedirect.com/science/article/pii/S0012369215486222?via%3Dihub)]: **RT alone vs. HFX RT vs. Dillman SRT**.   
  SCRT is superior to standard and HFX RT, adding a 2 mo OS benefit.
  + 458 pts. Stage II-IIIB. 1989-1992.
  + MS 11→ 12→ 13m. 5y OS < 10% in all arms, although Dillman superior at 8%.
* **China** [[Kong IJROBP '20](https://doi.org/10.1016/j.ijrobp.2020.03.038)]: Retro. **Induction chemo→ 60/15**.

TBL [QS](http://www.quadshotnews.com/2020/04/easy-does-it.html%5C): Exercise caution and careful patient selection if considering hypofractionation for stage III NSCLC.

Constraints associated with severe toxicity compare favorably to the recommended constraints on [[SUNSET](#2btlcyn3xrm9)] (Table 2). See the [[Constraints and Toxicity](https://docs.google.com/document/d/1DnTzXxvgAsnW9eR7Br-W7ajBAFXL2IIZhvoRNcLYTK0/edit#heading=h.e0bpk65tyqu3)] section, specifically the Hypofractionation section, for more.

* + 42 patients. 2012-2016. N2 55%, N3 31%. MFU nearly 4y.
    - RT volumes post-induction chemo. PTVp 0.5-1.0 cm, PTVn 0.5-0.8 cm. There were no specific dose limits for the heart, trachea, and main bronchi. Attempted to minimize esophageal overlap to be less than 4 cm. Attempted to limit transverse overlap to < ⅓ of the esophagus, circumferential esophageal irradiation was not allowed.
  + 16 patients (38%) did not receive the intended dose of 60 Gy, including acute esophagitis in 6 cases.
  + MS 48 mo!
  + 5y PFS 25%.
  + Isolated LRR in 12% (n=5).
  + G3+ radiation pneumonitis 14% (n=6). G5 toxicity 5% (n=2).
  + G3 radiation esophagitis 12% (n=5) and 2% (n=1) had G4 esophageal toxicity.

### [CCRT](#_u2qcktecac9d)

CCRT appears to provide a 2-3 mo OS benefit over SCRT [[RTOG 94-10](#w7qrf21pbfei), [Auperin](#89cjok8xd5cm)].

CCRT→ Durvalumab (Cat 1), with median survival not reached (29 months in control arm) [[PACIFIC](#kix.8o8cpe3mdnov)].

* **CALGB 39801** [[Vokes JCO '07](http://ascopubs.org/doi/abs/10.1200/JCO.2006.07.3569?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed), [Stinchcombe JTO '09](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2778485/)]: **± 2c induction→ CCRT 66 Gy.** Induction chemo with no benefit prior to CCRT.
  + 366 pts. Unresectable stage III NSCLC. 1998-2002.
    - Induction Carbo AUC 6, paclitaxel 200. CCRT Carboplatin AUC 2, paclitaxel 50.
  + 2y OS ~30%.
  + G3+ neutropenia 38% w induction: G4 26→ 40%.

* **RTOG 9410** [[Curran JNCI '11]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186782/): **Dillman SCRT to 63 vs. CCRT 63 vs. 69.6 Gy CCRT BID**.  
  Confirmed CCRT as standard of care, though still has 30% local failure at two years.  
  Less LF in concurrent arms with the same rate of DM suggests LC influences survival.
  + 610 pts. Inoperable II-IIIA/B NSCLC. 98% stage III, over half IIIB.
    - Dillman: CDDP 100 d1, 29. Vinblastine 5 q1w q5w x2c. RT starts day 50.
    - CCRT: CDDP 100 d1, 29. Vinblastine 5 q1w q5w x2c.
    - CRT BID: CDDP 50 d1,8,29,36 w Etoposide 50 BID x10w.
      * CTV1\_45/50.4: GTV + regional nodes + any intrathoracic or SCV nodes > 2.5 cm.
      * CTV2\_63/69.6: GTV + known nodes + any nodes > 2 cm
  + MS 15→ 17→ 16 mo, 5y OS 10→ 16→ 13%.
  + 2y LF 39→ 30→ 29%. 2y local IFF as first failure 30→ 25→ 20%.
    - 2y DM as first failure nearly 50%! Of these, 13% brain mets, 33% other mets.
    - In-field thoracic nodal failure ~10%, OOF thoracic nodal failure ~3%.
  + G3+ esophagitis 4→ 22→ 45%. G3+ pulmonary ~15%.

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| **CCRT Dose escalation: The problem with > 70 Gy**   * There is level I evidence suggestive against radiation dose escalation [[RTOG 06-17](#rjeb8sfzf5ot)]. * Difficult to justify doses > 70 Gy even though local control is still an issue (5y LRF ~35%, 5y LC > 50% per 06-17). * Standard dose is 60-66 Gy with chemotherapy. * Retrospective data [[from 2019](#81n83icjfhfv)] favors at least 66 Gy based on normal tissue constraints ("iso-toxicity").   **Patterns of Failure**: Definitive CCRT in the thorax (i.e., NSCLC and [[Esophageal](https://docs.google.com/document/d/13NEZCS6s13MVLixabbO2vjY73zHxJ37qE16gBbApSdY/edit#heading=h.8xvjyk728j95)]): Long term LRF is ~50% (usually IFF for primary failure) while regional failure is ~33% (usually marginal or OOF). LRF typically outweighs distant failure. This is eerily similar to definitive CCRT esophageal data and [[PACIFIC](#kix.8o8cpe3mdnov)] trial. SqCC tends to fail [[locally](#_12dcu6uefto4)]. |

* **RTOG 0617** [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4649), [Bradley Lanc Onc '15](https://www.sciencedirect.com/science/article/pii/S1470204514712070?via%3Dihub), ['17](https://www.redjournal.org/article/S0360-3016(17)31300-7/fulltext), ['20](https://www.ncbi.nlm.nih.gov/pubmed/31841363)]: **60 vs. 74 Gy Carbo/Pacli ± Cetuximab**.   
  See the summary box above for Patterns of Failure.

Confirms 60 Gy as standard, first set by Perez in the 1970s. The highest reported MS in the literature until [[PACIFIC](#xpwgdlid9n6k)].

Recommend IMRT for LA NSCLC. 74 Gy arm may have had inferior outcomes as tx-related deaths highest in 74 Gy + Cetux, effect of RT on heart (Heart V40 predictive of mortality, and V40 is lower with IMRT).

74 Gy toxic, worse local control and overall survival. *Were margins too small to dose escalate? Was there under-dosing of disease in order to meet protocol constraints?* Potential answer: [[Isotoxic dose escalation](#81n83icjfhfv)] based on normal tissue constraints.

No difference with the addition of cetuximab.

Required carboplatin and paclitaxel consolidation in all, with or without cetuximab. Ironically, even though this de-escalated RT, escalated adjuvant chemotherapy was required in both arms based on little evidence.

TBL [QS](http://www.quadshotnews.com/2019/12/too-hot.html): Long-term results of RTOG 06-17 confirm that 60 Gy at 2 Gy per fraction is the standard chemoradiation regimen for locally-advanced NSCLC.

* + 544 pts. Unresectable stage III, not N3. MFU 5y.
    - Carboplatin AUC 2 and paclitaxel 45 q1w x6c→ adjuvant Carbo AUC 6 and paclitaxel 200.
    - Cetuximab with a loading dose of 400 followed by weekly 250.
    - RT: 4D encouraged, but allowed IMRT or 3D (50/50).
      * GTV includes nodes > 1 cm short axis on CT or pre-treatment PET with SUV > 3.
      * CTV = GTV + 0.5 - 1 cm.
      * PTV = CTV/ITV + 1.5 cm CC and 1.0 cm radial. May trim to 0.5 cm if towards skin/cord.
      * PTV = CTV + 1.0 cm CC and 0.5 cm radial if breath hold or gating and daily imaging.
  + 1y LC ~75→ 84% (p=0.13). 5y LC ~62→ 54% (p=0.068).
  + 5y PFS ~23→ 13% (p=0.06). 5y RF ~35%, 5y DM > 50%.
  + **MS 29→ 20 mo**, 1y OS 80→ 70%, 2y OS 58→ 45%, 5y OS ~32→ 23% (p=0.06).
  + Acute G3+ esophagitis 7→ 21%.
  + G3+ ~77%.
    - Late G3+ dysphagia 3→ 12%, G3+ esophagitis 5→ 17%. G3+ pulmonary ~20%.
  + On MVA, standard dose, tumor location, institution accrual volume, maximum esophagitis/dysphagia grade, PTV volume, **heart V5 and heart V30 and V50** were associated with improved OS.
  + RTOG 0617 QoL secondary analysis [[Movsas JAMA Onc '16](https://www.ncbi.nlm.nih.gov/pubmed/26606200)]: Despite few differences in clinician reported toxicity between treatment arms, QoL analysis demonstrated a clinically meaningful decline in QoL in the 74 Gy arm at 3 mo. At 12 mo, fewer patients who received IMRT (vs. 3DCRT) had clinically meaningful decline in FACT-LCS (46→ 12%).
* **RTOG 0617 IMRT secondary analysis** [[Chun JCO '17]](http://ascopubs.org/doi/abs/10.1200/JCO.2016.69.1378): **3D vs. IMRT**.   
  Lung V5 is not associated with G3+ pneumonitis, but Lung V20 is.

Heart V40 is predictive of mortality, and is lower with IMRT.

* + G3+ pneumonitis 8→ 3.5%. Lung V5 is higher with IMRT, but overall heart V20+ lower w IMRT.
  + Lung V5 NS, but **Lung V20** is associated with increased G3+ pneumonitis risk.
  + **Heart V40** are predictive of mortality, and heart V40 is lower with IMRT.
* Heart V50 is associated with decreased OS [[Eaton JNCI '16](https://www.ncbi.nlm.nih.gov/pubmed/27206636)].
* Heart V50 is independently associated with worse OS. Heart V50 < 25% (not used on [[06-17](#rjeb8sfzf5ot)]) should be standard. [Speirs JTO ‘17](#jgrlfoasvoc2)

* **High dose RT based on normal tissue constraints** [[Zhao RTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31869678)]: Retro. **Standard (< 66 Gy)** **vs. High dose (≥ 66 Gy)**.

We also know that VMAT is preferred due to no compromised overall survival versus IMRT or 3D [[Peng IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32007366)]

* + 140 pts. Unresectable stage III NSCLC. 2006-2012.
  + MS 21→ 34 mo.
  + 5y OS 17→ 38%.
  + MPFS 11→ 19 mo.
  + No difference in G3+ toxicity was noted.

* **PET-Plan / ARO-2009-09** [[Nestle Lanc Onc '20](https://www.ncbi.nlm.nih.gov/pubmed/32171429)]: **PET/CT with ENI/atelectasis vs. PET-alone volumes**.

PET-planning is non-inferior to PET/CT based planning. Aggressive ENI and coverage of atelectasis was utilized on the control arm in this study (it was not a true ENI question - Fig 1A). More patients on the PET-alone volume arm were able to receive > 66 Gy.

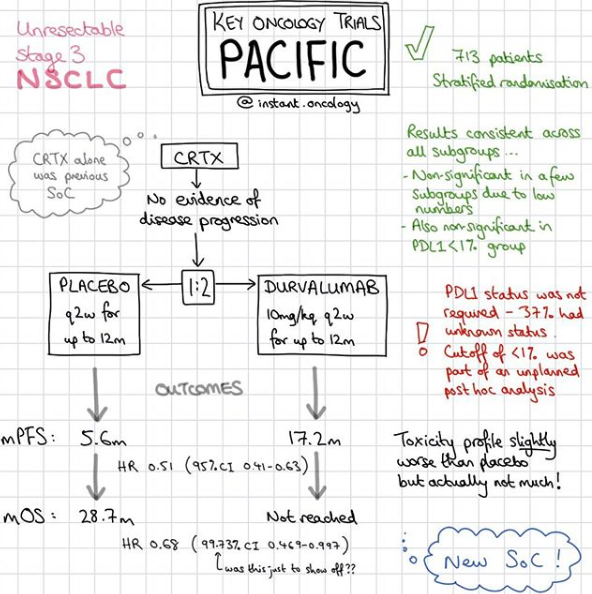
* + 311 pts. Inoperable advanced NSCLC. 2009-2015. MFU 2.5y.
    - 60-74 Gy prescribed for each individual patient on the basis of normal tissue constraints (isotoxic radiotherapy). Heart V40 < 50% used, despite V50 < 25% being strongly associated with death.[Speirs](https://www.jto.org/article/S1556-0864(16)31144-3/fulltext)
    - Conventional RT: PET-based GTV of primary was expanded up to 3 cm of eventual tumor associated atelectasis. Lymph nodes > 1 cm SAD but PET-negative were included. 50/25 ENI for unaffected lymph node levels with > 10% likelihood of LN metastases. See Figure 1A.
  + 1y LRF per protocol of 29→ 14%. 1y LRF ITT of ~30→ 18%.
  + Mean dose 65→ 67 Gy.
  + Doses 68-74 Gy of 33→ 47%. *Nearly half of patients on PET-alone volumes were able to receive > 66 Gy.*
  + Doses 60-66 Gy of 66→ 53%. *Around 2/3 of patients received 60-66 Gy on the PET/CT ENI arm.*
  + 3y per protocol OOF progression ~8→ 4%.
  + 3y per protocol IFF ~38→ 22% (p=0.13).
  + 3y per protocol locoregional progression ~47→ 26%.
  + MS ~37→ 29 mo.
  + Acute G3+ dysphagia ~16%. Late lung toxicity ~11%.
* UCLA **HyCRT-SABR** [[Lee ASTRO ‘19](https://www.eventscribe.com/2019/ASTRO/fsPopup.asp?Mode=presInfo&PresentationID=559283)]: Phase II. **CCRT 40/10→ 25/5 vs. 30/5 vs. 35/5** to PET ITV after 7-9 fractions.

This is the most aggressive hypofractionation regimen studied with concurrent chemotherapy, utilizing an intelligent adaptive cone-done to ITV only. Patients treated with an adaptive 70/15 appear to have the most favorable outcomes.

* + 28 pts. Inoperable stage II/III. Consolidative systemic therapy in 25%, mostly CarboP. MFU 1.5y.
    - 40/10 to ITV + 5 mm (PTV). Boost to ITV without margin.
    - CCRT with three weekly infusions of carboplatin and paclitaxel.
    - Dose limiting toxicity of ≥ 33% within 90 days was not met for any cohort.
  + LC at 1 / 2y for 25/5 boost of 75→ 63%.
  + LC at 1 / 2y for 30/5 boost of 100→ 88%.
  + MS 27 mo, which is comparable to 60 Gy arm of RTOG 06-17 and control arm of PACIFIC.
* **Proton collaborative group LUN005** [[NCT01770418](https://clinicaltrials.gov/ct2/show/NCT01770418), [Hoppe IJROBP '20](https://doi.org/10.1016/j.ijrobp.2020.03.015)]: Phase I/II. **60/(15-17-20-24) + CarboP**.

TBL [QS](http://www.quadshotnews.com/2020/04/hypofractio-wait.html): If strict normal tissue constraints can be met, hypofractionation (with protons..?) may not be off the table for advanced-stage NSCLC.

* + 18 patients. 56% N2. Stage II-III NSCLC. Accrual was slow and incomplete for 60/15 due to strict but important dose constraints that were difficult to meet.
    - RT: ITVp = iGTV + 0.6 mm. There was no expansion on lymph nodes. PTV = 0.5 - 1.0 cm, with larger margins for tumors moving > 1 cm.
    - Dose constraints in Supplemental table 2 (not yet available in pre-pub).
  + There were no DLTs.

[](https://www.instagram.com/p/B-6m89AA-9E/?utm_source=ig_web_copy_link)

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| Around 1/3 of NSCLC are diagnosed at stage III. MPFS ~8-10 mo with 5y OS ~15-25% prior to [[PACIFIC](#kix.8o8cpe3mdnov)] trial.  Local control with definitive CCRT is only around 50-60%.  Dose escalation above 70 Gy has been demonstrated to be detrimental for conventional fractionation. |

* **PACIFIC** [[Antonia NEJM '17,](https://www.nejm.org/doi/full/10.1056/NEJMoa1709937) ['18](https://www.nejm.org/doi/full/10.1056/NEJMoa1809697?query=featured_home), [ASTRO LBA6 ‘19](https://www.astro.org/ASTRO/media/ASTRO/Meetings%20and%20Education/PDFs/AM19/2019-LBAs.pdf), [Gray JTO '19](https://www.jto.org/article/S1556-0864(19)33529-4/fulltext)]: **NACCRT** (54-66 Gy) **± Durvalumab q2w up to 1y**.   
  Protocol in Appendix.

See [[Old School definitive CCRT](#_t13rsjlyvgp)] section, which discusses the New School concept of "isotoxic dose escalation".

Adjuvant Durvalumab standard of care for Stage III definitively treated with CCRT.

No one knows if targetable EGFR or ALK mutations should receive osimertinib [QS](http://www.quadshotnews.com/2018/09/new-age-aura.html) or alectinib [QS](http://www.quadshotnews.com/2017/10/battle-of-brains.html) first, as this trial barely enrolled any patients who had targetable mutations (~5% of all). See the [[ADAURA](#46pra0xb0adl)] trial.

Improved OS when Durvalumab started within 14d after RT.

TBL [QS](http://www.quadshotnews.com/2019/09/even-more-pacific.html): Patterns of recurrence occur most frequently in the thorax followed by the brain in both arms, whough recurrences across all sites were delayed with the addition of durvalumab.

* + 713 pts. IIIA/B unresectable NSCLC who have not progressed following Plt-based cCRT (≥ 2c). MFU nearly 3y.
    - Durvalumab (PD-L1) 10 mg/kg q2w up to 12 mo given within 1-42d after CCRT.
    - CCRT: ≥ 2c Pt-based (etoposide, vinblast/relbine, taxane, or pemetrexed), RT 54-66 Gy.
    - MLD < 20 Gy or V20 < 35%. Mean esophagus dose < 34 Gy. Heart V45 < 35%, V30 < 30%.
  + MPFS 5.6→ 17.2 mo. 1y PFS 35→ 56%.
    - Even < 25% PDL1 status still responded, though 0% subset was NS.
  + **2y OS 56→ 66%**, 3y OS 43→ 57%. MS 29 mo→ NR.
  + TT death or distant progression 16→ 28 mo.
  + Response rate 16→ 28%, with duration of response >18 mo of 47→ 73%.
  + EGFR positive subset appears to have no benefit (only 6% of all pts on trial, n=54).
  + Patterns of recurrence: Progression or death in 65→ 45%.
    - Intra-thoracic only progression ~48→ 37%. *Around 80% of progression is intra-thoracic only.*
    - Extrathoracic only progression ~13→ 7%. *Around 15% of progression is extra-thoracic only.*
    - Combined intra and extra-thoracic progression in ~3.4→ 1.9%.
    - New extrathoracic lesions at first progression 17→ 9%.
    - MTT first progression 9→ 25 mo.
    - Most new distant lesions were detected in a single organ, with > 90% of pts having ≤ 5 lesions, which suggests local ablative therapy may extend survival.
  + Toxicity: G3/4 ~30%, G5 ~5%. G3-4 pneumonitis ~2.6→ 3.4%.
  + Any grade immune-mediated AEs 8→ 24%. *This suggests immune events can happen in the absence of ICI.*
  + PRO [[Hui LancOnc '19](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30519-4/fulltext)]: There appears to be no compromise in PROs with durvalumab.
* **Around 1/4 of patients do not initiate durvalumab due to disease progression or CCRT toxicity** [[Shaveridan RTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31786421)].
* **Concurrent atezolizumab appears safe** [[Lin JTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31778797)]: Phase II. 66/30-33. G3+ irAE 20% (n=6).
* **Concurrent pembrolizumab appears safe-ish** [[Jabbour JCO '19](https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.8511)]: Phase II. 60/30. G3+ irAE 18% (n=4), including 1 G5 RP.

* **ETOP NICOLAS** [[Peters Lung Ca '19](https://www.lungcancerjournal.info/article/S0169-5002(19)30441-6/abstract)]: Phase II. **CCRT with Nivolumab**.
  + 82 pts. Stage IIIA/B NSCLC. MFU 13 mo.
    - RT 60-66 Gy given with C2 of Nivolumab.
    - Nivolumab 360 q3w x4c→ 480 q4w up to 1y.
  + Interim analysis demonstrated no increased risk of AE for severe pneumonitis.
  + G5 pulmonary fibrosis in one patient.
  + G3+ RP in 10.4%. G3+ RILT 16%.
* **KEYNOTE 799** [[Jabbour ASCO '20](https://meetinglibrary.asco.org/record/185983/abstract)]: Phase II. **CCRT with Pembrolizumab** up to 1 year.

Pembro with CCRT demonstrates promising anti-tumor activity. Toxicity was as anticipated. Enrollment continuing for CisPem arm.

* + 195 patients (112 CarboP, 73 CisPem). Unresectable Stage III NSCLC. MFU 8 mo.
    - RT 60/30 given with C2 of Pembrolizumab.
    - Investigators choice CarboP or CDDP/Pemetrexed (AC only).
  + ORR for CarboP / CisPem of 67→ 57%.
  + Median DOR NR.
  + G3+ Treatment-related AE for CarboP / CisPem of 64→ 41%.
  + G5 RP in 5 patients, all in the CarboP arm.

## [Resectable Stage III NSCLC](#_lx2epxcmsg6)

1. **Surgery→ Chemo ± RT** [[LACE meta for chemo](#2yto9p97n4x1), [PORT Meta](#lzs6w7rjvkpn) and [ANITA for RT](#eo0e21jjvt86)].
2. **Chemo→ Surgery→ ± RT** [[NSCLC Meta-analysis collaborative group](#h9zbh0js30d2)].
3. **CCRT→ Surgery** [[Albain](#fe2c038zyqzk), [Eberhardt](#92lqqnk97mp3)].
4. **CCRT** [[RTOG 06-17](#rjeb8sfzf5ot), [PACIFIC](#kix.8o8cpe3mdnov)].

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| **\*\*Themes to keep in mind\*\***  RCTs have not shown that two local treatments are better than one local treatment.  RCTs have not shown which local treatment is better.  "While there are many potential treatment options, none yields a high probability of cure" - Schild |

### [Surgery→ Chemo ± RT](#_164x49br3mq1)

* Carefully select pts that can be completely resected: T3N1, or T4 disease due to multiple tumors in one lung.
* [[Resectability](#x9x55wc3qhk3)] should be determined upfront (prior to initiation of CCRT).
* **Resectable**: Pre-op CCRT→ surgery 2-4 weeks afterwards→ Chemo.

T3N1 or T4 due to multiple nodules in one lung may be completely resected.

* + **Incidental stage III at surgery→ Chemo ± RT** for N2 or SM+.
    - Consider adjuvant chemo for ≥ 4 cm, give for N1 disease (e.g. CE 100 q2w x4c).
    - There is a 5% OS5 benefit with adjuvant chemo in stage II/III disease [[LACE](#2yto9p97n4x1)].
  + **Known stage III**: **NAC/CCRT→ Surgery ± PORT** (if not received neoadjuvantly) for N2 or SM+.

* **ADAURA** [[Herbst ASCO '20](https://meetinglibrary.asco.org/record/191929/abstract)]: **R0/1→ ± Osimertinib** x3y **after optional adjuvant systemic therapy**.

TBL [QS](http://www.quadshotnews.com/2020/06/adaurable.html): The face of adjuvant therapy for resected NSCLC has changed with the addition of the targeted therapy osimertinib proving to dramatically extend life without recurrence. See the [[PACIFIC](#kix.8o8cpe3mdnov)] trial.

It is likely that brain staging with CT was acceptable and PET/CT was not mandated. By including patients not staged with standard of care, this trial may include occult metastatic disease which favors adjuvant treatment.

When patients in the control arm progressed, did they receive osimertinib? Seems doubtful.

* + 682 patients. Non-squamous EGFR exon 19 del/L858R. Stage IB-IIIA NSCLC (31% IB, 69% II/IIIA).
  + 2y DFS for stage II-IIIA patients of 44→ 90% (HR 0.17).
  + 2y DFS in the overall population of 53→ 89% (HR 0.21).
* Let's assume surgery first… Then what?
  + Many trials support adjuvant chemo for > 4 cm or LN+ tumors [i.e. [CALGB 9633](#9jpqanq3igxt) exploratory analysis].
  + Recall: There is a **5%** 5y OS benefit with chemo in II/III disease [[LACE](#2yto9p97n4x1)].

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| **PORT in NSCLC**: [[PORT Meta](#lzs6w7rjvkpn), [ANITA](#eo0e21jjvt86), NCDB and the [LUNG-ART Trial](#jqiyx32hj0hi)].   * R1 or N2 should receive PORT. * If PORT recommended, it should be given sequentially after chemotherapy unless evidence of gross disease. * N1 should only receive PORT if not receiving chemotherapy [ANITA]. * See the [[Lung-ART](#jqiyx32hj0hi)] trial for a great reference on nodal volumes. |

### [PORT](#_164x49br3mq1)

See Summary Box above.

Order of postoperative treatment: Chemo→ RT unless positive margin. CCRT→ chemo for positive margin. For positive margin but no concurrent, R2 gets 66 Gy while R1 gets 60 Gy.

* R1 clear cut, more controversial for R0N+ disease.
* **R0, N+**: [[**PORT Meta '98,**](https://www.sciencedirect.com/science/article/pii/S0140673698063417?via%3Dihub) ['16](https://www.ncbi.nlm.nih.gov/pubmed/27684386)]: **Surgery ± PORT**.

**P**retty **O**ld **R**adio**T**herapy Meta Analysis.

Inferior OS benefit unless III or N2. Ongoing trials are evaluating the role of PORT in N2 disease.

* + Also, 25% of patients were T1N0. 80% Cobalt. Majority 2D. Larger fields.
  + Heart often in the field. Patients are commonly dying from cardiac comorbidities.
  + 2y OS 58→ 53%.
* **R1**: There may be a survival benefit.
* **N2**: [SEER,](http://ascopubs.org/doi/abs/10.1200/JCO.2005.04.6110?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed) [ANITA](https://www.sciencedirect.com/science/article/pii/S0360301608001946?via%3Dihub)and NCDB analyses suggest some value for PORT.
  + [[**SEER** Lally JCO '06](http://ascopubs.org/doi/abs/10.1200/JCO.2005.04.6110?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: HR 0.86 for N2 disease. Detriment for N1 or N0 disease.

* + [[**ANITA** Douillard IJROBP '08](https://www.sciencedirect.com/science/article/pii/S0360301608001946?via%3Dihub)]: ± adjuvant CDDP and **vinorelbine**.   
    PORT recommended for pN+, but not mandatory.   
    When asked for adjuvant chemo, Cisplatin + Vinorelbine is level 1 evidence.
    - pN2 pts with OS benefit regardless of chemo.
    - pN1 with OS benefit in the absence of chemo and OS detriment if chemo is given.
  + [[**NCDB** Robinson JCO '15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4348635/)]: Improved OS with PORT ≥ 45 Gy for pN2 disease.

* **LUNG-ART** / EORTC 22055 [[Protocol](http://www.ifct.fr/images/stories/Protocoles/DocsPratiques/IFCT-0503-LungArt/Protocole_LungART_v8.pdf)]: Phase III. **N2 disease→ ± PORT to 54/30 ± seq CTX**Refer to protocol (brief summary below) for useful guidelines on contouring nodal stations for post-op N2 RT.

See the [[PORT Treatment Planning](#_g10gqc6wm2cu)] section for more information.

Primary completion Feb 2018, Study completion Feb 2022.

* + All patients have bronchial stump, ipsi hilum, and extension to mediastinal pleura facing resection bed included in CTV [[Spoelstra IJROBP '10](https://www.sciencedirect.com/science/article/pii/S0360301609004714)].
    - All right sided patients have 4R and 7 covered.
    - All left sided patients have 4L, 5, 6 and 7 covered.
  + Cover one level above and one level below involved nodal levels.
  + Maximum lower limit\* 4 cm below carina, 5 cm in carina involved.
    - \*Unless lower stations are involved.
  + Maximum upper limit 1 cm above sternal notch but ipsi SCV may be treated.
    - At the sternal notch for stations 4, 6.
    - Top of aortic arch for stations 5, 7, 8.

### [NAC](#_164x49br3mq1) and NAICI

* NAC improves survival compared to surgery alone, OS HR 0.87 [[NSCLC Meta-analysis collaborative group Lancet '14]](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)62159-5/abstract).
* NAC vs. adjuvant chemo yields no difference in OS [[NATCH RCT](http://ascopubs.org/doi/full/10.1200/JCO.2009.27.6204)].

Critique: Lots of stage I patients who are not thought to benefit from chemo.

* + Nearly 100% compliance with preop chemo, only 66% compliance with post op chemo.

What about pre-op chemo vs. Neoadj CCRT?

* **SAKK 16/00** [[Pless Lancet '15]](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60294-X/abstract?code=lancet-site): **Cis-Doc→ ± RT alone** (44 Gy/3 wk)**→ Surgery**.  
  There appears to be no benefit with the addition of RT sequentially after induction chemo.
  + 232 pts. Induction SCRT in stage IIIA/N2.
  + No benefit with the addition of radiation therapy sequentially after induction chemotherapy.
  + Agrees with Shah ATS 2012 [Girard 2010, Thomas '08]

What about Chemo→ surgery vs. RT?

* [**German LCCG** [Thomas Lanc Onc '08]](https://www.sciencedirect.com/science/article/pii/S1470204508701566?via%3Dihub): **EP x3c→ preop hyperfractionated CCRT vs. Surgery + PORT**.  
  NACCRT improves response rates but not OS.
  + 524 pts. IIIA/IIIB w invasive mediastinal staging.
    - Induction chemo: CDDP 55 d1+4, Etoposide 100 d1-4 d3w x3c.
    - CCRT: 45 Gy (1.5 Gy BID) w carboplatin/vindesine x3c→ surgery if possible→ RT boost to 24 Gy in 1.5 Gy BID if inoperable or R1/R2 resection.
    - PORT: 54 Gy in surgery arm if R0, 68.4 Gy if inoperable or R1/2 resection.
  + 5y OS ~16%, 5y PFS ~14%.
  + R0 32→ 37%. In those w R0, mediastinal downstaging 46→ 29%.
  + Pre-op CCRT increased G3-4 hematologic and esophagitis.
  + If pneumonectomy (35%), mortality 6→ 14% with preop CCRT.

* **EORTC 08941** [[Van Meerbeeck JNCI '07]](https://academic.oup.com/jnci/article/99/6/442/2522267): **CDDP x3c→** 61% respond→ **RT vs. Surgery** (40% PORT).

Radiation therapy alone (no CCRT) appears to be equivalent to surgery.

Surgery does not improve OS or PFS compared to CCRT alone for stage IIIA N2 NSCLC.

* + 579 pts. IIIA/N2. **RT (60-62.5 Gy) vs. Surgery**.
    - RT: 60-62 Gy to involved mediastinum with 46 Gy to uninvolved mediastinum.
      * Only 55% compliance to RT prescription.
    - PORT to 56 Gy for SM+. 40% received PORT.
  + pCR 5%, 4% mortality. 47% pneumonectomy with 4% surgical mortality.
  + MS ~17 mo, PFS ~10 mo. Fewer LRF 55→ 32% but more DM 39→ 61% with surgery.
* **Immunotherapy induction prior to surgery**

* + **NEOSTAR** [[Cascone ASCO '19](https://meetinglibrary.asco.org/record/173490/abstract)]: Phase II. **Nivolumab 3 mg/kg (d1,15,29) ± Ipilimumab 1 mg/kg (d1)**
    - 44 pts. Stage I-IIIA (single N2), only 9 pts N2. 60% AC. Primary endpoints: MPR (≤ 10% viable tumor).
    - MPR 20→ 43%. PD in 15%.
    - pCR 9→ 21% (n=6 overall).
    - CD3+ and CD103+ tissue resident memory CD8 TILs 54→ 81%.
    - Median percent viable tumor for PD-L1 ≤ 1% / > 1% of 20→ 80%.
  + Shu (2016-2019) [[Lancet Onc ‘20](https://www.ncbi.nlm.nih.gov/pubmed/32386568)]: Phase II. **Carbo/Nab-paclitaxel/Nivo x4c→ Surgery**.

TBL [QS](http://www.quadshotnews.com/2020/05/a-bit-of-atez.html): Adding immunotherapy to neoadjuvant chemotherapy for resectable NSCLC results in encouraging rates of major pathologic response.

* + - 30 patients. Stage IB-IIIA. 57% AC. 77% Stage IIIA. 55% PD-L1 positive. MFU 13 mo.
    - MPR 57%. pCR 33%.
    - Post-hoc analysis demonstrated 58% of patients with confirmed N2 disease were downstaged to N0.

### [CCRT first (or alone)](#_164x49br3mq1)

CCRT→ Durvalumab (Cat 1), with median survival not reached (29 months in control arm) [[PACIFIC](#kix.8o8cpe3mdnov)].

* Two RCTs explore this question, namely INT 01-39 and ESPATUE.
* Always plan a definitive dose. Lobectomy planned 6w after CRT. Recommend PET/CT 2-4w after surgery,
* **Superior sulcus** (**Pancoast**) **are a special case**  
  T3 = CW, brachial plexus. T4 = VB, subclavian.

* + **SWOG 9416**[[Rusch JCO '07]](http://ascopubs.org/doi/abs/10.1200/JCO.2006.08.2826?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): Phase II, single arm. **45/CE→ resection** (80%).   
    Superior sulcus tumors are optimally treated with CCRT followed by surgery and adjuvant chemotherapy.
    - 111 pts. NACCRT for T3-4 N0-1 superior sulcus. 20% non-resectable and rec'd 61.2 Gy.
      * CDDP **50** d1,8,29,36, etoposide **50** d1-5, d29-33 w 2c adjuvant (4c total).
      * RT: Tumor + ipsilateral SCV. Did not include mediastinum/hilum.
    - **5y OS 54% with R0**, 44% overall. 94% R0 resection in the 80% that went to surgery (75% R0 overall).
    - pCR 29%, minimal microscopic residual 26%. *Over 50% had pCR or minimal residual.*
    - LR ~20%. DM 67% with half in brain. Most fail in the brain.
  + Suntharalingam and Kwong with median preop dose **59.4 Gy with pCR nearly 50%** and 5y OS 50%.

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| **Clinical Pearl: Mediastinal Nodal Clearance** (MNC) **in NACCRT vs. NAC**.   * MNC is approximately 2/3 when using NACCRT, while it occurs at *most* 1/5 of the time after NAC alone. * There is a suggestion of *doubling* overall survival with mediastinal nodal clearance. * Due to this reason, any patient being considered for NAC in lung cancer should be considered for NACCRT. |

* **Implications on pCR beyond Mediastinal Nodal Clearance with high dose CCRT** [[Vyfhuis IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618302505?via%3Dihub#fig1)]:

pCR in primary in addition to MNC did not appear to influence OS or FFR.

* + Retro. 111 stage III pts who received trimodality, ≥ 60 Gy CCRT. EBUS is most pts. 33% AC.
    - RTOG 0229 CCRT and adjuvant chemo in 74%.
    - Initially 70% N2 with 33% multi-station.
  + Mediastinal nodal clearance (MNC) 74% by EBUS. 88 pts underwent surgery.
    - MNC in RTOG 02-29 of 63% (61.2 Gy). MNC in RTOG 01-39 of 38% (45 Gy).
    - MNC for NAC ranges from 12-20% [[Betticher JCO '03](https://www.sciencedirect.com/science/article/pii/S1525730412002513), [Thomas Lanc Onc '08](https://www.sciencedirect.com/science/article/pii/S1470204508701566), [Liao CLC '13](https://www.sciencedirect.com/science/article/pii/S1525730412002513)].
  + pCR 50%! This is even with nearly 40% adenocarcinoma - classically, 20% pCR for AC in esophagus.
  + MS for ± MNC 29→ 61 mo.
    - 2y OS for ± MNC 68→ 71%, 5y OS for ± MNC 14→ 59%.
    - 2y OS for ± MNC 52→ 75% in RTOG 02-29.
  + MTTF for ± MNC 18→ 38 mo.
    - 2y FFR for ± MNC 32→ 53%, 5y FFR for ± MNC 8→ 44%.
  + If MNC is achieved, > 50% are without failure. 30% DM.
* [**RTOG 0229**](https://www.sciencedirect.com/science/article/pii/S0360301611036273?via%3Dihub) [[Suntharalingam IJROBP '12](https://www.sciencedirect.com/science/article/pii/S0360301611036273?via%3Dihub)]:Phase II. **NACCRT to 61.2 Gy**.
  + 57 pts. Stage III (pN2/3). PET/CT, MRI brain, Mediastinoscopy/thoracoscopy/Chamberlain mandated.
    - CCRT: Carboplatin AUC 2 and paclitaxel 50 q1w x6c.
    - 50.4 Gy to the mediastinum and primary with 10.8 Gy boost to all gross dz.
      * Boost: GTV, any nodes > 1 cm, and 1-1.5 cm CTV.
    - Consolidation chemo w paclitaxel 200 and carboplatin AUC 6 q3w x2c.
    - Evaluation at 4 weeks, resection within 8 weeks.
  + 37 pts proceeded to resection, 75% R0.
  + Mediastinal nodal clearance (MNC) 63%! 2y OS 54%, 2y OS for ± MNC 52→ 75%.
  + Total pCR 8%. There appears to be no benefit for improving pCR in the setting of MNC (see above).
  + 14% G3 post-op pulmonary complications, 3% risk of mortality (n=1).

* **INT 0139** [[**Albain** Lancet '09]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4407808/): **CCRT 45 Gy→ Surgery** (if no PD) **vs. CCRT 61.2 Gy**→ All got adjuvant CE x2c.   
  RT was 2D and large (ENI). 50% were pN0 after 45 Gy!

Exploratory analysis suggested lobectomy is better than CCRT alone. Pneumonectomy deaths unrealistically high.

Modern surgeons are comfortable cutting after 50-60 Gy so long as it is within 3 months after treatment.

* + 396 resecetable pts. T1-3**pN2**M0. CEx2 45Gy→ if no PD Surgery vs. 61.2 Gy→ CE x2.
    - Cisplatin 50, Etoposide 50, with the first two during the course of thoracic RT.
  + 5y iLF 22→ 10%.
  + 5y PFS 22→ 11%. MPFS 10.5→ 12.8m.
  + ~5y OS 27→ 20% (p=0.1).
    - Note: MS of those who did not make it to surgery of 8 mo.
    - Exploratory analysis suggests Lobectomy is better than CCRT alone with MS 22→ 33 mo.
      * For lobectomy, surgery doubles overall survival w **5y OS** 18→ **36%**.
  + Death without progression 18→ 10%.
  + pCR 14%, with 5y OS 42% in pCR.
    - MNC 38%. Compare to > 60% MNC in RTOG 0229, which gave 61.2 Gy.
  + Pneumonectomy operative mortality rate 8% overall, or 26% for right sided pneumonectomy!

* **ESPATUE** [[Eberhardt JCO '15]](http://ascopubs.org/doi/full/10.1200/JCO.2015.62.6812): **Induction chemo→ BID CCRT to 45 Gy→ Surgery vs. CCRT to 65-71 Gy**.  
  These patients were optimally selected for surgery, with panel discussion for operability.

Both approaches resulted in excellent outcomes.

* + 246 pts. IIIA/B (70% IIIB). 2/3 received lobectomy.
    - CP x3 q3w→ HFX CCRT CVenorelbine 1.5 BID to 45 Gy→ (panel discussion if operable)→ 65-71 Gy with CVenorelbine vs. Surgery.
  + pCR 33% in surgery arm.
  + 5y OS ~42%. 5y PFS ~33%.
  + Risk of death from pneumonectomy **ZERO**.
* Some institutions treat to higher pre-op dose (60 Gy) with good outcomes [[Shaikh](https://insights.ovid.com/pubmed?pmid=17551302), [Seder](https://www.sciencedirect.com/science/article/pii/S0003497513004736?via%3Dihub)].
* Recall: For superior sulcus, median tumor dose of 59.4 Gy has a pCR ~50%!

## [Elective Nodal Irradiation](#_lx2epxcmsg6)

* ENI: Isolated outside-field RT failures < 8%.
  + However, many of these patients received > 40 Gy to the mediastinum.
  + Recall: 2y cardiac events are in the double-digits for MHD > 20 Gy!
  + Treat nodes ≥ 1 cm SAD, avid on PET (SUV > 3.0) or biopsy proven.
    - Also include if 2+ nodes in a high risk station, within 1 cm of primary per RTOG 11-06.

Everyone quotes the above rate of isolated nodal failure (< 8%), but it is archaic. A more appropriate term would be EMI (Elective Mediastinal Irradiation). To say that there is no role for ENI in the modern era is not true, as no Phase III trial exists asking about definitive ENI in an intelligent manner with modern technology ([[PET-Plan was not a pure ENI trial](#qqm2ojo8sjj4)], and it did not use [[heart V50 < 25%](#jgrlfoasvoc2)], which appears to be a significant factor for treatment-related morbidity). Also, isolated out of field nodal failures is not a great endpoint. Instead, be sure to look at \*any\* component of nodal (namely mediastinal) failure. Beware of old dogma and consider ENI so long as Mean Heart Dose is < 10-20 Gy, but do so at your own peril from being chastised by your colleagues even though it makes so much sense. In fact, mediastinal nodal clearance may be associated with a [[DOUBLING of overall survival](#tf2fioskkctm)], and salvage options for mediastinal recurrences are poor as many patients also present with distant metastasis in this setting. Also, if you are going to be applying ENI in the preoperative setting, be sure to be aware of 2 year cardiac events according to Mean Heart Dose per the [[Pooled RTOG Analysis](#gra27hkb8d9y)]. Finally, stage III lung cancer has a 5y overall survival of around 20%, so we should be doing everything we can to improve outcomes so long as ENI is done in an intelligent manner and dose constraints to the mediastinum are met.

Heart V50 < 25% [[appears to matter the most](#jgrlfoasvoc2)] but has not been used on any prospective protocols.

* Comprehensive ENI is not recommended due to low observed rates of failure in uninvolved nodes without ENI.
* **MSKCC** [[Rosenweig JCO '07]](http://ascopubs.org/doi/full/10.1200/JCO.2007.13.2191): Median **66 Gy** (50-90 Gy).   
  Only 6% of pts w isolated new nodal failure in the absence of local failure.

Recall: Many of these patients received 50.4 Gy to the entire mediastinum (not done today).

* + 524 pts. 1991-2005. 40% RT alone, 40% induction chemo, 15% CCRT. MFU 41 mo.
    - RT: Nodes included in GTV if biopsy positive, > 1.5 cm SAD, or increased SUV on FDG-PET.
    - PTV added 10-15 mm.
  + LC at 2y / 5y of 51→ 39%.
  + OS at 2y / 5y of 43→ 19%.
  + Only 6% of patients had elective nodal failure. MTTNF 6 mo. 2y ENF 8%.
* **China** [[Yuan AJCO '07](https://www.ncbi.nlm.nih.gov/pubmed/17551299)]: Phase III. **ENI to 60-64 Gy vs. IFRT to 68-74 Gy**.   
  Conclusion: Worse LC, OS and pneumonitis with ENI/EMI.
  + Fields should include pre-chemo GTV (PTV + 1 cm) and nodes with SAD ≥ 1 cm (PTV + 0.5 cm).
  + 200 pts. Inoperable stage III.
    - CDDP-based induction x4-6c, with CCRT started after the second cycle of chemotherapy.
    - RT volumes: Pre Chemo, biopsy positive nodes, and nodes ≥ 1 cm SAD (PTV + 0.5 cm).
    - ENI: Included ipsi hilum, mediastinum (from inf head of clavicle to 5-8 cm below carina), and sometimes the SCV. 44 Gy delivered at a minimum, with 16-20 Gy boost when feasible.
  + 5y LC 36→ 51%, pneumonitis 29→ 17%.
  + OOF ~5%, 5y IFF 38→ 55%.
  + 2y OS 25→ 39%.
* See [[PET-Plan](#qqm2ojo8sjj4)] study, which demonstrated non-inferiority (and, in fact, less locoregional failures) when PET-alone volumes are utilized. This study was not a true ENI question, as it included up to 3 cm of non-avid atelectasis and also included areas without CT correlate but with > 10% risk of nodal involvement.

## [PCI and NSCLC](#_lx2epxcmsg6)

* **RTOG 0214** [[Gore JCO '11](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056462/), [QoL](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056463/), [Sun JAMA Onc '19](https://jamanetwork.com/journals/jamaoncology/fullarticle/2728245)]: Definitively treated stage III NSCLC **± 30/15 PCI**.  
  TBL [QS](http://www.quadshotnews.com/2019/03/the-brain-game.html): There’s about as much evidence for PCI in NSCLC as SCLC, and it’s all probably moot in the era of MRI. Lack of OS due to low accrual and low power.
  + 356 stage III pts w no progression after initial definitive local tx. All got MRI brain or CT if MRI contraindicated.
  + **1y BM 18→ 8%;** 5 and 10y BM 28→ 17%.
  + 1y OS ~76%, 5y OS ~25%, 10y OS 13→ 18% (p=0.12).
  + 5y DFS 16→ 19%, 10y DFS 8→ 13%.
  + WBRT led to **decline in 1y HVLT** (immediate/delayed recall) despite reducing incidence of new BM.
    - ~ADL, QoL, MMSE at 1y, but some were statistically significant at 3 mo (transient edema early on?).

* **NVALT-11/DLCRG-02** [[Komacki JCO '17](http://ascopubs.org/doi/abs/10.1200/JCO.2017.77.5817), [De Ruysscher JCO '18](http://ascopubs.org/doi/10.1200/JCO.2017.77.5817), [QoL](https://www.ncbi.nlm.nih.gov/pubmed/31733490)]: Definitive CRT ± Surgery→ **± PCI**.
  + 175 stage III NSCLC staged w CT + contrast or MRI brain. Endpoint 2y BM. MFU 4y.
    - RT 36/18, 30/12 or 30/10.
  + Nearly all pts have neurocognitive dysfunction before PCI and after chemotherapy. Most commonly, deficits in verbal memory, frontal lobe dysfunction, and fine motor coordination. Only 11 of 30 pts had follow up testing after PCI, and no significant differences found compared to pre-treatment tests.
  + 4y symptomatic BM 27→ 7%. TTDBM HR 0.23. ~OS.
  + G1-2 memory impairment 8→ 30% and cognitive disturbance 3→ 19%.
  + HRQoL only diff at 3 mo, similar thereafter.

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## [Reirradiation](#_lx2epxcmsg6)

* Peripheral tumors < 5 cm with local control 33-60% for repeat SBRT.
* **Salvage Therapy for LRR after SBRT** [[Brooks JTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31712134)]
  + Survival for LR is similar to that of patients with primary SBRT without recurrence, and survival for those with salvaged RR is similar to that of patients with de novo stage III disease.
  + iLR occurs up to 6% of the time, while iRRs occur up to 8% of the time.
* Conventional
  + 0-3 mm margin preferred.
* SBRT
  + [[De Bari CTR '15]](https://www.ncbi.nlm.nih.gov/pubmed/25913714)
* Protons
  + Proton therapy [[McAvoy RTO '13]](https://www.thegreenjournal.com/article/S0167-8140(13)00400-3/fulltext)
  + [[McAvoy IJROBP '14]](https://www.redjournal.org/article/S0360-3016(14)03537-8/fulltext?mobileUi=0)
  + IMPT [[Ho and Chang IJROBP '17]](https://www.redjournal.org/article/S0360-3016(17)30060-3/abstract)
  + No difference in RP w passively scattered protons [[Liao JCO '17](https://ascopubs.org/doi/full/10.1200/JCO.2017.74.0720)]
* Many published cases of 120-250 Gy to the mediastinum.
* M-DaRT: Moffitt database. 4,000 patients. DVH data. Toxicity Data. Outcomes data. 250 reirradiation cases. Will permit incorporation of time between RT courses. Machine learning/AI.
* Keep cumulative dose to esophagus under 90 Gy, keep cumulative dose to TBT to 120 Gy - Joe Chang.
* Clinical outcomes and toxicity predictors of thoracic re-irradiation [[Yang CTRO '20](https://www.ncbi.nlm.nih.gov/pubmed/32280792)]: Retro.
  + 50 pts. Conventional or SBRT Reirradiation 2009-2017. 11 conventional, 31 hypofrac, 8 SBRT.
  + Lung V5, V20, and MLD were associated with G2+ lung toxicity.

## [Toxicity](#_lx2epxcmsg6)

* **Heart**: **MHD ≤ 20 Gy, V50 ≤ 25%**

* + **Cardiac morbidity: Pooled analysis of 6 dose escalation trials for stage III NSCLC** [[Wang JCO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5455462/)]

Mean heart dose should be limited to less than 20 Gy if at all possible.

* + - 2y cardiac events for < 10 Gy / 10-20 Gy / >20 Gy MHD of 4→ 7→ 21%.

* + **Heart V50 independently predicts for decreased OS** [[Speirs JTO '17](https://www.jto.org/article/S1556-0864(16)31144-3/fulltext)]: 66 Gy (50-84.9 Gy).

Heart V50 < 25% (not used on [[RTOG 06-17](#rjeb8sfzf5ot)]) should be standard.

* + - 416 pts. Single institute. 333 plans re-contoured per 06-17. LA-NSCLC.
    - 1y OS for Heart V50 ± 25% of 47→ 70%. 2y OS 27→ 46%.
* **Esophagus**: **Mean < 34 Gy**, **Max 105% Rx**, **V60 ≤ 17%**, V55 < 33%
  + Palma paper: eval V5-V70 for esophagus, and V50-V60 predicted G2 and G3 events.
  + Management: Sucralfate, MMW, ranitidine, fluconazole.
  + Grade 3 esophagitis: >24h IVF or TPN.
  + Grade 4 esophagitis: Life threatening.
* **Lung**

Pathophysiology of radiotherapy-induced lung injury [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1234226689409978369?s=20)].

* + **RP for combined V20** [[Graham IJROBP '99]](https://www.sciencedirect.com/science/article/pii/S0360301699001832?via%3Dihub): Retro. Less than half received concurrent chemo.   
    QUANTEC V20 < 30% for < 20% risk of RP. Recall: CCRT may increase risk of RP per [[STRIPE](#m38qrqqzr43q)].

Goal: Keep V20 < 37% for ~10% risk of RP.

* + - 99 inoperable patients.
    - V20 ≤ 22% with 0% RP.
    - V20 ≤ 31% with < 10% RP.
    - V20 ≤ 40% with < 15% RP.
    - V20 > 40% with nearly 40%.
  + Genetic variant HIPK2 appears to be associated with radiation pneumonitis, appearing to matter as much as MLD ≥ 15 Gy and V20 ≥ 24% [[Tang RTO '20](https://ro-journal.biomedcentral.com/articles/10.1186/s13014-019-1456-0)]
* **Radiation pneumonitis**

ASCO Guideline: Mgmt [of Immune-Related AE in Pts Tx with Immune Checkpoint Inhibitor Tx](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues#/29866) *February 14, 2018*

* + Typically occurs 1 - 9 mo after RT. Risk for symptomatic RP is 5-15%.
  + Type 1 pneumocytes die, type 2 proliferate resulting in subacute inflammatory reaction.
  + Sx: Low grade fevers, chills, cough, dyspnea, hypoxia.
  + Dx: Diffusion capacity decreased in early phase, radiographically diffuse inhomogeneous opacification in tx field.
  + Grade 2: Hold immunotherapy. Treat with prednisone 1-2 mg/kg/d po (or 60 mg/d prednisone) and TMP/SMZ for PCP ppx. Often produces dramatic and quick responses in symptoms. Prolonged taper by 5-10 mg/wk over 4-6 weeks.
  + Grade 3-4: Permanently discontinue ICI. If no improvement after prednisone 1-2 mg/kg/d IV for 48 hours, may add infliximab, MMF, or cyclophosphamide. Taper over 4-6 weeks.
  + Improves up to 18 mo, but no improvement after 18 mo.

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| **Grade** | **RTOG** | **CTCAE** |
| **1** | Mild dry cough or dyspnea on exertion. | Asymptomatic, radiographic only. |
| **2** | Cough requiring narcotic antitussives or dyspnea not at rest. | Sx **± steroids** not interfering with ADL. |
| **3** | Dyspnea at rest, intermittent O2 or **steroids required**. | Sx **± steroids** interfering with ADL, O2 indicated. |
| **4** | Continuous O2 or assisted **ventilation** required. | Life-threatening, assisted **ventilation** required. |
| **5** | **Death** due to RP. | **Death** due to RP. |

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  ARRO: [[NSCLC](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/NSCLCIIIB.pdf)], [[Resectable LA-NSCLC](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/Resectablelung.pdf)], [[Thymoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Thymoma.pdf)].  Zaorsky: [[LN stations in lungs](https://twitter.com/NicholasZaorsky/status/1211640873634664453)].  Contouring   * eContour [[Thoracic OARs and lobar anatomy](https://econtour.org/cases/89), [Kong IJROBP '11](https://www.ncbi.nlm.nih.gov/pubmed/20934273)], [[PORT for pN2](https://econtour.org/cases/96)]. * Cardiac Contouring Atlas (Supplement) [[Duane RTO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5356506/)] * RTOG 1106 OARs and Targets [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-lung)]: PET-Guided therapy for stage III NSCLC. [RoR](#p1qgl9x43th3) * ESTRO ACROP guidelines for target volume definition for LA-NSCLC [[Nestle RTO '18](https://www.thegreenjournal.com/article/S0167-8140(18)30115-4/fulltext)]. [RoR](#7m90wr8h9gsx) * Australia & NZ consensus guidelines for use of advanced technologies in RT for LA-NSCLC [[Dwyer JMIRO '16](https://www.ncbi.nlm.nih.gov/pubmed/27470188)]. * Margin selection to compensate for loss of target dose coverage due to target motion [[Foster JACMP '15](https://www.ncbi.nlm.nih.gov/pubmed/25679166)]. * IAEA consensus: PET/CT imaging for target volume delineation in curative intent RT for NSCLC [[Konert RTO '15](https://www.ncbi.nlm.nih.gov/pubmed/25869338)] * CT-based definition of thoracic LN stations: An atlas from the University of Michigan [[Chapet IJROBP '05](https://www.ncbi.nlm.nih.gov/pubmed/16111586)] [RoR](#_6jx2f37knu1t)   Review Articles   * Implications on pCR beyond Mediastinal Nodal Clearance with high dose CCRT [[Vyfhuis IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618302505?via%3Dihub#fig1)]. [RoR](#tf2fioskkctm)   Society Guidelines   * [ASTRO Guideline: Definitive and Adjuvant RT in Locally Advanced NSCLC](https://www.astro.org/Patient-Care-and-Research/Clinical-Practice-Statements/ASTRO-39;s-guideline-on-definitive-and-adjuvant-RT)*June 2015* [RoR](#rwh1mjpib8up) * ASCO Guideline: [Adjuvant Chemo and Adjuvant RT for Stages I-IIIA Resectable NSCLC](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/10226) *April 24, 2017* [RoR](#m7i6kd44jxna) * ASCO Guideline: [Therapy for Stage IV Non–Small-Cell Lung Cancer without Driver Alterations](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/10201) *January 28, 2020* [RoR](#xjv5dd9pjsex) * ASCO Guideline: [Molecular Testing for Selection of Pts w Lung Cancer for Tx w Targeted TKIs](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/9776) *February 5, 2018* [RoR](#_wp55nx1rut9o) * ASCO Guidelines for Surveillance after Definitive Curative-Intent therapy [[Schneider JCO '19](https://www.ncbi.nlm.nih.gov/pubmed/31829901)] [RoR](#x0pt4mmhjq2i)   Relevant Accessible Radiation Protocols   * Definitive Chemoradiation   + RTOG 0617 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4649)]: 60 vs. 74 Gy Carbo/Pacli ± Cetuximab. [RoR](#rjeb8sfzf5ot)   + RTOG 1308 [[Table 1 Giaddui Rad Onc '16](https://www.ncbi.nlm.nih.gov/pubmed/27142674)]: Phase III. Photon vs. Proton dose-escalated CCRT. [RoR](#to0a6x1hf507) * Post-Operative   + LUNG-ART / EORTC 22055 [[Protocol](http://www.ifct.fr/images/stories/Protocoles/DocsPratiques/IFCT-0503-LungArt/Protocole_LungART_v8.pdf)]: Phase III. N2 disease→ ± PORT to 54/30 ± seq CTX. [RoR](#jqiyx32hj0hi) * Isotoxic RT:   + High dose RT based on normal tissue constraints [[Zhao RTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31869678)]: Retro. Standard (< 66 Gy) vs.≥ 66 Gy. [RoR](#81n83icjfhfv)   Quality of Life/Toxicity   * RTOG 0617 QoL secondary analysis [[Movsas JAMA Onc '16](https://www.ncbi.nlm.nih.gov/pubmed/26606200)].[RoR](#rjeb8sfzf5ot) * RTOG 0617 IMRT vs 3D secondary analysis [[Chun JCO '17]](http://ascopubs.org/doi/abs/10.1200/JCO.2016.69.1378).[RoR](#rjeb8sfzf5ot) * Heart V50 independently predicts for decreased OS [[Speirs JTO '17](https://www.jto.org/article/S1556-0864(16)31144-3/fulltext)]. [RoR](#jgrlfoasvoc2) * Cardiac morbidity: Pooled analysis of 6 dose escalation trials for stage III NSCLC [[Wang JCO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5455462/)] [RoR](#jgrlfoasvoc2) * Dess [[JCO '17](https://www.ncbi.nlm.nih.gov/pubmed/28301264)]: Prospective trials. Cardiac morbidity for ± baseline heart disease and CCRT. [RoR](#jgrlfoasvoc2) * Exploring the relationship of RT dose and length of esophagus to weight loss in lung cancer [QS](http://www.quadshotnews.com/2020/03/the-lengths-some-people-go-to.html) [[Han PRO '20](https://www.practicalradonc.org/article/S1879-8500(20)30062-X/fulltext)]: Retro. [RoR](#jgrlfoasvoc2) * RP for combined V20 [[Graham IJROBP '99]](https://www.sciencedirect.com/science/article/pii/S0360301699001832?via%3Dihub): Retro. Less than half received concurrent chemo. [RoR](#jgrlfoasvoc2) * Optimal Chemotherapy for CCRT remains unknown! [[Eberhardt JCO '15]](http://ascopubs.org/doi/full/10.1200/JCO.2014.58.9812) [RoR](#_8fm890uhgxjw)   + STRIPE pneumonitis meta-analysis [[Palma IJROBP '13]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448004/): Median 60 Gy CCRT. CarboP vs. EP. [RoR](#_8fm890uhgxjw)   + STRIPE esophagitis meta-analysis [[Palma IJROBP '13](https://www.sciencedirect.com/science/article/pii/S0360301613029003)] [RoR](#_8fm890uhgxjw)   + VA Health [[Santana-Davila JCO '15](http://ascopubs.org/doi/full/10.1200/JCO.2014.56.2587)]: Retro. CCRT CarboP vs. EP [RoR](#_8fm890uhgxjw) * PACIFIC Trial Toxicity (Table 3) [[Antonia NEJM '17](https://www.nejm.org/doi/full/10.1056/NEJMoa1709937)]. [RoR](#kix.8o8cpe3mdnov)   + Around 1/4 of patients do not initiate durva due to disease progression or CCRT toxicity [[Shaveridan RTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31786421)]. * China [QS](http://www.quadshotnews.com/2020/04/easy-does-it.html%5C) [[Kong IJROBP '20](https://doi.org/10.1016/j.ijrobp.2020.03.038)]: Retro. Stage II-III NSCLC. Induction chemo→ 60/15. [RoR](#_16zvai86raju) |

## [Treatment planning](#_lx2epxcmsg6)

See the Summary Box above and the [[SBRT Treatment Planning](#_g75vmdnm0cmm)] section.

* Simulate supine with arms up, vac lock bag. 4D CT with IV contrast from C5 to iliac crest.
  + If tumor motion > 7-10 mm then active breathing control/gating 30-70 on scan.
  + For treatment amplitude gating (confirm with fluoro) or phase gating.
  + If motion < 7 mm then create ITV.
* Iso at carina.
* PET/CT fusion - within 4 weeks of treatment planning.
* Use 6-10 MV beams in the lung.
* Contour primary on MIP or 4D and normal limit structures on average.
* Constraint troubleshooting (esp V20):
  + Increase weighting of AP/PA vs. oblique.
  + Add extra beams (consider IMRT but watch V5).
  + Add non-coplanar beams.
  + Neoadjuvant chemotherapy.
  + Shrink margins/4D/ITV.
    - If no 4D imaging, can scan at inspiration and expiration then fuse, or do slow-acquisition CT.
  + Tx at inspiration/gate
  + Compromise PTV, ensure ITV coverage.
* Daily KV imaging or daily CBCT to match to tumor (SBRT) or carina (advanced).

### [Intact](#_hd4mik808feb)

* **ESTRO ACROP guidelines for target volume definition for LA-NSCLC** [[Nestle RTO '18](https://www.thegreenjournal.com/article/S0167-8140(18)30115-4/fulltext)]:
  + PET/CT should be performed within three weeks prior to treatment.
  + Nodes ≥ 1 cm SAD or increased focal uptake should be biopsied if results may influence targets.
  + Diagnostic MRI should be considered if chest wall invasion, superior sulcus, or paraspinal.
  + GTVp should use lung windows, while invasion of mediastinum should use mediastinal windows. Regions of atelectasis visible on CT images beyond the edge of increased FDG uptake may be excluded from GTV.
  + GTVn should include all involved lymph nodes or lymph node stations based on pre-chemotherapy clinical, pathological and imaging information, even if a node has completely disappeared on imaging.
  + Lymph nodes that are PET avid and EBUS negative should be included in the GTV as the false negative rates of EBUS/EUS are high. PET positive nodes may only be omitted if there is a clear non-malignant biopsy explanation for the FDG positivity or if a mediastinoscopy has been performed showing no malignant cells in the lymph node.
  + CTVp should expand the GTVp by 5-8 mm. Manually edit out bones or heart.
  + CTVn should expand the GTVn by 5-8 mm ± inclusion of the whole pathologically affected LN station.
  + Elective inclusion of the hilum and/or neighboring nodal LN stations can be considered. Inclusion of uninvolved areas between involved nodal stations (especially the hilum) is optional.
  + ITV may be delineated by adding all CTVs from different breathing phases on 4DCT or by contouring the CTV on MIP CT. Mid-ventilation or mid-position approaches are also acceptable.
  + The trachea, PBT, great vessels and chest wall do not need to be defined for conventionally fractionated or hypofractionated RT.
* **RTOG 1106 OARs and Targets** [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-lung)]: PET-Guided therapy for stage III NSCLC. [RoR](#p1qgl9x43th3)
  + GTV includes LN ≥ 1 cm short axis or avid on PET (SUV > 3.0) or biopsy proven.
    - Also include if 2+ nodes in a high risk station, within 1 cm of primary per RTOG 11-06.
  + CTV = GTV + 5-10 mm, though 6-8 mm margin required to cover 95% of microscopic disease:
    - Pathologic analysis [[Giraud IJROBP '00]](https://www.sciencedirect.com/science/article/pii/S0360301600007501?via%3Dihub): 354 slides reviewed for microscopic disease extension.
      * To include 95% of microscopic dz, 8 mm margin for AC and 6 mm margin for SqCC rec.
      * Mean extension 2.7 mm for AC and 1.5 mm for SqCC.
  + PTV: Add 5-10 mm margin to CTV depending on respiratory motion management.
  + CTV = (iGTVn + 5mm) + (iGTVp + 8 mm).
  + PTV = CTV + 0.5 cm.
  + CCRT to 60-66 Gy is reasonable, although the former may be preferred in order to spare healthy lung.
  + May consider treating up to 77.4 Gy without concurrent chemo so long as V20 ≤ 35%. May also consider 45-60/15 hypofractionation.

### [PORT](#_hd4mik808feb)

Give CCRT if gross residual disease.

Give SCRT (chemo first) if N2 or ECE.

* CTV = bronchial stump + ipsi hilum/mediastinum ± subcarinal. Add 0.7 - 1.0 cm for CTV.
  + Cover one nodal station above and below pathologically involved stations.
* PTV = CTV + 0.5 - 1 cm. 5 mm if daily CBCT, up to 1 cm if not.

Give 50.4/28 or 50/25 for microscopic disease, boost gross disease or ECE an additional 10 Gy.

May consider up to 60-70 Gy for gross disease per NCCN.

* + PORT to 50-54 Gy after R0 for pN2 patients, given sequentially after chemo first.
  + PORT to 54-60 Gy considered after R1 or ENE, with concurrent or sequential chemo.
* LUNG-ART / EORTC 22055 [[Protocol](http://www.ifct.fr/images/stories/Protocoles/DocsPratiques/IFCT-0503-LungArt/Protocole_LungART_v8.pdf)]: Phase III. N2 disease→ ± PORT to 54/30 ± seq CTX [RoR](#jqiyx32hj0hi)
  + Include bronchial stump, ipsi hilum, and extension to mediastinal pleura facing resection bed included in CTV.
    - All right sided patients have 4R and 7 covered.
    - All left sided patients have 4L, 5, 6 and 7 covered.
  + Cover one level above and one level below involved nodal levels.
  + Maximum upper limit 1 cm above sternal notch but ipsi SCV may be treated.
    - At the sternal notch for stations 4, 6.
    - Top of aortic arch for stations 5, 7, 8.
  + Maximum lower limit\* 4 cm below carina, 5 cm in carina involved.

\*Unless lower stations are involved.

### [Palliation](#_hd4mik808feb)

See [[Palliation of the Lung](https://docs.google.com/document/d/1CfbqB4YnaPB8U3r2LykLv2v3bRLJyYQV0tvX4Js2Mog/edit#heading=h.bsbwppn0ds6d)] in the Palliative | Brain Mets | Benign section.

* **ASTRO Guideline: Palliative thoracic RT in lung cancer** [[Rodrigues PRO '11](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3808743/)]:
  + 30/10 is associated with modest improvements in OS and total symptom score at the cost of increased esophagitis.
  + Consider 20/5, 17/2 q1w, or 10/1 for patients requesting shorter treatment courses or with poor PS.
  + There is no role for routine endobronchial brachytherapy in routine initial palliative treatment, but is reasonable for obstructive symptomatology including lung collapse, or for hemoptysis after EBRT failure.
* **ASTRO Guideline: Palliative thoracic RT in lung cancer update** [[Moeller PRO '18](https://www.practicalradonc.org/article/S1879-8500(18)30069-9/abstract)]:
  + Patients with stage III NSCLC deemed unsuitable for curative therapy but who are candidates for chemotherapy, have an ECOG PS 0-2 and have a life expectancy of at least 3 mos, administration of a platinum-containing chemotherapy doublet concurrently with moderately hypofractionated palliative thoracic radiation therapy over treatment with either modality alone.
  + In patients with stage IV NSCLC, routine use of concurrent thoracic CCRT is not recommended.
  + Poland [[Nawrocki JCO '10](https://www.sciencedirect.com/science/article/pii/S1556086415305888?via%3Dihub)] Phase II. **30/10 ± CDDP/Vinorelbine** x3c. RT given concurrently with cycle 3.  
    Longer courses of RT appear superior to 10/1 or 16/2. Chemotherapy appears helpful.
    - 99 patients. "Incurable" stage III NSCLC (FEV1 ≤ 40% predicted or GTV > 8 cm). ECOG 0-2.
      * CDDP 80 d1, Vinorelbine 25 d1, 8. RT given concurrently with cycle 3.
    - MS 9→ 13 mo.
    - 1y OS 25→ 57%, 2y OS 6→ 24%.
    - MPFS 5→ 7 mo.
    - Response rate ~27→ 53%.
  + Norweigan [[Strøm BJC '13](https://www.nature.com/articles/bjc2013466)]: **Carboplatin/Vinorelbine** x4c **± 42/15**. RT given concurrently with cycle 2.

Longer courses of RT appear superior to 10/1 or 16/2. Chemotherapy appears helpful.

* + - 191 pts. Incurable stage III NSCLC (GTV ≥ 8 cm, ECOG ≥ 2, or 10% weight loss in 6 mo).
      * Carboplatin AUC 5 d1, Vinorelbine 60 d1,8.
    - MS 9.7→ 12.6 mo.
    - 1y OS 34→ 53%.
    - HRQoL declined during treatment with CCRT, but then evened out over time.
* **IAEA** [[Jeremic ASTRO '17](https://www.ncbi.nlm.nih.gov/pubmed/26163093), [Rathod ASTRO '17](https://www.redjournal.org/article/S0360-3016(17)31296-8/fulltext)]: **± 10/1 or 16/2 q1w→ Plt chemo x3**.  
  Short course thoracic RT prior to chemo improves QoL. Effect is sustained over time.

No impact on palliative RT in outcomes or toxicity.

* + 185 pts. Advanced NSCLC IIIB-IV.
  + RT improved global HRQoL, role and social functioning, pain, dyspnea, N/V, and lung-specific symptoms.
  + QoL improved at 2 weeks and was maintained.
  + ITT MS ~6 mo.
  + 1y OS 19→ 33%. 2y OS ~6→ 16% (p=0.19).
  + 1y LRPFS 12→ 20%, 2y LRPFS ~3→ 9% (p=0.52).

## [Follow up](#_lx2epxcmsg6)

* **Differential Relapse Patterns for NSCLC Subtypes** [[McAleese Clin Onc '19](https://www.ncbi.nlm.nih.gov/pubmed/31351746)]: Retro. **AC vs. SqCC**.

There is a difference in relapse patterns between NSCLC histological subtypes, indicating that these are distinct entities. This may have implications for follow-up policy and strategies to improve disease control.

* + 498 pts. 2004-2016. MFU 16 mo.
  + Relapse in 58%.
  + Local relapse as first relapse in 24→ 42%.
  + Brain relapse as first relapse in 14→ 3%.
  + The actuarial local control rate was worse for SqCC (HR 0.6) and the brain DMFS was worse for AC (HR 4.1).
* **KEAP1/NFE2L2 predict for local recurrence after RT but not surgery** [[Binkley ASCO '20](https://meetinglibrary.asco.org/record/188280/abstract)]:
  + 232 patients with localized NSCLC. 47 LA-NSCLC received CCRT, 50 ES-NSCLC received SBRT.
  + 2y LR in the combined RT cohort for K-Nwt / K-Nmt of 13→ 42%.
* CT chest q6 mo x2y, then annually. PET/CT should not be used as a surveillance tool [[ASCO Guidelines '19](#x0pt4mmhjq2i)]
* 5y OS I/II/IIIA/IIIB/IV 75→ 50→ 20-25→ 15-20→ 5%.
* OS in untreated cancer:
  + [Calif Ca registry] OS(CSS) MS IA 13m (25m), IB 8m (10m).
    - 5y OS IA 9% (23%), 5y OS IB 5% (12%).
  + [SEER] Median OS with RT 1.7y, w/o RT =1.2y.
* H&P, CT chest ± contrast q3m x3y then q6m. LDCT yearly after 5 years.
* Smoking cessation.
* PET/CT only if abnormal CT.
* Vaccinations: Influenza, pneumovax.

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# [Oligo and Metastatic NSCLC](#_lx2epxcmsg6)

See the [[Oligometastases](https://docs.google.com/document/d/1CfbqB4YnaPB8U3r2LykLv2v3bRLJyYQV0tvX4Js2Mog/edit#bookmark=kix.7v620793i97)] section and [[Current multidisciplinary management of brain mets](https://docs.google.com/document/d/1CfbqB4YnaPB8U3r2LykLv2v3bRLJyYQV0tvX4Js2Mog/edit#bookmark=id.focksuac7esp)] for more information.

See NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)] and the [[Future Directions](#_g18j10rquitr)] for NSCLC section for more.

Curing Metastatic Disease with Ablative RT: Separating Truth from Wish [[Kamran and Zietman IJROBP '20](https://pubmed.ncbi.nlm.nih.gov/32531389/)].

Curing Metastatic Disease with RT: Myth or Reality? Arguing for Reality [[Rahimi and Timmerman IJROBP '20](https://pubmed.ncbi.nlm.nih.gov/32531388/)].

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| --- |
| **Oligo Review of NSCLC Oligometastases** [[Giulani IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32014142)]: No study below is in the era of immunotherapy.   * "Oligomez" was a phase II trial of patients with 1-3 NSCLC mets treated with initial systemic therapy without progression at 3 mo. PFS was tripled with LCT, and OS was at least doubled (caution interpreting OS results). Treatment of lung primary for oligo persistent disease (counted as "0 mets") was allowed. Unlike SABR-COMET, crossover was allowed. There appeared to be a detriment in OS for delayed LCT [RoR](#riv6fmqaercy) * Iyengar was a phase II trial from UTSW of patients with mostly 1-3 NSCLC mets treated with initial systemic therapy without progression after around 3 months. PFS and OS were (caution interpreting OS results) more than doubled with SBRT. [RoR](#okay236kleuw) * SABR-COMET was a phase II trial of patients with mostly 1-3 mets from various solid tumors treated with initial systemic therapy without primary progression at 3 mo. PFS was doubled with SBRT, with near-significant improvement in OS (caution interpreting results). Patients with prostate cancer were heavily randomized to the SBRT arm (6→ 21%), which may have influenced results favorably towards the SBRT arm. Subgroup analyses excluded prostate cancer patients, and results remained favorable. [RoR](https://docs.google.com/document/d/1CfbqB4YnaPB8U3r2LykLv2v3bRLJyYQV0tvX4Js2Mog/edit#bookmark=kix.7v620793i97) |

* If M1a with contralateral solitary nodules, treat as two primary lung tumors (NCCN).
* Standard of care: 4-6c plt-doublet (or immunotherapy) ± maintenance therapy if non-targetable.
  + MS ~12 mo. Around 70% will achieve partial response or stable disease to first line systemic treatment.
* **RPA for Oligometastatic NSCLC** [[Ashworth CLC '14](https://www.sciencedirect.com/science/article/pii/S1525730414000771)]: **Metachronous vs. Synchronous, N0 vs. Synchronous, N+**.

Groups above are defined as LR, IR, and HR, respectively. Around 30% of patients with oligometastatic disease will have durable long term survival… This was the impetus for Iyengar, Gomez and SABR-COMET!

* + 757 NSCLC pts with 1-5 synchronous or metachronous mets treated with LCT.
  + MS 26 mo. OS at 1 / 5y of 70→ 29%.
  + 1y OS of 88→ 76→ 54%.
  + 5y OS of 52→ 29→ 12%.
* **Definition of synchronous oligo-metastatic NSCLC** [[Dingemans JTO '19](https://www.sciencedirect.com/science/article/pii/S1556086419306550?via%3Dihub)]:  
  Patients with NSCLC with 5 or fewer metastases in 3 or fewer organs can be considered oligometastatic after staging with PET/CT and MRI brain. TBL [QS](http://www.quadshotnews.com/2019/08/oligo-what.html): A European consensus statement on the definition of synchronous oligometastatic NSCLC has been created, which will potentially inform future clinical trial design, appropriate patient selection for local therapy, and (when we get American definitions) payer coverage.
* **SBRT for extra-CNS oligoprogressive disease** [[Gan IJROBP '14](https://pubmed.ncbi.nlm.nih.gov/24462383/)]: **ALK positive, Crizotinib + SBRT**.

When patients are not denied the value of systemic therapy, SBRT may serve to prolong overall survival and the duration of which patients receive systemic therapy before moving to subsequent therapy.

* + 38 pts on crizotinib (ALK+). 33 progressed, of these, 14 extra-CNS progression (eCNSP).
    - eCNS OPD received 1-3 courses of local ablative therapy with RT.
  + LC at 6 / 12 mo of 100→ 86%.
  + 1y LC for SRS-equivalent dose ± 25 Gy of 60→ 100%.
  + Median time taking crizotinib for ± SBRT of 10→ 28 mo.
  + 2y OS for patients continuing to take crizotinib ± 12 mo of 12→ 72%.

* **Gomez** (2012-2016) [[Lancet '16](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30532-0/abstract), [JCO '19](https://ascopubs.org/doi/10.1200/JCO.19.00201)]: Phase II. **MT/O vs. Local Consolidative Therapy** (Surgery, RT or CMT).  
  Protocol available in supplement of the 2019 publication.

TBL [QS](http://www.quadshotnews.com/2019/05/get-up-and-gomez.html): Low-volume de novo genuine oligometastatic NSCLC that passes the stress test of not progressing on initial systemic therapy deserves consolidative treatment, and that might include conventional treatment of the primary lung disease.

This trial closed early due to PFS benefit with LCT.There is a suggestion of inferior OS with delayed LCT in those who crossed over. Delay to LCT appears detrimental.

Use caution / take a huge grain of salt when interpreting OS advantage with LCT, as this is a phase II trial.  
OS results are not definitive. Is the PFS benefit enough to treat?

* + 49 pts. Stage IV NSCLC with ≤ 3 mets after front line chemo. ECOG 0-2. Primary endpoint PFS. MFU 39 mo.
    - Front line chemo: 4c plt doublet chemo or 3 mo EGFR/ALK targeted therapy. Pre-immunotherapy era.
      * Required no progression after at least 4c of front line chemo.
    - MT/O: Standard maintenance tx or surveillance. **Crossover allowed** at the time of progression in MT/O group.
    - LCT: Patients with a CR in metastatic sites and a persistent primary were allowed in the study (0 mets).
      * Treatment of lung primary (n=18): CCRT (n=6, 60-66 Gy), 45-60/15 (n=7), Surgery (n=3, two rec'd PORT), 70/10 (n=1), 67.5/27 (n=1).
      * Breakdown of all patients: Surgery (n=7, two rec'd PORT), CCRT to primary (n=6, one conventional RT alone), SBRT (n=13), moderate hypofractionation (n=11), SRS (n=7, one post-op), 30/10 (n=3).
    - Patient characteristics: Around 2/3 had 0-1 sites of metastasis. Nearly all synchronous. Few CNS or EGFR.
  + MPFS 4→ 14 mo. MTT new lesions of ~6→ 14 mo (p=0.11). MS 17→ 41 mo.
  + Survival after progression 9→ 38 mo.
  + Of the 20 pts who experienced progression in MT/O, 9 rec'd LCT to all lesions after progression w MS 17 mo.
    - Suggestion of inf OS with crossover to complete LCT after PD/toxicity with standard maintenance.
  + No additional G3+ in either arm!

* **UTSW** (2014-2016) [[Protocol (Supplement) Iyengar JAMA Onc '18](https://www.ncbi.nlm.nih.gov/pubmed/28973074)]: Phase II. **Maintenance chemotherapy ± SABR**.
  + 29 pts. Oligometastatic NSCLC (primary + up to 5 mets) s/p induction chemo x4-6c with PR or SD.
    - RT: 21-27/1, 26.5-33/3, 30-37.5/5. Tumors not amenable could receive 45/15.
  + MPFS 4→ 10 mo. PFS in the control group is similar to more widely metastatic patients.
  + Toxic effects similar in both arms.
  + No IFF and fewer overall recurrences in SABR arm.
* See [[**SABR-COMET**](https://docs.google.com/document/d/1CfbqB4YnaPB8U3r2LykLv2v3bRLJyYQV0tvX4Js2Mog/edit#bookmark=kix.7v620793i97)] (2012-2016) in the Oligometastases section [[Protocol (Supplement) Palma Lancet '19](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32487-5/fulltext)]. Prostate cancer patients were heavily randomized to the SABR arm on this trial. Doubling of PFS with SBRT in the setting of controlled primary x 3 months. Mostly 3 sites of disease. No crossover allowed (unlike Gomez). No treatment of primary allowed (unlike Gomez).
* **UPenn** [[Bauml JAMA Onc ‘19](https://www.ncbi.nlm.nih.gov/pubmed/31294762)]: Phase II. **Local ablative therapy→ Pembro** x16c.
  + 51 NSCLC pts with ≤ 4 sites of mets treated with SBRT to all known sites of disease. 2015-2017.
  + MPFS 19 mo, which is greater than the historical median of 7 mo.
  + OS at 1 / 2y of 91→ 78%.
* **SINDAS** (2016-2019) [[Wang ASCO '20](https://meetinglibrary.asco.org/record/187450/abstract)]: Phase III. **TKI ± up-front SBRT to all sites of disease**.

The SINDAS trial for EGFRmt NSCLC suggests an overall survival benefit of 9 months for up-front SBRT to ≤ 5 oligo sites in addition to a TKI! Too bad OS wasn't doubled as suggested in OligoGomez, but hey, Phase III data is always nice!

TBL QS: While we await details of the full pub, this preliminary reporting adds significant fuel to the excitement of upfront consolidative therapy for oligometastatic EGFR-mutated NSCLC—even in the era of TKIs.

* + 133 pts. EGFRmt. ≤ 5 metastatic sites. Systemic therapy naive. No brain mets. MFU 1.5y.
  + MPFS 13→ 20 mo.
  + MS 17→ 26 mo.
  + G3-4 RP ~3→ 7% (p > 0.05), G3-4 esophagitis ~4%.
* **UC-Denver Patterns of Failure after first-line systemic therapy for mNSCLC** [[Rusthoven Acta Oncol '09](https://pubmed.ncbi.nlm.nih.gov/19373699/)]: Retro.

The predominant pattern of failure after first-line systemic therapy for mNSCLC involves local progression in ~90% of pts.

* + 387 patients screened, 64 met eligibility criteria and 34 were SBRT-eligible. 2005-2008.
  + First extra-cranial progression iDM / iLF ± DM of 9→ 64→ 91%.
  + Among SBRT-eligible patients, first extra-cranial progression iDM / iLF ± DM of 14→ 68→ 86%.
* There are many open multi-institutional trials looks into local consolidative therapy in oligometastatic disease: NRG-LU002 (up to 3 mets), SABR-COMET 3 (up to 3 lesions), NORTHSTAR (up to 5 lesions) and SABR-COMET 10 (up to 10 lesions). See NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)] and the [[Future Directions](#_g18j10rquitr)] for NSCLC section for more.

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# [Systemic therapy for NSCLC](#_lx2epxcmsg6)

Around 1/3 of pts are diagnosed at stage III.

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| * Consider adjuvant systemic treatment for lesions ≥ 4 cm per exploratory analysis on [[CALGB 9633](#9jpqanq3igxt)]. * Give Durvalumab consolidation for IIIA/B unresectable treated definitively with CCRT [[PACIFIC](#kix.8o8cpe3mdnov)]. * Progression on the first line EGFR and T790M should receive Osimertinib; if T790M negative then chemotherapy.   **ASCO Guideline:** [**Therapy for Stage IV Non–Small-Cell Lung Cancer without Driver Alterations**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/10201) *January 28, 2020*  High PD-L1 ( > 50%) AC or SqCC should receive Pembro alone ± standard chemotherapy [[KEYNOTE 024](#5cpp9ixd4clc)].  PD-L1 (0-49%) AC should receive Pembro/Carboplatin/Pemetrexed [[KEYNOTE 407](#cny0ar61pzpf), [189](#bgimj6grw2xo)].  PD-L1 (0-49%) SqCC should receive Pembro/Carbo/(paclitaxel or nab-paclitaxel). No pemetrexed per [[Scagliotti](#qun6lvau5o4o)].  Single-agent Pembro is an option for low-positive (e.g. 1-49%) PD-L1 [[KEYNOTE 42](#6ty86d8r8zr0)].   * Immune naive, PD-L1 positive pts may use Nivo, pembro or atez. No Pembro for PD-L1 0%, as it has not been tested. * Immune naive, PD-L1 negative/unknown may use nivolumab [[CheckMate 057, 017](#qyvf65ur47xl)] or atezolizumab [[POPLAR](#6qiwjejnict), [OAK](#2jav53yyg0w9)]. * Pts who cannot receive immunotherapy after chemotherapy should receive docetaxel. * Pemetrexed recommended for non-squamous histology [[Scagliotti](#qun6lvau5o4o)]. * Pemetrexed (survival detriment) and bevacizumab (hemorrhages) are contraindicated in SqCC [[Scagliotti](#qun6lvau5o4o), [Johnson](#tvuswbsnh3c5)]. * Progression on the first line EGFR and T790M should receive Osimertinib; if T790M negative then chemotherapy. * Carbopatin and pemetrexed is preferred over docetaxel for eldery with AC [[Okamoto JAMA Onc '20](https://www.ncbi.nlm.nih.gov/pubmed/32163097)].   TBL [QS](http://www.quadshotnews.com/2020/03/a-senior-moment.html): For patients ≥75 years old, carboplatin and pemetrexed is currently the cytotoxic chemo of choice.  **ASCO Guideline:** [**Molecular Testing for Selection of Pts w Lung Cancer for Tx w Targeted TKIs**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/9776) *February 5, 2018*   * Confirms CAP/IASLC/AMP guidelines [[JTO '18](https://www.iaslc.org/capiaslcamp-molecular-testing-guideline)] req's analytical methods to be able to detect mutations in a sample w as little as 20% cancer cells. * IHC testing of EGFR is strongly discouraged. IHC may be an alternative to FISH testing for ROS1 and ALK. * New in 2017: ROS1 recommended for AC pts. Next gen labs also get ERBB2, MET, BRAF, KRAS, RET. * Also give recs for non-AC NSCLC, targeted pts who relapsed on targeted therapy, and testing for CTCs. * Use 5% sensitivity analysis for EGFR T790Mmt in pts w secondary resistance to EGFR inhibition. * Cell-free DNA may be used to "rule in" targetable mutations when tissue is limited or hard to obtain. * Now, Osimertinib NCCN Cat 1 preferred as of 2018. ORR in the brain 90%, including 2x ORR if RT 6 mo prior [QS](http://www.quadshotnews.com/2018/09/new-age-aura.html). * ROS1 rearrangement should receive Crizotinib, and if previously received crizotinib, then offer chemo.   **First line**: Targetable mutations, if present (Adenocarcinoma only).   * KRAS 20-25%, EGFR 15%, ALK 5%, ROS1 1-2%. * KRAS mutation is associated with lack of sensitivity for EGFR inhibitors. * EGFR in 25%: Osimertinib first line [QS](http://www.quadshotnews.com/2018/09/new-age-aura.html). * Alk in 2-7%. Crizotinib→ ceritinib or alectinib before non-targeted therapy.   + Alectinib now first line over any other ALK agent [QS](http://www.quadshotnews.com/2017/10/battle-of-brains.html). * ROS1 (1-2%): crizotinib (and ALK), ceritinib second line.   **First line for non-targetable/Second line for targetable**:  Pembrolizumab alone for PD-L1 ≥ 50%, or platinum doublet with pembrolizumab for unknown or PD-L1 < 50%.   * AC: Platinum doublet (may include pemetrexed) ± bevacizumab with maintenance. * SqCC: Platinum doublet (no pemetrexed) without maintenance.   **Third line**: Nivolumab or Pembrolizumab vs. Docetaxel ± ramucirumab (VEGFR2).   * Nivo or Pembro adds 3 mo to OS vs. docetaxel alone [KEYNOTE 010, [CheckMate 057, 017](#qyvf65ur47xl)]. * Ramucirumab adds 1 mo to OS when added to docetaxel [[REVEL](https://www.sciencedirect.com/science/article/pii/S014067361460845X?via%3Dihub)].   **Metastatic disease**:  Like Nivo/Ipi→ Nivo or BRAF/MEKi for melanoma, there is a ~50% intracranial response rate for asymptomatic BM.  Cut this number in half for PD-1 inhibition alone [QS](http://www.quadshotnews.com/2020/04/mind-control.html) [[Goldberg Lanc Onc '20](https://www.sciencedirect.com/science/article/pii/S147020452030111X?via%3Dihub)]. See [[Omission of RT](https://docs.google.com/document/d/1CfbqB4YnaPB8U3r2LykLv2v3bRLJyYQV0tvX4Js2Mog/edit#heading=h.f046epe5r5yp)] in the Brain Mets section.   * Second line: **Nivolumab** (PD-1) or **Atezolizumab** (PD-L1).   + Nivolumab alone. Previously Pembro alone second line ≥ 1% per [010](#68ukthy4bysa).   + Atezolizumab alone |

## [Targeted therapy](#_wp55nx1rut9o)

* AC 50% > 35% SqCC > Large cell = SCLC 15-20%.
  + AC can transform to SCLC 5% of the time.
* Targetable mutations in ~20% of all NSCLC, vast majority AC.
* **Frequency**: KRAS (20-25%) > EGFR (15%) > ALK (5%) > ROS1(1-2%).
  + **Prognosis**:EGFR ≅ ALK > KRAS > Wild type.
* **KRAS** (20-25%): Associated with lack of sensitivity for EGFR inhibitors.

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| As of 4/19/2018, **Osimertinib** FDA approved and **now** **NCCN first line preferred Cat 1 for EGFRm**!   * Osimertinib has the best penetration into the brain, though it appears to be best if rec'd prior RT within 6 mo. * TBL [QS](http://www.quadshotnews.com/2018/09/new-age-aura.html): Osimertinib has more intracranial activity and lower rates of intracranial progression than other EGFR-TKIs such as gefitinib and erlotinib. |

### [Targeted Therapy: EGFR](#_iwtyyd6s6gm9)

* **EGFR** (10-15%): Erlotinib/Gefitinib→ Afatinib/dacomitinib→ **Osimertinib** (if T790M) before non-targeted tx.
  + EGFR 90% exon 19/21. Exon 19 best px. Exon 21 (L858R) missense mutation, less common.
    - **Exon 20 = T790M** (Osimertinib).
  + Most pts progress within the first 2y. **Of those, 50% develop T790M mutations** (rociletinib, osimertinib). They are 10x more likely to develop T790M than progress to SCLC (6%).
* **Resistance mechanisms to Osimertinib** [[Leonetti BJC ‘19](https://www.ncbi.nlm.nih.gov/pubmed/31564718)]
  + Includes MET/HER2 amplification, activation of the RAS-mitogen-activated protein kinase (MAPK) or RAS-phosphatidylinositol 3-kinase (PI3K) pathways.
* **AURA** [[Ramalingam JCO '17](https://ascopubs.org/doi/full/10.1200/JCO.2017.74.7576)]: **First-line Osimertinib 80 vs. 160 mg**.
  + 60 tx-naive pts with locally advanced or metastatic EGFRm NSCLC. MFU 19 mo.
  + ORR 67→ 87%.
  + MPFS 22→ 19 mo.
  + Of 38 pts who had post-progression plasma samples, 50% had no ctDNA.
  + No acquired EGFR T790M was detected.
* **AURA3 Brain Met subset** [[Wu JCO '18](http://ascopubs.org/doi/full/10.1200/JCO.2018.77.9363)]: **Plt-pemetrexed vs. osimertinib**.
  + 116 asymptomatic, stable BM not on steroids.
  + MTT failure or death 6→ 12 mo.
  + CNS ORR 17→ 40% with TTR 6→ 9 mo.
  + **There is a near doubling of ORR if the patient received RT within 6 mo prior to osimertinib**.
* **FLAURA** [[Ramalingam NEJM '20](https://www.nejm.org/doi/full/10.1056/NEJMoa1913662)]: **Historical TKI vs. Osimertinib**.  
  Osimertinib improves OS compared to first-gen EGFR-TKIs when given first-line for advanced EGFR-mutated NSCLC.

Three times as many patients continued on Osimertinib, and median survival is prolonged even in the context of crossover.

TBL[QS](http://www.quadshotnews.com/2020/01/slow-simer.html): Osimertinib, just like dacomitinib, given first-line for advanced EGFR-mutated NSCLC ineligible for definitive surgery or radiation has proven to confer superior overall survival times when compared to older-generation EGFR-TKIs.

* + 556 pts. De novo advanced or metastatic NSCLC, exon 19 or 21 (L858R) EGFR. 2014-2016.
    - Osimertinib 80 qday vs. gefitinib 250 qday or erlotinib 150 qday.
    - CNS metastasis in 20% of patients.
    - Crossover eligible if progression or mutation. Around 1/3 of historical TKIs received salvage osimertinib.
  + MPFS 10→ 19 mo. HR for progression or death 0.46.
  + MS 32→ 39 mo.
  + Osimertinib appears to have no benefit over historical TKIs in the L858R or Asian subgroups.
  + 3y continued EGFR of 9→ 28%. Median exposure 12→ 21 mo.
  + G3+ AE ~45%.
* **FLAURA Brain Met subset** [[Reungwetwattana JCO '18](http://ascopubs.org/doi/full/10.1200/JCO.2018.78.3118)]: **Historical TKI vs. Osimertinib** until progression or toxicity.
  + 128 asymptomatic pts, with 41 pts measurable dz (e.g. ≥ 1 cm or on two MRI slices). 25% prior RT. MFU 15 mo.
  + MCNSPFS 14 mo→ NR.
  + CNS ORR 43→ 66%, or for measurable CNS dz 68→ 91%.
    - FLAURA did not mention impact on ORR if rec'd prior RT.

* **Management of brain mets in EGFRmt, TKI-naive pts** [[Magnuson JCO '17](http://ascopubs.org/doi/full/10.1200/JCO.2016.69.7144)]: **EGFR-TKI vs. WBRT vs. SRS**.

Deferring RT is associated with inferior OS, but no Osimertinib [QS](http://www.quadshotnews.com/2018/09/new-age-aura.html) was used on this trial.

Patients who received upfront WBRT were more likely to have > 10 brain metastasis.

* + 351 pts from 6 institutions developed brain mets. T790M or failure to receive TKI after WBRT/SRS excluded.
  + MS 25→ 30→ 46 mo.
  + TTP ~17→ 23→ 24 mo. There appears to be less progression in WBRT arm vs. EGFR-TKI.
  + MVA with SRS or WBRT→ EGFR-TKI, ECOF, and EGFR exon 19 and absence of extracranial met with better OS.
  + SRS and EGFR-TKI cohorts share similar prognostic features, but WBRT is more likely to be less favorable.

* **Management of EGFRmt brain mets** [[Miyawaki IJROBP '19](https://www.sciencedirect.com/science/article/pii/S0360301619303074?via%3Dihub)]: Retro. **EGFR-TKI vs. Local therapy**.  
  Upfront local therapy followed by EGFR-TKI is more effective than upfront EGFR-TKI for the survival of untreated patients with 1-4 brain metastasis.
  + 176 pts. Stratified by 1-4 BM and > 4 BM (82% rec'd WBRT). No pts rec'd front line osimertinib.
  + MS ~25 mo.
  + For pts w 1-4 BM, MS 23→ 35 mo.
  + There was no difference in upfront local therapy for pts with > 4 BM.
* **Rechallenging LMD** [QS](http://www.quadshotnews.com/2019/07/on-line.html) [[Flippot JTO '19](https://www.jto.org/article/S1556-0864(19)30370-3/fulltext)]: **Progression on EGFR rechallenged w inc dose or different EGFR**.
  + Multi institutional retrospective. 87 patients.
  + MS 4→ 8 mo for 50 pts who were rechallenged with increased dose or different EGFRi.

* **BLOOM study** [[Yang JCO ‘19](https://www.ncbi.nlm.nih.gov/pubmed/31809241), [Clin Onc '20](https://ascopubs.org/doi/full/10.1200/JCO.19.00457)]: Phase I. Progression on EGFR→ **Osimertinib 160 mg** po qday.

Osimertinib may be effective for LMD, with less than half of patients responding.

* + 41 pts with cytologically confirmed LMD.
    - RT: Half received prior RT (n=20), with nearly half having received WBRT (n=15).
    - Only 10 patients had received prior brain irradiation within three months before starting the study.
    - Overall response rate appeared similar regardless of receipt of prior WBRT.
  + Investigator ORR for LMD 41%. MTTP of LMD 15 mo. Median duration of osimertinib 8.5 mo.
  + Central review ORR for LMD 62%. MTTP of LMD 15 mo.
  + MS 11 mo.
  + Neurologic function improved in 57% of patients.
* **Tata memorial** [[Noronha JCO '18](https://ascopubs.org/doi/10.1200/JCO.19.01154)]: Phase III. **Gefitinib ± Carboplatin/Pemetrexed**→ maintenance Pemetrexed.  
  TBL [QS](http://www.quadshotnews.com/2019/08/more-is-more.html): Following [dacomitinib](http://www.quadshotnews.com/2018/06/whats-up-dac.html), combo gefitinib + carbo/Alimta is only the second systemic regimen in a long, long time to prove an OS advantage for advanced EGFR-mutated NSCLC ineligible for definitive surgery or radiation.
  + 350 patients. 2016-2018. Brain mets 20%. MFU 17 mo.
    - Gefitinib 250 mg ± pemetrexed 500 and Carboplatin AUC 5 q3w x4c→ maintenance Pemetrexed.
  + Radiologic ORR 63→ 75%.
  + MPFS 8→ 16 mo.
  + MS 17 mo→ NR.
  + Clinically relevant G3+ toxicity 25→ 51%.
* **RELAY** [[Nakagawa Lanc Onc '19](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30634-5/fulltext)]: **Erlotinib ± ramucirumab** (VEGFR antagonist).
  + 449 pts with EGFR 19/21. MFU 21 mo.
  + MPFS 12→ 19 mo.
  + G3-4 emergent AE in 54→ 72%. Hypertension associated with ramucirumab.

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### [Targeted therapy: ALK](#_iwtyyd6s6gm9)

* **Alk** (2-7%): **Crizotinib**→ **ceritinib, alectinib, brigatinib** or before non-targeted tx.
* ~33% present with brain mets, and > 50% will eventually develop brain mets.
* If progression on first generation (crizotinib), no biopsy is necessary and switch to second generation.
* If progression on second generation, recommend bx to look for **G1202R** mutation (Lorlatinib).
* Alk typically 5%, but subset for invasive, solid, micropapillary, acinar, minimally invasive from 15% down to 2.5% for minimally invasive. Then pap predominant, lepidocrocite, ACIS ≤ 2%.
* Like first generation EGFR agents, many patients develop resistance to Crizotinib. Intracranial ORR with crizotinib is poor. Alectinib and Brigatinib have improved intracranial and extracranial response rates. Therefore, alectinib or brigatinib (as opposed to crizotinib) should be considered for patients with asymptomatic brain metastasis.
* **Alectinib**: 25% CR in **CNS**, 50% PR in CNS, 25% SD in CNS. **Now first line!**
  + **ALEX** [[Peters NEJM '17](https://www.nejm.org/doi/full/10.1056/NEJMoa1704795), [ESMO '17](https://cslide.ctimeetingtech.com/library/esmo/browse/search/2d5y#2Bb5m0UB)]: **Crizotinib vs. Alectinib**.

TBL [QS](http://www.quadshotnews.com/2017/10/battle-of-brains.html): For ALK-rearranged NSCLC, alectinib has more intracranial activity than crizotinib.

* + - 303 previously untreated ALK pts. 50% asymptomatic BM ± RT. MFU 1.5y.
    - 1y PFS 49→ 68%
    - 1y CNS progression 45→ 12%. At least double CNS progression if ALK-pretreated.
    - In those with BM (n=43), CNS ORR 50→ 81% with CR 5→ 38% and TTR 6→ 17 mo.
      * With RT: 1y CNS progression 50→ 9%.
      * No prior RT: 1y CNS progression 62→ 20%.
    - G3+ 50→ 41%.
  + **ALTA** [[Huber JTO ‘19](https://www.ncbi.nlm.nih.gov/m/pubmed/31756496)]: **Brigatinib 90 vs. 180 mg** for Crizotinib-refractory ALK NSCLC.   
    This paper does not tease out how intracranial response might be influenced by prior brain RT.
    - 222 crizotinib refractory pts. Brain lesions in 70%. Prior SBRT allowed. MFU ~2y.
      * Brigatinib 180 mg qd with 7 day lead in at 90 mg.
    - ORR 46→ 56%.
    - MPFS 9→ 17 mo.
    - MS 30→ 34 mo.
    - Intracranial ORR 50%. Median duration of intracranial response 9→ 17 mo.
      * Less than half received prior RT to the brain. Of those, RT more than half six months prior.
    - Patients with > 25% shrinkage appear to have a MPFS of a year or more.
  + **Lorlatinib** (ALK/ROS) overcomes **G1202R** mutation. It is selectively brain-penetrant.

Approved in Nov 2018 for second/third line treatment.

* + - Phase 1 trial promising [[Shaw Lanc Onc '17](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30680-0/fulltext)], waiting phase III [NCT03052608](https://clinicaltrials.gov/ct2/show/NCT03052608) to demonstrate superiority over alectinib.
* **ROS1** (1-2%): **Crizotinib** or **Ceritinib** first line. **Entrectinib** recently gained FDA approval.
* **MET** (3-4%) testing is now recommended. Crizotinib.
  + **VISION** [[Paik NEJM '20](https://www.nejm.org/doi/full/10.1056/NEJMoa2004407)]: Phase II. **Tepotinib**.

TBL [QS](http://www.quadshotnews.com/2020/06/meet-met.html): Almost half achieved a response by RECIST criteria and two-thirds a deep (14%) or complete (53%) molecular response to the highly-selective MET-inhibitor tepotinib.

* + - 99 patients. Advanced or metastatic NSCLC. Confirmed MET exon 14 skipping mutation.
    - ORR 46% with median DOR 11 mo in the combined-biopsy group.
    - ORR 48% in liquid-biopsy group (n=66) and ORR 50% in the tissue-biopsy group (n=60). Only 27 patients had positive results according to both methods.
    - ORR was 56% regardless of previous therapy received for advanced or metastatic disease.
    - Molecular response as measured by circulating free DNA was observed in 67% of patients with matched liquid-biopsy samples at baseline and during treatment.
    - G3+ AE 28%, including peripheral edema in 7%. AE leading to permanent discontinuation in 11%.

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| **Optimal Chemotherapy for CCRT remains unknown!** [[Eberhardt JCO '15]](http://ascopubs.org/doi/full/10.1200/JCO.2014.58.9812)   * Most common options are cisplatin/**etoposide**, **carbo**/**paclitaxel** or **cisplatin**/**vinca alkaloids**.   + Broadest evidence include cisplatin doublets. * Carboplatin is usually given at AUC 2 with CCRT, and from AUC 5-6 in the adjuvant setting. * CDDP, Etoposide, and paclitaxel are all given as 50's. * Non-squamous histologies may consider CDDP or Carboplatin with pemetrexed. The PROCLAIM study looked at subbing pemetrexed for etoposide, demonstrating equivalence with less G3-4 toxicity. * Squamous histologies should not receive bevacizumab or pemetrexed. * Carboplatin and paclitaxel appear to have higher rates of radiation pneumonitis. * Cisplatin and etoposide may have better OS and less rates of RP, but at the cost of worse esophagitis. When evaluated in the VA setting, Cisplatin and etoposide had no OS advantage and worse toxicity than carboP. |

## [Concurrent Chemotherapy](#_wp55nx1rut9o)

* **CDDP 50** d1,8,29,36 and **etoposide 50** d1-5, d29-33 or **carbo** AUC **2 and paclitaxel 50 q1w** ± 2c adjuvant\*.

\*If adjuvant is given: Carbo AUC **6**, paclitaxel 200 q3w x4c.

* + SWOG regimen: CDDP **50** d1,8,29,36, etoposide **50** d1-5, d29-33 ± 2c adjuvant (4c total).
  + CDDP or carboplatin + Pemetrexed for non-squamous histologies.
  + Squamous histologies should not receive bevacizumab or pemetrexed.
* Most common options **carbo**/**paclitaxel** and **cisplatin**/**etoposide** or **cisplatin**/**vinca alkaloids**.
  + Broadest evidence includes cisplatin doublets.

* + **China** [[Liang Ann Onc '17](https://academic.oup.com/annonc/article/28/4/777/2964585)]: Phase III. **CCRT 60-66 + CarboP vs. EP**.  
    Cisplatin and etoposide may have better OS and less RP, but worse esophagitis.
    - 191 pts. Stage III NSCLC. MFU 6y.
      * CP: Carboplatin AUC 2, paclitaxel 45 q1w.
      * EP: CDDP 50 d1,8 and etoposide 50 d1-5 q4w x2c.
    - 3y OS 26→ 41%. MS ~21→ 23 mo (p=0.095).
    - G2+ pneumonitis 33→ 19%, G3+ esophagitis 6→ 20%.

* + **STRIPE pneumonitis meta-analysis** [[Palma IJROBP '13]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448004/): Median 60 Gy CCRT. **CarboP vs. EP**.  
    Highest risk of pneumonitis > 50% in patients > 65y receiving carboplatin/paclitaxel.

Refer to paper for useful statistics and RPA. See Figure 1 for dose constraints.

* + - 836 pts. MFU 2.3y.
    - CarboP may have higher rates of pneumonitis, esp if > 65y old (60% RP).
    - For CarboP > 65y, MLD ≤ 10 Gy may be preferred (Figure 1).
    - For Cisplatin/etoposide, V20 < 25% may be preferred (Figure 1).
    - OR 3.33 for CarboP vs. CE.
  + **STRIPE esophagitis meta-analysis** [[Palma IJROBP '13](https://www.sciencedirect.com/science/article/pii/S0360301613029003)]:

Goal for Esophageal dose V60 < 17% (Figure 1).

* + - 91% rec'd platinum based chemotherapy, does not tease out CarboP vs. CE.
    - G2 / G3 / G4 esophagitis of 32→ 17→ 0.9%. Life-threatening in < 1% of pts.
    - V60 best predictor for G2+ and G3+ radiation esophagitis.
    - G3 esophagitis for V60 ± 17% of 22→ 10%.
  + **VA Health** [[Santana-Davila JCO '15](http://ascopubs.org/doi/full/10.1200/JCO.2014.56.2587)]: Retro. **CCRT CarboP vs. EP**.  
    Cisplatin and etoposide with no OS advantage, but more toxicity than carboplatin and paclitaxel.
    - 1,842 pts. EP in 27%.
    - No difference in OS even with propensity score adjusted model and high-volume EP centers.
    - Hospitalizations 1.7→ 2.4, outpatient visits 13→ 18, infection complications 39→ 43%, AKI or dehydration 21→ 31%, mucositis or esophagitis 14→ 19%.
* **Pemetrexed**: Do not give for SqCC.

* + Scagliotti [[JCO '08](http://ascopubs.org/doi/full/10.1200/JCO.2007.15.0375)]: Phase III. **Plt-based + gemcitabine vs. pemetrexed**.  
    Do not give pemetrexed to SqCC histology due to detriment in SqCC subset on this study.
    - 1,725 IIIB-IV pts. No prior chemo or surgery. Prior RT ok if at least 4 weeks prior to study.
      * CDDP 75 d1 + Gem 1,250 d1,8 vs. pemetrexed 500 d1 q3w, up to 6c.
    - MS 10.3 mos.
      * MS for AC of 10.9→ 12.6 mo
      * MS for large cell of 6.7→ 10.4 mo.
      * MS for SqCC of 10.8→ 9.4 mo. Detriment with SqCC.
    - Toxicity: Pemetrexed with less G3-4 neutropenia, anemia, and thrombocytopenia, less febrile neutropenia, less alopecia. More G3-4 nausea.
  + **PROCLAIM** [[Senan JCO '16](http://ascopubs.org/doi/full/10.1200/JCO.2015.64.8824)]: **CCRT 60-66 Gy + EP vs. CDDP/Pemetrexed**.  
    Pemetrexed is not superior but has less G3-4 events than EP.
    - 555 unresectable IIIA/B pts**. Non-squamous**.
      * CDDP 75, pemetrexed 500 q3w x3c→ q3w x4c.
      * CDDP 50, Etoposide 50 q4w x2c→ q4w x2c.
    - MS ~26 mo. G3-4 77→ 64%, neutropenia 45→ 24%.
* **VEGF**: **Bevacizumab**: VEGF ligand. **Ramucirumab** VEGFR2.
  + Consider bevacizumab + chemo for AC with no recent history of hemoptysis, do not give alone.
  + Bevacizumab with higher toxicity and no survival benefit in elderly patients [[1]](http://ascopubs.org/doi/abs/10.1200/JCO.2007.13.1144?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed).
  + Bevacizumab: more hemoptysis in SqCC (in this subgroup pemetrexed ineffective).

* + Johnson [[JCO '04](http://ascopubs.org/doi/full/10.1200/JCO.2004.11.022)]: Phase II. **Carboplatin and paclitaxel ± bevacizumab**.  
    Major hemoptysis is associated with SqCC histology, tumor necrosis and cavitation, and dz location close to major blood vessels.
    - 99 pts. No prior RT or chemo. If dz progression, crossover to single agent bev 15 q3w allowed.
      * Carboplatin AUC 6, paclitaxel 200 q3w ± Bevacizumab 7.5 or 15 mg/kg.
    - ORR 19→ 32%. MS 15→ 18mo.
    - 19 pts crossed over to single agent bev, 5 w SD and 1y OS 47%.

## 

## [Adjuvant Systemic Therapy](#_wp55nx1rut9o)

Consider adjuvant systemic treatment for lesions ≥ 4 cm per exploratory analysis on [[CALGB 9633](#9jpqanq3igxt)].

Give Durvalumab consolidation for IIIA/B unresectable treated definitively with CCRT [[PACIFIC](#kix.8o8cpe3mdnov)].

Preferred (nonsquamous): CDDP 75 d1, pemetrexed 500 d1 q3w x4c.

Preferred (squamous): CDDP 75 d1, gemcitabine 1250 d1,8 or docetaxel 75 d1 q3w x4c.

* **CALGB 9633** [[Strauss JCO '08]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2652093/): R0/1 Stage IB (T2N0) **± Adjuvant Paclitaxel/Carboplatin**.
  + Stopped early due to OS benefit on initial analysis, but the final results were not significant.
    - Chemo: Adjuvant Paclitaxel 200, carboplatin AUC 6 q3w x4c.
  + 3y OS 70→ 79% w 5y OS ~60%.
  + Exploratory analysis for tumors ≥ 4 cm: MDFS 63→ 96 mo and OS 77→ 99 mo.
* **KCSG-LU05-04** [JCO '15]: CCRT inoperable stage III NSCLC **± Adjuvant CDDP/Docetaxel consolidation**.  
  No role for adjuvant CDDP/docetaxel.
  + 420 pts. CCRT 66 CDDP 20 + docetaxel 20 q1w x6c→ ± CDDP/Docetaxel 35 d1/8 q3w.
  + Primary endpoint 40% improvement in PFS.
  + MPFS ~8.5 mo.

* **LACE Meta** [[**Pignon** JCO '08]](http://ascopubs.org/doi/abs/10.1200/JCO.2007.13.9030?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **± consolidative chemotherapy after R0 resection**.
  + 4,584 pts on 5 RCTs. Mix of stage I-III.
  + **~5% OS benefit** for adjuvant cisplatin-based chemo at 5y.
  + Subset: No OS benefit for stage IA or IB disease, but CALGB 9633 not included.
    - OS HR for stage IA / IB / II / III of 1.4→ 0.93→ 0.83→ 0.8.
* **Meta** [[Tsujino JTO '13](https://www.jto.org/article/S1556-0864(15)33474-2/fulltext)]: **± consolidative chemotherapy after definitive CCRT**.  
  This notion that consolidative systemic therapy does not affect OS after CCRT all changed with the [[PACIFIC](#kix.8o8cpe3mdnov)] trial.
  + Total of 41 studies.
  + MS ~18 mo.
  + Consolidative chemo without improvement in OS after definitive CCRT over the past two decades.
  + Low efficiency for second line chemo after platinum doublet.
  + Highly toxic therapy with little clear benefit.
* **ECOG-ACRIN 5508** [Ramalingam JCO '19]: **Adjuvant CarpoP/Bevacizumab→ pemetrexed vs. bev vs. combo**.  
  TBL [QS](http://www.quadshotnews.com/2019/08/low-maintenance.html): Combination bevacizumab and pemetrexed maintenance therapy for advanced non-squamous, non-small cell lung cancer does not improve survival over bev monotherapy.
  + 1516 patients. Advanced non-squamous NSCLC. MFU 4y.
  + MS ~15 mo.
  + MPFS 4.2→ 5.1→ 7.5 mo.
  + G3+ toxicity 37→ 29→ 50%.
  + Due to increased G3+ toxicity, combination bevacizumab and pemetrexed could not be recommended.

## [Immunotherapy](#_wp55nx1rut9o)

See the [[PACIFIC](#kix.8o8cpe3mdnov)] trial in the definitive CCRT section for more.

* Immunotherapy was first approved in SqCC due to lack of targetable mutations.
* Only Pembro is approved for the first line (if PD-L1 ≥ 50%)! Regardless of if metastatic or locally advanced.
* Types
  + **Nivolumab**/**Pembrolizumab**: IgG4 inhibits PD-1 receptor.
  + **Atezolizumab/Durvalumab**: PD-L1.
    - Dosing frequency: Durvalumab **10** mg/kg q2w up to 12 mo. Nivo q2w, pembro q3w.
  + CTLA-4: Commonly on Regulatory T cells.
    - CTLA-4 + Nivolumab. Hepatitis, colitis, dermatitis. Some endocrine.

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| **Nivolumab AE** [[Weber JCO '17]](http://ascopubs.org/doi/full/10.1200/JCO.2015.66.1389): Pooled review of melanomas (Good reference for AE of Nivo). **Nivo 3 mg/kg q2w**. Most side effects are primarily low grade, resolving with established safety guidelines. Use of systemic suppressive immune-modulating (e.g. corticosteroid) agents did not affect ORR.   * 576 pts. Melanoma. 54% prior ipilimumab. Median 9 mo nivolumab. * 70% overall, **10% G3-4**. Tx-related AE leading to discontinuation in 3% (any grade), most commonly colitis, increased AST, increased lipase, and pneumonitis. * GI 2-3%. Hepatic 1% (peri-portal, mostly T cells). Colitis. Dermatitis. Neuro 1%. * Median time to onset of AEs range from 5w (skin) and 15w (renal). * Around 24% (n=114) rec'd corticosteroids. **ORR for ± corticosteroids ~30%**.   **Adverse events in Immunotherapy**:***X*-itis** [[Postow NEJM '18]](https://www.nejm.org/doi/10.1056/NEJMra1703481):   * Most commonly colitis, hepatitis, dermatitis, endocrine abnormalities. * Hypophysitis: Persistent HA, sudden loss of libido, persistent fatigue.   + Suppression of multiple hormones, particularly hydrocortisone. Image with MRI. Treat early and aggressively for best results. EASILY MISSED but < 1%. * Cytokine release syndrome: Treat with infliximab.   **Immunotherapy events are likely overstated** [[Rodrigo JAMA '18](https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2717560) [QS](http://www.quadshotnews.com/2018/12/placebo-effect.html), [Moreau-Bachelard, Coquan, Le Tourneau NEJM '19](https://www.nejm.org/doi/full/10.1056/NEJMc1900053)]  TBL [QS](http://www.quadshotnews.com/2019/05/imputable.html): Previous reporting indicates rates of adverse events with immune checkpoint inhibitors may be overblown. That’s because most patients enrolled in relevant trials (e.g., for refractory metastatic disease) are pretty prone to adverse events at baseline. This Parisian group does a quick tally among 51 recent placebo-controlled trials of anti-cancer agents to determine that more than a quarter of grade 3+ toxicities attributed to anti-cancer drugs also occur in the placebo arm.  **Targeted therapy with SBRT**: **Reviews here** [[Simone TLCR '15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4630515/), [Kroeze CTR '17](https://www.sciencedirect.com/science/article/pii/S0305737216301384?via%3Dihub), [Zeng Lancet '14]](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70026-9/fulltext).   * Awaiting RTOG 1306. * Brief summary:   + VEGF is associated with fatal hemoptysis for lung SBRT or bowel perforations for abdominal SBRT.   + BRAF V600E is associated with severe dermatitis with SBRT.  Consider holding BRAF and/or MEK inhibitors ≥ 3d around RT, while only ≥ 1d for SRS or SBRT.   + TKIs can lead to higher rates of pneumonitis with SBRT.   **Pembro with RT** [[Luke/Lemons JCO '18]](http://ascopubs.org/doi/full/10.1200/JCO.2017.76.2229): Phase I. **Pembro within 7d after the end of SBRT**. This toxicity isn't really different than Pembro alone, but seems to correlate to area irradiated. Also see [[KEYNOTE 001](#cggvjbxthfke)].   * 73 Stage IV patients progressing on prior tx. 2016-2017. Target volumes < 65 mL (5 cm tumor). MFU 5.5 mo.   + SBRT to 2 sites in 69/73 pts. Treated 2-4 metastatic sites.   + 30/3 for bone/spinal.   + 45/3 for peripheral lung/liver/abd/pelvis.   + 50/5 for central lung/mediastinal/cervical. * 6 G3 toxicity (3 pneumonitis, 2 colitis, 1 hepatitis). 10% dose limiting toxicity. * G3 RP in 13% of pts (n=3/23) receiving lung SBRT. * Objective response 13.5% (2 CR, 8 PR, 21 SD, 38 PD). |

* **Radiation + Immunotherapy induced lymphopenia?** [[Pike NEJM '18]](https://www.redjournal.org/article/S0360-3016(18)33755-6/pdf)

* **Pembro-RT Trial** [[Theelen ASCO '18](https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.9023), [JAMA Onc '19](https://jamanetwork.com/journals/jamaoncology/article-abstract/2738064)]: Phase II. **± SBRT→ Pembro within 7d after the end of SBRT**.  
  TBL [QS](http://www.quadshotnews.com/2019/07/synergy-is-better-than-my-way-or-your.html): Inserting a quick shot of SBRT prior to pembro for refractory NSCLC is clearly safe and may double response rates, suggesting it is more practical than not to extrapolate Gomez data in the setting of pembro.
  + 76 pts. ≥ 2nd line chemo for advanced NSCLC. Bx of tumor at baseline and after 2c pembro.
    - Pembro 200 q3w. PD-L1 ≥ 50% in 13→ 29% (control arm had less PD-L1).
    - SBRT 24/3 within 7 days prior to the first cycle.
  + 12w ORR ~18→ 36% (p=0.07). MPFS ~1.9→ 6.6 mo (p=0.19), MS ~7.6→ 15.9 mo (p=0.16).
    - Improvements in ORR with SBRT are most marked in patients who have a PD-L1 of 0%.
    - PD-L1 was not balanced between groups, which may have confounded outcomes.
  + G3+ in ~20%. Most commonly fatigue, nausea, fever, hypothyroidism.
* **Colitis and Immunotherapy** [**QS**](http://www.quadshotnews.com/2019/06/another-run-at-it.html)[[Abu-Sbeih JCO '19](https://ascopubs.org/doi/full/10.1200/JCO.19.00320)]: Retro. What happens if ICI is re-initiated?
  + 167 patients. CTLA-4 in 32 pts, PD-(L)1 in 135 pts. Re-started immune checkpoint inhibition at median of 49d.
  + Recurrent colitis in 1/3 of patients at a median of 53d, mostly G1-2.
  + Risk of immune mediated diarrhea and colitis lower if resuming PD-(L)1 than resumption of CTLA-4 therapy
* **Checkmate 227** [[Hellmann NEJM '18](https://www.nejm.org/doi/full/10.1056/NEJMoa1801946), [Ramalingam ASCO '20](https://meetinglibrary.asco.org/record/184651/abstract)]: **Chemo vs. Nivolumab ± Ipilimumab**.   
  ORR doubled with the addition of Ipi to Nivo vs. chemo; though Tx-related AE leading to discontinuation also doubled.
  + Stage IV or recurrent NSCLC, chemo naive. Irrespective of PDL1 or histo. MFU nearly 4y.
    - For those < 1% PD-L1, Chemo vs. Chemo/Nivo vs. Nivo/Ipi. *Nivo alone is not given if < 1% PD-L1.*
    - Nivo 240, or Nivo 3 / Ipi 1.
  + High mutational burden subset (≥ 10 mutations/megabase):
    - For chemo vs. Nivo+Ipi: 1y PFS 13→ 43%. MPFS 6→ 7 mo. ORR 27→ 45%.
    - Benefit persists for < 1% PD-L1.
  + Low mutational burden subset (< 10 mutations/Mb):
    - For chemo vs. Nivo+Ipi: 1y PFS ~17→ 25% (NS), MPFS 5.5→ 3.2 (NS).
  + For PD-L1 ≥ 1%, 3y OS 22→ 29→ 33%. 3y PFS 4→ 12→ 18%. Confirmed responders remaining in response 4→ 32→ 38%.
  + For PD-L1 < 1%, 3y OS 15→ 20→ 34%. 3y PFS 2→ 8→ 13%. Confirmed responders remaining in response 0→ 15→ 34%.
  + PFS is not better with Nivo alone in any subgroup.
  + Patients with PD-L1 ≥ 1% with ≥ PR at 6 mo had longer subsequent survival with Nivo/Ipi than chemo, but patients with SD or PD at 6 mo had generally similar subsequent OS between treatments.
  + Toxicity quite significant of Ipi/Nivo, similar to platinum based chemo:
    - G3-4 36→ 19→ 31%.
    - Tx-related AE leading to discontinuation: 5→ 7→ 12%. *Essentially doubled.*
* **CheckMate 9LA** [[Reck ASCO '20](https://meetinglibrary.asco.org/record/184688/abstract)]: **Chemo x4c vs. Nivo 360/Ipi 1 + Chemo x2c→ maintenance ICI**.
  + 700 pts. Stage IV or recurrent NSCLC. No targetable mutations. MFU 13 mo.
  + MS 11→ 16 mo.
  + 1y OS 47→ 63%.
  + G3-4 AE 38→ 47%.

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| **First line for locally advanced or Metastatic disease** (if no targetable mutations)   * Current 2018 data suggests PD-L1 needs to be ≥ 1% for Pembro alone first line [[KEYNOTE 42](#6ty86d8r8zr0)]. * Previously, PD-L1 had to be ≥ 50% for first line Pembro alone [[KEYNOTE 024](#5cpp9ixd4clc)].   + Much stronger data for PD-L1 ≥ 50%, with suggestion of death RRR of 50%. |

**First line: Locally advanced/Metastatic disease. Pembro alone for PD-L1 ≥ 1%**.

* **KEYNOTE 024** [[Reck NEJM '16](https://www.nejm.org/doi/10.1056/NEJMoa1606774), ['19](http://ascopubs.org/doi/full/10.1200/JCO.18.00149)]: **Platinum chemo vs. Pembro** 200 **q3w**. PD-L1 ≥ 50%.  
  Pembro was originally approved as the first line for metastatic dz w PD-L1 ≥ 50% and no targetable mutations!

G3+ toxicity was around 33% for Pembro alone. Compare to 66% for Pembro + Chemo [[KEYNOTE 189](#bgimj6grw2xo)].

* + 305 pts. Previously untreated Stage IV NSCLC w PD-L1 ≥ 50% without EGFR or ALK.
    - 1,653 assessable for PD-L1. 30% PDL1 ≥ 50%.
  + MPFS 6→ 10 mo. MS 14→ 30 mo. 1y OS 54→ 70%.
    - Death RRR of 50%.
  + Response 28→ 45%. Durability 6.3 mo→ NR.
    - Most respond by 2 mo.
    - 44% of control crossed over at 1y (82% at 2y) to receive Pembro.
  + Toxicity 90→ 73%, G3+ 53→ 31%.
  + Retrospective study [[Aguilar Ann Onc '20](https://www.annalsofoncology.org/article/S0923-7534(19)60984-1/fulltext)] demonstrated an ORR of 60% for PD-L1 ≥ 90%.

TBL [QS](http://www.quadshotnews.com/2020/02/on-spectrum.html): Degree of PD-L1 expression is a predictive biomarker in a continuous fashion.

* **KEYNOTE 042** [[ASCO abstract '18,](http://abstracts.asco.org/214/AbstView_214_226263.html) [Mok Lancet '19](https://www.sciencedirect.com/science/article/pii/S0140673618324097)]: **Platinum chemo vs. Pembro** 200 **q3w**. PD-L1 ≥ 1%.  
  Pembro alone can be the first line for PD-L1 ≥ 1%! [Not in NCCN yet]

TBL [QS](http://www.quadshotnews.com/2020/02/smoke-detector.html): Interestingly, subgroup analyses demonstrated no OS benefit among never smokers, even those with PD-L1 expression > 50%.

* + 1,274 pts. SqCC or AC, treatment naive LA or metastatic NSCLC without EGFR or ALK. MFU 1y.
    - PDL1 ≥ 20% in 64%; PDL1 ≥ 50% in 47%.
    - Carbo/paclitaxel or carbo/pemetrexed ≤ 6 cycles.
  + Still taking drug at 1y of 5→ 14%.
  + MS improved by 4-8 mo!
    - PDL1 ≥ 1%: MS 12.1→ 16.7 mo, HR 0.81.
    - PDL1 ≥ 20%: MS 13→ 17.7 mo, HR 0.77.
    - PDL1 ≥ 50%: MS 12.2→ 20 mo, HR 0.61.
  + G3+ toxicity 41→ 18%.

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| **First line for Metastatic disease** (if no targetable mutations)   * Current 2018 data suggests Pembro should be added to platinum chemo as first line, regardless of histology or PD-L1 expression, except for PD-L1 ≥ 50%, which may receive pembrolizumab alone [[KEYNOTE 42](#6ty86d8r8zr0)]. * Every patient with metastatic NSCLC should have immunotherapy involved in first line therapy. |

**First line: Metastatic disease, Pembrolizumab ± platinum based chemo, no PD-L1 testing required.**

* **Checkmate 026** [[Carbone NEJM '16]](https://www.nejm.org/doi/full/10.1056/NEJMoa1613493): **Docetaxel** 75 **q3w vs. Nivolumab q2w**. PDL1 ≥ 5%. Allowed PDL1 ≥ 1%.  
  Conclusion: Nivo not first line!
  + 541 pts. Previously untreated stage IV NSCLC or recurrent NSCLC.
    - 1047 assessable for PD-L1. 71% PD-L1 ≥ 1%. 51% PD-L1 ≥ 5%.
  + MPFS ~5mo. MS ~14m.
  + Response 33→ 25%. Time to respond 3 mo. Duration 6→ 12mo.
    - Subgroup: Only patients with high mutation burden had PFS advantage.

* **KEYNOTE 021** [[Langer Lancet '16]](https://www.sciencedirect.com/science/article/pii/S1470204516304983?via%3Dihub): Phase 2. **Carbo/pemetrexed ± Pembro.**   
  The addition of pembrolizumab to carbo/pemetrexed only has a PFS benefit.
  + 123 pts. AC. Previously untreated stage IV non-SqCC NSCLC without EGFR or ALK mutations.
  + Response rate 30→ 55%. MPFS 9→ 13 mo.
  + Precursor to KEYNOTE 189.

* **KEYNOTE 189** [[Gandhi NEJM '18,](https://www.nejm.org/doi/full/10.1056/NEJMoa1801005) [Gadgeel ASCO '19](https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.9013), [JCO '20](https://www.ncbi.nlm.nih.gov/pubmed/32150489)]: **Chemo ± Pembro**. Any PD-L1.   
  Approximate doubling of OS, PFS, and PFS2 with pembro + chemo, even for PD-L1 < 1% group.

G3+ toxicity was 66% for Pembro + Chemo. Compare to 33% for Pembro alone [[KEYNOTE 024](#5cpp9ixd4clc)].

TBL [QS](http://www.quadshotnews.com/2020/03/double-down.html): First-line pembro has transformed the landscape of wild-type NSCLC.

* + 616 pts. AC. Previously untreated stage IV non-SqCC NSCLC without EGFR or ALKmt. MFU 2y.
    - Allowed patients with untreated brain metastases ≤ 1.5 cm who do not require steroids.
    - Chemo: Pemetrexed 500 + CDDP 75 or Carbo AUC 5 q3w x4c→ pemetrexed 500 q3w.
      * Pembro 200 mg q3w up to 35 cycles.
      * Crossover allowed upon progressive disease. 40% crossed over from the control arm.
  + MS 11→ 22 mo. 1y OS 49→ 69%, regardless of PD-L1 status.
    - This is notable because Pembro alone is not believed to have a significant benefit in AC histology.
  + MPFS 5→ 9 mo.
  + ORR 19→ 48%. Median duration of response 7.8→ 11.2 mo.
  + Crossover MPFS on pembro 17→ 9 mo. *First line pembro with longer MPFS.*
  + Nearly 100% with AE, and 66% G3-5.
    - AE leading to treatment discontinuation 8→ 14%.
  + PROs [[Garassino Lanc Onc '20](https://www.ncbi.nlm.nih.gov/pubmed/32035514)]: There were improved GHS/QoL scores at week 21 with the addition of pembro.

* **KEYNOTE 407** [[Paz-Ares NEJM '18](https://www.nejm.org/doi/full/10.1056/NEJMoa1810865), [QoL](https://www.ncbi.nlm.nih.gov/pubmed/31751163)]: **Carbo/paclitaxel ± Pembro**. Any PD-L1.   
  There is an OS benefit for the addition of pembrolizumab to carboplatin and paclitaxel, regardless of PD-L1.
  + 559 pts. SqCC. Previously untreated stage IV SqCC NSCLC.
    - Allowed patients with untreated brain metastases ≤ 1.5 cm who do not require steroids.
    - Pembro 200 mg/w + Carbo AUC 6 q3w and paclitaxel 200 q3c or nab-paclitaxel 100 q1w x4c.
  + MS 11→ 15.9 mo, regardless of PD-L1 status.
  + Nearly 100% with AE, and 69% G3-5.
    - AE leading to treatment discontinuation 6→ 13%.
  + Objective response rate 38→ 60%. Median duration of response 4.8→ 7.7 mo.
    - 43% crossed over from the control arm.
  + HRQoL maintained or improved with the addition of pembro to chemo at weeks 8 and weeks 18.

**Second line for metastatic disease**:

* First approved in SqCC in March of 2015 due to results from CheckMate 063, the precursor for 017.
* **Nivolumab**, **Pembro** and **Atez** all add 3 months to OS vs. docetaxel alone. ~33% have durable responses at 2 years.
  + Most respond by 2 mo for any histology, sometimes 6/12 mo for SqCC.
  + Lack of PFS benefit in 057 and 010 in context of OS benefit suggests PFS may not be the best prognosticator.
* **KEYNOTE 001** [[Shaverdian Lanc Onc '17](https://www.ncbi.nlm.nih.gov/pubmed/28551359), [Garon JCO '19](https://www.ncbi.nlm.nih.gov/pubmed/31154919)]: Phase Ib. Pembro 2 mg/kg q3w or Pembro 10 mg/kg q2-3w.   
  There was a high 5y OS rate for patients with treatment naive or previously treated NSCLC. This was particularly pronounced for patients with PD-L1 ≥ 50%. There appears to be an OS benefit in patients who were treated with prior RT.
  + 101 treatment naive and 449 previously treated locally advanced/metastatic NSCLC. MFU 5y.
    - Extracranial RT in 38 pts (mostly thoracic), median 9.5 mo before pembrolizumab.
  + MS for treatment naive / previously treated of 22→ 11 mo.
  + 5y OS for treatment naive / previously treated of 23→ 16%.
  + In patients with PD-L1 ≥ 50%, 5y OS for treatment naive / previously treated of 25→ 30%.
  + MPFS for ± prior extracranial RT of 2→ 6 mo. MS for ± prior extracranial RT of 5→ 12 mo.
  + MS for ± prior RT of 5→ 11 mo.
  + One new-onset treatment related G3 AE occurred from year 3 to year 5.

* + There appeared to be a trend towards increased pulmonary toxicity with receipt of prior thoracic RT, but no difference in overall G3 toxicity.

* **CheckMate 017 / 057 pooled** [[JCO '17](http://ascopubs.org/doi/full/10.1200/JCO.2017.74.3062), [Vokes Ann Onc '18](https://academic.oup.com/annonc/article/29/4/959/4835443), [Antonia Lanc Onc '19](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30407-3/fulltext)]: **Docetaxel** 75 **q3w** **vs. Nivolumab q2w**.

Some patients have a durable response to Nivolumab, even four years later!

Would the survival be even higher if these patients had received radiation therapy?

* + Stage IIIb/IV pts. Must have disease recurrence after one prior platinum containing regimen.
  + No pts in either docetaxel group had an ongoing response at 2 years.
  + Death RRR of 28% [HR 0.72].
  + Treatment related AE 88→ 68% any grade, 55→ 10% G3/4.
  + Pooled 3y OS 8→ 17%. Pooled 4y OS 5→ 14%.
  + 4y OS 14% with nivolumab. For PDL1 ≥ 1%, 4y OS 19%. For PD-L1 < 1%, 4y OS 11%.
  + Of the 854 pts, 192 had baseline liver metastasis. For pts with liver mets, OS HR 0.68.
  + **CheckMate 017** [[Brahmer NEJM '15]](https://www.nejm.org/doi/full/10.1056/NEJMoa1504627): 272 IIIb/IV **SqCC** pts. PDL1 testing not needed for SqCC!
    - MS 6→ 9.2m. 1y OS 24→ 42%. Death RRR of 41%.
    - Response 9→ 20%.
      * Most respond by 2 mo, sometimes 6/12 months. Benefit regardless of PDL1.
    - MPFS 2.8→ 3.5 mo.
      * More durable responses. PDL1 expression did not matter.
    - 2y OS 8→ 23%. Durable response in 10 (37%) of 27 confirmed responders.
  + **CheckMate 057** [[Borghaei NEJM '15]](https://www.nejm.org/doi/full/10.1056/NEJMoa1507643): 582 IIIb/IV **AC** pts.Magnitude of benefit dependent on PDL1 expression.
    - MS 9.4→ 12.2m. 1y OS 39→ 51%. Death RRR of 27%.
    - Response 12→ 19%. Durability 5.6→ 17.2 mo.
      * Most respond by 2 mo, majority 5 mo. Strong predictive association of 1/5/10% PDL1.
    - MPFS 4.2→ 2.3m but 1y PFS 8→ 19%, but with OS advantage PFS might not appropriately capture the true benefit of nivo.
    - EGFR+ does not seem to benefit, never smokers don’t benefit due to somatic mutations.
    - 2y OS 16→ 29%. Durable response in 19 (34%) of 56 confirmed responders.

* **KEYNOTE 010** [[Herbst Lancet '16](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)01281-7/fulltext), [JCO '20](https://www.ncbi.nlm.nih.gov/pubmed/32078391)]: **Docetaxel** 75 **vs. Pembro 2 vs. 10** mg/kg, all **q3w**. PDL1 ≥ 1%.  
  There is equivalence between all pembro dosing regimens, but superiority over docetaxel.
  + 1034 pts. Must have disease progression after ≥ 2 cycles of platinum containing regimen, or an appropriate TKI for EGFR or ALK rearrangement. No active brain mets. EGFR did not respond well. MFU 3.5y.
    - 2222 pts assessable for PD-L1. 66% PDL1 ≥ 1%, including 28% with PD-L1 ≥ 50%.
    - ~70% nonsquamous.
  + Six months after study completion, half had died.
  + MS 8.5→ 10.4→ 12.7 mo. 3y OS 11→ 23%.
    - For PDL1 ≥ 50%, MS 8.2→ 14.9→ 17.3 mo, 3y OS 13→ 35%.
  + MPFS ~4 mo, but with OS advantage PFS might not appropriately capture the true benefit of pembro.
    - For PDL1 ≥ 50%, mPFS 4→ 5→ 5 mo.
  + Response rate 8→ 30→ 30%.
    - Duration of response 8 mo→ NR→ NR.
  + 79 of 690 pts completed 35c / 2y of Pembro. After completing treatment, 1y OS 99% and 1y PFS 73%. 95% ORR and 64% had ongoing responses.
  + G3+ AE in 18% of patients. 14 pts received second-course pembro. 5 completed 17 cycles, 43% had PR and 36% had SD.
* **PROLUNG** [[Arrieta JAMA Onc '20](https://www.ncbi.nlm.nih.gov/pubmed/32271354)]: Phase II. Docetaxel ± Pembrolizumab.
  + 78 pts. Progression after platinum-based chemo and EGFRi. 32% had an EGFR/ALKmt. 2016-2019. MFU 9 mo.
    - Docetaxel 75 d1, Pembro 200 d8 q3w up to 6c.
  + ORR 16→ 43%.
  + Non-EGFR ORR ~12→ 36% (p=0.06).
  + EGFR ORR ~23→ 58% (p=0.14).
  + MPFS 4→ 9.5 mo.
  + Non-EGFR MPFS 4→ 9.5 mo.
  + EGFR MPFS 3.5→ 7 mo.
  + G1-2 pneumonitis 5→ 23%. Any grade hypothyroidism 3→ 28%.
* Atezolizumab: PDL1! Unlike Nivo, pembro (PD1). Two trials:

* + **POPLAR study** [[Lancet '16]](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00587-0/fulltext): Phase II. **Docetaxel vs. Atezolizumab**.
    - MS 9.7→ 12.6m. Benefit not seen in no PD-L1.

* + **OAK study** [[Lancet '17]](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32517-X/fulltext): **Docetaxel vs. Atezolizumab**. *Any PD-L1.*
    - 1225 pts. IIIB/IV failing ≥ 1 platinum based chemo.
      * Atez 1.2g q3w vs. Docetaxel [75].
    - MS 9.6→ 13.8m. Benefit regardless of PDL-1 status.
    - G3/4 43→ 15%.
  + **IMPOWER 150** [Socinski NEJM '18]: Any PD-L1.
    - 1202 pts. Stage IV recurrent metastatic non-squamous NSCLC, chemo naive.
    - Regardless of PD-L1.
  + **IMPOWER 131**: SqCC.

# [NSCLC: Future Directions](#_6sfwza45y5km)

See NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)].

## Curative Intent

Given the 30% risk of DM and 40% LRR for early NSCLC on [[RTOG 02-36](#a7j9wvgpo9h0)], four new trials are looking at immunotherapy in early stage NSCLC (See [[SBRT for tumors > 5 cm](#_31j3vr6mrwkq)] section for more):

1. **SWOG/NRG S1914** [[Simone/Daly NCT04214262](https://clinicaltrials.gov/ct2/show/NCT04214262)]: Phase III. **SBRT ± Induction/Consolidation Atezolizumab**.
   * High risk, Early stage NSCLC. Inoperable or refuses surgery.
   * Histologically proven 7th ed stage I-IIa NSCLC ≤ 7 cm without nodal or DM.
     + Atezolizumab q3w x8c (6 mo).
   * 1+ HR feature of: Diameter ≥ 2 cm, SUV max ≥ 6.2, G2-3 or undifferentiated histology.
   * Stratified by: central vs. peripheral, size ± 4 cm, PS 0-1 vs. 2.
2. **UCLA** [[Lee NCT03148327](https://clinicaltrials.gov/ct2/show/NCT03148327)]: Phase I/II. **SBRT ± induction/consolidation Durvalumab**.

Concurrent Durvalumab appears safe (not yet published, but phase I completed).

* + Inoperable or refuses surgery.
  + Histologically proven stage I-IIa NSCLC ≤ 7 cm without nodal or DM.

1. **PACIFIC 4 / RTOG 3515** [[Robinson NCT03833154](https://clinicaltrials.gov/ct2/show/NCT03833154)]: **SBRT ± adjuvant Durvalumab** 1.5g q1m x 24 mo.
   * Clinical stage I/II node negative (T1-3 N0). Medically inoperable or refuses surgery.
     + Durva 1500 mg q4w x 24 mo.
   * Randomization within 7 days of completing SBRT.
2. **NRG LU004 / ARCHON-1** [[NCT03801902](https://clinicaltrials.gov/ct2/show/NCT03801902)]: Phase I. **60/30 vs. 60/15 + concurrent/adjuvant durvalumab**.
   * Stage II-III NSCLC or locally advanced recurrent disease from prior surgery.
   * Unresectable or inoperable. PD-L1 ≥ 50%. No chemotherapy.
   * 6 patients in each course. Mandatory hold of 60→ 90 days after RT. An additional 6 patients will be enrolled in each cohort if deemed safe.

* **A151216 / ALCHEMIST-SCREEN** [[NCT02194738](https://clinicaltrials.gov/ct2/show/NCT02194738)]: R0. **Genetic testing for Surgical candidates**.
  + Completely resected stage IB ( ≥ 4 cm), II or IIIA with negative margins.
* **A081105** [[NCT02193282](https://clinicaltrials.gov/ct2/show/NCT02193282)]: Phase III. **R0→ ± Adjuvant Erlotinib**.
  + ALCHEMIST-SCREEN criteria + AC, EGFRmt.
* **E4512** [[NCT02201992](https://clinicaltrials.gov/ct2/show/NCT02201992)]: Phase III. **R0→ ± Adjuvant Crizotinib**.
  + ALCHEMIST-SCREEN criteria + AC, ALK fusion positive.

* **RTOG 1308** [[Giaddui Rad Onc '16](https://www.ncbi.nlm.nih.gov/pubmed/27142674), [NCT01993810](https://clinicaltrials.gov/ct2/show/NCT01993810)]: Phase III. **Photon vs. Proton CCRT**.
  + Dosimetric compliance criteria in Table 1. Does not use Heart V50 < 25% (Now standard per NCCN). [RoR](#jgrlfoasvoc2)
  + Stage II/IIIB NSCLC. Unresectable or inoperable.
  + Maintenance therapy with CarboPaclitaxel (SqCC/AC), CarboPemetrexed (AC) or Durvalumab.

* **RTOG 1106** [[NCT01507428](https://clinicaltrials.gov/ct2/show/NCT01507428)]: Phase II. PET-Guided therapy for stage III NSCLC.

RTOG 1106 OARs and Targets [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-lung)]

* + GTVp on Avg for 4DCT or free breathing with full exhale. PET avidity (SUV > 1.5x uptake of 1cc blood).
  + GTVn ≥ 1 cm short axis, pN+, abnormal appearing, 2+ nodes in high risk station, within 1 cm of primary.

## Non-curative Intent

There are many open multi-institutional trials looks into local consolidative therapy in [[oligometastatic disease](#_4f6vjyau5afh)]:

1. **NRG-LU002** [[NCT03137771](https://clinicaltrials.gov/ct2/show/NCT03137771)]: Phase II/III. **Maintenance systemic treatment ± SBRT for up to 3 mets**.
   * Pts who completed 4c of first line chemotherapy or immunotherapy. Requires treated brain lesions.
     + Excludes targetable mutations, untreated brain mets and metastatic disease to esophagus, stomach, intestines or mesenteric lymph nodes.
     + Single fraction: 21-27 Gy. Acceptable deviation ≥ 16 Gy.
     + Three fraction: 26.5-33 Gy. Acceptable deviation ≥ 24.5 Gy.
     + Five fraction: 30-37.5 Gy. Acceptable deviation ≥ 28 Gy.
     + Fifteen fraction: 45 Gy for disease not amenable to SBRT in ≤ 5 fractions.
   * No evidence of progression and ≤ 3 sites of mets amenable to surgery or SBRT plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance therapy. Protocol allows up to 20 Mets at Dx.
   * EGFR or ALK patients are excluded.
2. **SABR-COMET 3** [[Protocol](https://bmccancer.biomedcentral.com/track/pdf/10.1186/s12885-020-06876-4), [NCT03862911](https://clinicaltrials.gov/ct2/show/NCT03862911)]: Phase III. Now open, up to 3 lesions.
   * See Table 1 for fractionation schemes.
3. **SABR-COMET 10** [[NCT03721341](https://clinicaltrials.gov/ct2/show/NCT03721341)]: Phase III. 4-10 lesions.
4. **STOP-NSCLC** [[NCT02756793](https://clinicaltrials.gov/ct2/show/NCT02756793)]: Phase II. **Any cytotoxic or targeted treatment ± SBRT**.
   * NSCLC. ≤ 5 oligoprogressive mets. Maximum 3 lesions in any single organ (EC or CNS mets).
     + Patients on the control arm may also receive palliative RT.
   * Primary endpoint: PFS. Secondary endpoints: OS, QoL, toxicity, LC rate, total time on chemo, duration of systemic treatment after SBRT, location of sites of further progression.
5. **HALT** [[NCT03256981](https://clinicaltrials.gov/ct2/show/NCT03256981)]: Phase II/III. **Targeted therapy ± SBRT**.
   * NSCLC with targetable mutation. ≤ 3 extracranial sites of oligoprogressive disease.
     + RT doses range from 30-52 Gy in 2-8 fractions to oligoprogressive disease.
   * Primary endpoint: PFS. Key secondary and exploratory endpoints: OS, time to change in systemic treatment, patterns of progression, acute and late toxicity, QoL, ctDNA, PET/CT findings in relation to outcome, time to failure of next treatment.
6. **NORTHSTAR** (MDACC): Phase II. Synchronous EGFR+. **Osimertinib ± LCT for up to 5 mets**.
   * 143 pts. 6-12 weeks Osimertinib, then randomized to ± LCT. Primary endpoint PFS.
   * If ≤ 3 active sites, then LCT to all sites. If > 3 active sites, then LCT to sites at discretion.
7. **BrightStar** (MDACC): Phase I. Synchronous ALK+. **Brigatinib ± LCT**.
   * 35 pts. 8 weeks brigatinib.
   * If ≤ 3 active sites, then LCT to all sites. If > 3 active sites, then LCT to sites at discretion.
8. **LONESTAR** (MDACC): Phase III. **Ipi 1 q6w + Nivo 3 q2w for 12 weeks→ Ipi/Nivo maintenance up to 2y ± LCT**.
   * Stage IV NSCLC. Immunotherapy naive. EGFR and ALK wild type.

* **EA5162** [[NCT03191149](https://clinicaltrials.gov/ct2/show/NCT03191149)]: Phase II. **Osimertinib**.
  + Stage IV, stage IIIB not eligible for definitive multimodality therapy or recurrent. EGFR exon 20 insertion mutation.
  + Palliative RT is allowed so long as > 14d for non-lung, > 28d for lung RT prior to study registration.
* **EA5163** [[NCT03793179](https://clinicaltrials.gov/ct2/show/NCT03793179)]: Phase III. **CarboPemetrexed ± Pembrolizumab**.
  + Stage IV, non-squamous disease. PD-L1 positive (TPS ≥ 1%).
  + Palliative RT is allowed so long as > 14d prior to study registration.
* **NRG-LU003** [[NCT03737994](https://clinicaltrials.gov/ct2/show/NCT03737994)]: Phase II. **Various ALKi combinations with chemo** (e.g. Carbo or CDDP/Pemetrexed).
  + Metastatic AC. ALK-positive. Previously treated progressive disease.
  + Palliative RT allowed for bone pain > 2d, SRS to the brain if >7d, and WBRT if >14d prior to study entry.
* **LUNGMAP screening study** [[NCT03851445](https://clinicaltrials.gov/ct2/show/NCT03851445)]: Phase II/III. **Genomic testing for previously treated NSCLC**.
  + Previously treated, stage IV or recurrent.
* **S1400F** [[NCT03373760](https://clinicaltrials.gov/ct2/show/NCT03373760)]: Phase II. **Durvalumab + Tremelimumab** (CTLA-4).
  + LUNGMAP + Anti-PD-(L)1 resistant SqCC.
* **S1400A** [[NCT03971474](https://clinicaltrials.gov/ct2/show/NCT03971474)]: Phase II. **Chemo + Pembrolizumab**.
  + LUNGMAP + Anti-PD-(L)1 resistant.
* **S1900B** [[NCT04268550](https://clinicaltrials.gov/ct2/show/NCT04268550)]: Phase II. **Selpercatinib**.
  + LUNGMAP + RET fusion positive.
* **S1900C** [[NCT04173507](https://clinicaltrials.gov/ct2/show/NCT04173507)]: Phase II. **Talazoparib + Avelumab**.
  + LUNGMAP + STK11 genomic alterations.

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# [Small Cell Lung Cancer](#_6sfwza45y5km)

[**StatPearls: Lung Small Cell (Oat Cell)**](https://www.ncbi.nlm.nih.gov/books/NBK482458/)*Last update: 2/14/2019.*

ARRO: [[Small Cell Lung Cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/ARROCaseSmallCell.pdf)].

AVARO [[Normal Thorax Anatomy](http://econtour.org/cases/89)], [[Thoracic nodal levels](http://econtour.org/cases/88)]

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| **ESMO Guidelines for Diagnosis, Treatment and Follow up** [[Früh Ann Onc '13](https://www.esmo.org/guidelines/lung-and-chest-tumours/small-cell-lung-cancer)]  **ASCO/ACCP Guideline:** [**Treatment of Small-Cell Lung Cancer**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/9991) *September 8, 2015*   * **LS-SCLC** (33%): Surgical resection recommended for select stage I SCLC.   + LS-SCLC receives CCRT for patients with good PS.   + Thoracic RT should be initiated early in the course of treatment, preferably with C1 or C2 of chemo.     - SER < 30d. Data suggests pts need to be able receive adequate chemotherapy for this to apply.     - OS decreases by 2% for every 1w of prolonged SER [[De Ruysscher JCO '06]](#8g80j0b22nvp).   + Chemo should consist of four cycles of a platinum agent and etoposide. * **ES-SCLC** (67%): Chemo standard w platinum agent plus etoposide or topo/irinotecan. Typically six cycles for ES-SCLC.   Carboplatin + Etoposide + Atezolizumab (PD-L1) now first line for ES-SCLC [[IMpower133](#a2sv4pgkksn3)] [QS](http://www.quadshotnews.com/2018/09/big-deal-for-small-cells.html)   * **PCI** prolongs survival in pts w LS-SCLC who achieve a CR or PR to initial therapy, also may do so for ES-SCLC.   Interestingly, with the results of [[NVALT-11/DLCRT-02](#z7uwrwjt12ey)] and [[RTOG 02-14]](#75disjmiglns), NSCLC has just about as much evidence for PCI as SCLC.[QS](http://www.quadshotnews.com/2019/03/the-brain-game.html) However, the rate of brain mets are lower for NSCLC therefore PCI is not recommended.  **ASTRO Guideline: RT for Small Cell Lung Cancer** [[Simone PRO '20](https://www.ncbi.nlm.nih.gov/pubmed/32222430)]:  Thoracic RT for LS-SCLC   * CCRT is standard of care for patients with good PS, and can be used for fit patients > 70y. * Earlier thoracic RT is recommended, with RT starting during C1-C2. Consider C3 if shrinkage would decrease RT toxicity. * 45/30 BID is recommended. * Treat all involved LNs at the time of diagnosis. Elective coverage of ipsilateral hilum is controversial.   Role of SBRT in Stage I-II Node Negative SCLC   * Consider SBRT for node-negative peripheral or central lesions, while conventional RT for ultracentral lesions (i.e., PTV touching mainstem bronchus, trachea, esophagus, mediastinum). Whenever feasible, invasive mediastinal staging is important.   Prophylactic cranial RT   * Restage after chemo with MRI brain. PCI is conditionally not recommended for stage I SCLC. * Stage II-III LS-SCLC patients < 70y with response to thoracic CCRT are recommended to receive PCI.   + Shared decision making for patients with limited PS, > 70y, and/or significant comorbidities. * ES-SCLC recommends shared decision making after response to chemo. Only ~20-25% of centers offer PCI for ES-SCLC. * 25/10 is the recommended dose for either LS or ES, though most evidence for ES-SCLC is 20/5.   Thoracic consolidation for ES-SCLC   * After chemo alone, patients with residual disease in the chest should be offered 30/10 (or higher doses if prolonged survival is expected, e.g., 45/15). * After chemo and immunotherapy (standard of care), consolidative chest RT is conditionally recommended for those with residual disease in the thorax. *Awaiting results of NRG LU007. See the [*[*Future Directions*](#_kcsj058yvbh4)*] section for more.* |

* 220k total lung cancer cases per year, 160k deaths.
  + 15-20% SCC, 3% large cell neuroendocrine (M:F 17:1, > 50 py). Small decrease in the last 30 years.
    - 15-20% of all lung tumors are SCLC, 66% extensive.
  + Brain mets in 10-15% at Dx→ 50% autopsy[[1](https://www.sciencedirect.com/science/article/pii/S0140673605675691?via%3Dihub)].
    - Up to 30% have BM after chemo! *Depends on timing of the MRI.*
    - 2y incidence of brain mets after CRT of 60-70%.
  + More than 95% are associated with smoking.
  + Improvement in survival in the past two decades has come from appropriate use of (thoracic) RT!
  + SCLC is the most common solid tumor associated with paraneoplastic syndromes.

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| **Paraneoplastic syndromes**   * **SCLC**: 7-16% have SIADH, ~3% have LES.   + ADH, ANP and ACTH can all be secreted by SCLC. *Treat SIADH with fluid restriction, saline.* * 10% of all NSCLC patients will have paraneoplastic syndromes.   + Hypercalcemia: PTHrP in primary **SqCC**.   + LES: Cerebellar ataxia, retinopathy in SCLC, with ~5% of SCLC demonstrating LES.     - Pre-synaptic Ca++ channels, prox weakness improves with reps, dry mouth, paresthesias. *Tx = IVIG.*   + Hypertrophic osteoarthropathy: bilateral clubbing, most commonly AC.   + Hypercoagulable: AC.   + Dermato/polymyositis: AC.   + Gynecomastia: Large cell.   + VIP diarrhea: Seen in carcinoid. *Treat with somatostatin.* |

* **Limited vs. Extensive stage**: MS 2-4 mo without tx.
  + **LS** (30%): **5y OS ~20-30%** with MS 20-30 mo.
    - VALSG defined LS as ipsilateral hemithorax, excluding malignant pleural or pericardial effusions.
    - Limited stage: AJCC stage I-III (M0), but excludes T3/T4 if **unable to fit in "tolerable" RT port**.
  + **ES** (70%): **5y OS < 5%** with MS 12 mo.
    - Extensive stage: AJCC IV (M1a/b) or too large to be encompassed in tolerable RT plan.
* **Work up**
  + Performance status, weight loss are prognostic.
  + Labs: Hyponatremia, alk phos, LDH are associated with a worse prognosis.
  + CT C/A, PET/CT, MRI brain, CBC, LFTs, **Calcium**, LDH, BUN/Cr.
    - LDH after treatment is a marker for recurrence.
    - PET/CT nearly 100% Sn, may upstage 20% initially diagnosed w LS-SCLC.
  + Additional workup: BMBx if elevated LDH, abnl peripheral smear, or cytopenias.
* **Pathology**
  + Small round blue cells. Crush artifact on pathology.
  + **Neuroendocrine**: CD56 (neural cell adhesion molecule), chromogranin A, synaptophysin, TTF-1, NSE.
    - SCLC > 10 mitosis/2 mm2, atypical carcinoid 2-10 mitoses/2mm2, typical carcinoid 0-1 mitosis/2mm2.
  + Epithelial markers: Keratin, EMA, TTF1.
  + Contrasted to NSCLC, alterations in EGFR, KRAS, ALK and p16 are rarely seen.

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| **Small round blue cells** (LEARN NMR): **L**ymphoma, **E**wing, **A**LL, **R**MS, **N**B, **N**euroepithelioma, **M**edullo, **R**b.   * **Ewing family**: Ewing's sarcoma (bone 87%), extraosseous Ewing's sarcoma (8%), peripheral PNET (5%), DSRCT, Askin's tumor (non-osseous PNET of chest wall). * Be able to list 7 types. Virtually all reactive for keratin and epithelial membrane antigen. 75% have 1+ neuroendocrine marker (chromogranin, synaptophysin, NSE, etc). |

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| **Chemotherapy in SCLC**  Easy boards answer: CDDP 75 d1, Etoposide 100 d1-3 q3w x4c, add concurrent/adjuvant Durva for ES-SCLC (Atez: CarboE only).   * Cisplatin and Etoposide (EP), with the former delivered on d1 and the latter delivered d1-3 x4-6c. * **Extensive Stage**: Always receive maintenance immunotherapy.   + Carboplatin **AUC 5** d1 etoposide **100** d1-3 **+ Atezolizumab** [[IMpower133](#a2sv4pgkksn3)] **or** **Durvalumab** [[CASPIAN](#myzsvi6f3bt3)].   + Cisplatin **75** d1 etoposide **100** d1-3 + **Durvalumab** [[CASPIAN](#myzsvi6f3bt3)]. * **Limited Stage**: Cisplatin / Etoposide q3w x4-6c: **75**/**100** [[CONVERT](#g5ydzigdyk9u)] or **60**/**120** [[Turrisi](#ameifz489gnc)] (old school). |

## [Systemic Therapy](#_b3a8at0dnvs)

See Summary Box on Chemotherapy above.

Easy boards answer: CDDP 75 d1, Etoposide 100 d1-3 q3w x4c, add concurrent/adjuvant Durva for ES-SCLC (Atez: CarboE only).

* Multiple RCTs eval chemo combos and timing. Two drug combos >1, but > 2 is not very beneficial and more toxic.
* EP (6-**4c**) remains standard first-line in most centers, CDDP can give about 1 mo prolonged OS but less QoL.
  + If in the brain, ~50% response in the brain.
* CE with 60-70% response rate, 20% CR.
  + Thoracic RT (61.2 RTOG or 70 CALGB) with 41% CR, 39% PR→ 40% LF.
* Can substitute carboplatin with less emesis and neuropathy, but more myelosuppression.
* Relapsed small cell may be treated with **topotecan** as second line, but immunotherapy now preferred:
  + **Checkmate 32** [[Antonia Lanc Onc '16](https://www.sciencedirect.com/science/article/pii/S1470204516300985?via%3Dihub)]: **Nivolumab ± ipilimumab**.
    - 216 pts. Recurrent dz.
    - ORR 12→ 21%.
    - 3 mo PFS 18→ 30%.
    - G3-4 toxicity 12→ 37%.
  + **KEYNOTE 028 and 158** [[Chung JTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31870883)]: **Two or more lines of therapy→ Pembrolizumab**.
    - 83 pts. Recurrent/metastatic SCLC. MFU 8 mo.
      * Pembro mostly 200 q3w (n=64).
    - ORR 19%. Median duration of response NR. 61% of responders had responses lasting ≥ 18 mo.
    - 2 pts had CR while 14 pts had PR.
    - G3+ in 10%.

* **IMpower133** [[Horn NEJM '18](https://www.nejm.org/doi/full/10.1056/NEJMoa1809064)]: **Carboplatin/Etoposide** x4c **± atezolizumab**. *No thoracic consolidation.*  
  See the [[Extensive stage](#_mr2dodxoiote)] section for more.

TBL [QS](http://www.quadshotnews.com/2018/09/big-deal-for-small-cells.html): In one of the first headways this disease has seen in decades, adding atezolizumab to carbo / etoposide for extensive stage SCLC prolongs progression free and overall survival.  
Why carboplatin/etoposide? Intention = palliative from the beginning.

* + 403 **ES-SCLC pts. First line!** Includes previously treated asymptomatic brain mets. MFU 14 mo.
    - Chemo: Carbo AUC 5, Etoposide 100 d1-3 q3w x4c.
    - PD-L1: Atez 1200 mg with maintenance atezolizumab.
      * During the maintenance phase, PCI allowed, but thoracic consolidation was not.
    - No thoracic consolidation allowed, but ~85% had lung involvement and 80% had thoracic LNs. Only 2.5% of patients on the atezolizumab arm experienced a complete response.
  + MS 10.3→ 12.3 mo. 1y OS 38→ 52%.
  + MPFS 4→ 5 mo. 1y PFS 5→ 13%. *Durable response for ICI is typically 15-20% across malignancies.*

* **CASPIAN** [[Paz-Ares Lancet ‘19](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32222-6/fulltext), [ASCO '20](https://meetinglibrary.asco.org/record/184541/abstract)]: **Platinum/Etoposide** x4c **± durvalumab ± tremelimumab** (CTLA-4).  
  See the [[Extensive stage](#_mr2dodxoiote)] section for more.

TBL [QS](http://www.quadshotnews.com/2019/10/big-and-small.html): Concurrent and maintenance durvalumab with platinum + etoposide chemo improves survival in patients with extensive-stage small cell lung cancer.

* + 537 pts. ES-SCLC. **First line!** MFU over 2y.
    - PCI at investigators discretion. No prior chest RT allowed.
    - Carbo AUC 5-6 or CDDP 75-80 d1 + etoposide 80-100 d1-3 q3w x4c→ maintenance durvalumab.
  + MS 10.5→ 13mo. 1y OS 40→ 54%. 2y OS ~14→ 22% (p=0.045).
  + MPFS ~5.5 mo. 1y PFS 5→ 18%. *Durable response for ICI is typically 15-20% across malignancies.*
* **ECOG-ACRIN EA5161** [[Leal ASCO '20](https://meetinglibrary.asco.org/record/184553/abstract)]: **Platinum/Etoposide** x4c **± Nivo**.

Small number of patients, short follow up. Atez and Durva will likely hold the front lines in this setting - at least for now.

* + 160 patients. ES-SCLC. First line! PCI at discretion.
  + MS 9→ 11 mo.
  + ORR 48→ 52%.
* **KEYNOTE-604** [[Rudin ASCO '20](https://meetinglibrary.asco.org/record/184545/abstract), [JCO '20](https://ascopubs.org/doi/10.1200/JCO.20.00793)]: **Platinum/Etoposide** x4c **± Pembro**. PCI at clinician discretion.

Pembro in addition to traditional chemo only prolongs OS in the as-treated analysis, not ITT. This won't be the first line.

TBL QS: Pembro, unlike atezo and durvalumab, does not improve survival when added to front-line platinum and etoposide for metastatic small cell lung cancer.

* + 453 pts. ES-SCLC. First line! No untreated brain mets (~12%). PCI in 13% (only if PR/CR). MFU nearly 2y.
  + ITT MS ~10→ 11 mo. *Did not meet significance threshold.*
  + ORR 60→ 70%.
* KEYNOTE 156: Relapsed/refractory SCLC.
* Rovalpituzumab: Expression in >80% SCLC.

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| **What is the role of RT for ES-SCLC in the immunotherapy era?** [[Nesbit TLCR '19](http://tlcr.amegroups.com/article/view/28932)]  See the [[Extensive stage](#_mr2dodxoiote)] and NRG-LU007 in the [[Future Directions](#_kcsj058yvbh4)] section for more.  TBL [QS](http://www.quadshotnews.com/2019/07/chest-bump.html): Where does radiation stand in the era of atezolizumab for extensive-stage small cell lung cancer? This helpful review takes a deep dive and comes away putting all its money on chest consolidation. With immune checkpoint inhibition on board, a growing number of responders will likely see a benefit with the proven-safe and possibly-synergistic addition of radiation to residual thoracic disease. On the other hand, with paces of brain mets slowing, prophylactic brain radiation seems less helpful than ever. |

## [Limited Stage](#_nruipiivq02s)

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| **Ultra Limited Stage**   * Clinical stage I or cN0. * Consider mediastinal staging, which can be PET only. * Is it technically resectable, and is the patient medically operable? If concerned about mediastinal disease, don't cut. * Principles remain the same as NSCLC, although adjuvant chemo is certainly recommended regardless of local therapy.   **Limited Stage (cN+)**   * Start RT early with the C1-2 of chemo. Recommend PCI if at least partial responder (Auperin suggests 5% OS benefit). * Thoracic RT improves overall survival by 5%, and reduces local failures by roughly 1/3. * 45/30 remains standard of care, although 66-70/33-35 Gy is reasonable. * Consider RT to ipsilateral hilum. Consider mediastinum or subcarinal coverage if no PET and/or nodal evaluation.   Limited Stage: CDDP / Etoposide q3w x4-6c: 60/120 [[Turrisi](#ameifz489gnc)] or 75/100 [[CONVERT](#g5ydzigdyk9u)].  Easy boards answer: CDDP 75 d1, Etoposide 100 d1-3 q3w x4c, add concurrent/adjuvant Durva for ES-SCLC (Atez: CarboE only). |

[Unique scenario: T1-T2N0](#_x7eot2pqwmlq)

* 5% are Stage I.
* NCCN says proceed with surgical resection if mediastinum is pathologically negative. N0→ CTX; N+→ CCRT.
* Role of adjuvant therapy in a population-based cohort of patients with early stage SCLC [Yang]
  + Those that received adjuvant chemo and RT to the brain only appear to do best if mediastinum is negative.
* JCOG 9101 [[Tsuchiya JTCVS '05](https://www.ncbi.nlm.nih.gov/pubmed/15867769)]: Phase II. **R0→ adjuvant EP x4c**.
  + 61 pts. Stage I-IIIA SCLC (90% stage I/II).
  + 3y OS 61%, or for stage I / II / III of 68→ 56→ 13%.
* Verma [[IJROBP '17](https://www.ncbi.nlm.nih.gov/pubmed/28011047)]: Retro. **LS-SCLC→ SBRT** (50/5).
  + 74 pts from 24 institutions. LS-SCLC. Inoperable. T1-2N0.
    - Chemo in 56%. PCI in 23%.
  + 3y LC 96%.
  + MDFS 50 mo. 3y DFS 53%.
  + MS 52 mo. 3y OS 34%.
  + Chemo led to an increase in OS and DFS, also seen on MVA.
  + Failures: 46% DM, 25% nodal, 21% elsewhere in lung.
* Surgical resection
  + pN0: Adjuvant EP x4c ± PCI.
    - ESTRO consensus suggests avoidance of PCI for elderly patients [[Putora RTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31887577)].
  + pN+: Adjuvant EP x4c + adjuvant mediastinal RT (50-60/25-30 depending on resection factors) + PCI.
* Non-operative: SBRT→ Adjuvant EP x4c ± PCI.

[Role of Radiation in LS](#_x7eot2pqwmlq)

* Thoracic RT used to be mainstay in the 1970s, then with chemo decreased in the 80s.
  + Improvement in survival in the past two decades has come from appropriate use of RT!
  + If poor performance status, chemotherapy alone reasonable (NCCN).
* Two Metas in 1992: Adding thoracic RT to chemo w 5% OS benefit and 25% LC benefit. *Also 5% benefit w PCI (Auperin).*
  + [**Pignon** [NEJM '92]](https://www.nejm.org/doi/10.1056/NEJM199212033272302?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov): **Chemo ± Thoracic RT**.   
    Thoracic consolidation has a **5.4%** OS benefit at 3y.
    - 2,103 pts from 13 RCTs. Didn't include elderly.
      * Chemo: Not Cisplatin/etoposide.
    - 3y OS 9→ 14%. Subgroup of > 55y without SS benefit.
    - Local control improved by 25-30%.
  + Warde [JCO '92]: **Chemo ± Thoracic RT**.  
    Thoracic consolidation has around 5% benefit in OS at 2y. Absolute 25% LC benefit with thoracic RT.
    - 11 trials.
    - LC 24→ 47%. 2y OS 15→ 20%. Pts under the age of 60y derived the most benefit.
* SEER: shift in age of LS, with pts ≥ 70 accounting for 60% of new pts. RT use increased for younger patients, not older.
* [Corso [JCO '15]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4678178/): Elderly NCDB showed survival benefit for >70y, seemed to be better for concurrent vs. sequential.

[When to deliver RT in LS](#_x7eot2pqwmlq)

Initiate during cycle 1 or cycle 2!

* Meta [[Fried JCO '04]](http://ascopubs.org/doi/full/10.1200/JCO.2004.01.178): **Early vs. Late RT**.

There is a clear benefit in early RT, starting at C1 or C2 (less than 9w after the start of chemo).

Compared to PCI: Subset of [[Auperin](#2iz1ptxc86ic)] suggested PCI should be started within 4 mo after chemo.

* + 7 trials for LS-SCLC.
  + Benefit of early vs. late RT was 5% for all pts, 10% with cisplatin, and 17% for pts receiving cisplatin and BID RT.

* **Start date of any treatment to End of RT** (**SER**)[[**De Ruysscher** JCO '06]](http://ascopubs.org/doi/abs/10.1200/JCO.2005.02.9793?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **Aim for SER < 30 days**!

OS dec by 2% for every 1w of prolonged SER.

"Time Between the First Day of Chemo and the Last Day of Chest RT is Most Important Predictor of OS in LS-SCLC"

* + Ex: Four cycles of chemo, RT on tail end has SER 12w. Move RT to beginning SER 6w, if Turrisi 3w.
    - They suggest every week of prolonged SER = OS decrease of 1.86%, while increasing esophagitis.
  + However, pts with massive LAD may benefit from 1-2 cycles prior to RT with the goal of starting RT by cycle 2 or 3. Target the post-chemo volumes with no increase in marginal failures.

[Fractionation in LS](#_x7eot2pqwmlq)

* **INT-0096** [[**Turrisi** NEJM '99](https://www.nejm.org/doi/10.1056/NEJM199901283400403?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov)]: **CCRT 45/25 QD vs. 45/30 BID**→ If CR, PCI.   
  OS benefit with BID comes at the cost of inc esophagitis, Turrisi standard but control arm with lower BED and is an easy bar to clear. Note that Start to End of RT is two weeks shorter than control arm.

The modern [[CONVERT](#g5ydzigdyk9u)] trial demonstrated no difference in esophagitis between 66/33 qday and 45/30 BID.

* + 417 pts. **CDDP** **60**, **Etoposide** **120** q3w x4c (Differs from modern CDDP 75 and etoposide 100 q3w ).
    - RT to ipsi hilum and b/l mediastinum, inferiorly 5 cm below carina or including hilum, whichever is lower.
    - CTV: (GTV + 1.5 cm) + (ipsi hilum + bilat mediastinum + 0.8 cm). No uninvolved SCV.
    - AM and PM tx on-cord for w1, then AM dose on-cord and PM off-cord using obliques w2-3.
    - Cord max **36 Gy** in BID arm, but currently **41 Gy** in RTOG 0538.
  + 2y OS ~41→ 47%. **5y OS 16→ 26%**. MS 19→ 23 mo.
  + Isolated LF ~52→ 36% (p=0.06).
  + G3+ esophagitis 11→ 27%. *Note there is 60-70% risk of esophagitis in small subgroup > 70y.*
* **JCOG 9104** [[Takada JCO '02](https://www.ncbi.nlm.nih.gov/pubmed/12118018)]: **SCRT vs. CCRT with CE x4c** (**45/30 BID**).

CCRT wins! Much less severe esophagitis than Turrisi.

* + 231 pts w LS-SCLC. CCRT started on day 2 of the first cycle of chemo.
    - CDDP 80 d1, Etoposide 100 d1-3.
  + MS ~20→ 27 mo (p=0.97). 5y OS 18→ 24%.
  + Severe esophagitis ~4→ 9% (p=0.17). More hematologic toxicity w CCRT.
* **THORA** [[Gronberg ASCO '20](https://meetinglibrary.asco.org/record/184539/abstract)]: Phase II. **45/30 BID vs. 60/40 BID with CE x4c**.

Ahh, the classic OS benefit without a PFS benefit. What to do with this information…? Final pub will be interesting.

* + 176 pts. 2014-2018.
  + MPFS ~14→ 20 mo (p=0.31).
  + 2y OS 46→ 73%. MS 23→ 42 mo.
  + G3-4 esophagitis ~20%. G3-4 pneumonitis ~0→ 4% (p=0.1)
* Other BID regimens, including Split course and an RTOG regimen which was removed from CALGB 30610:
  + [**NCCTG** [Schild IJROBP '04]](https://www.sciencedirect.com/science/article/pii/S0360301604003815?via%3Dihub): **50.4 vs. Split-course 48 in 1.5 Gy BID** starting at C4 of EP.
    - 262 pts. Planned split course in BID arm w 2w break.
    - MS ~20mo, 5y OS ~21%. Esophagitis increased in the hyperfractionated arm.
  + **RTOG 0239** [[Komaki IJROBP '12]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377848/): Phase I. **28.8/16→ BID RT to 61.2** (5 weeks).

This was included on [[CALGB 30610](#ai573yweolpf)] but was later dropped in favor of Qday arm to facilitate accrual.

* + - Subsequent phase II showed 41% CR, 39% PR and local failure in about 40% of pts.
    - 2y OS 37%, 2y LC 80%, 18% acute severe esophagitis. *Recall: 27% in Turrisi.*
* **CALGB 39808** [[Bogart IJROBP '04]](https://www.redjournal.org/article/S0360-3016(03)02217-X/fulltext): Single arm. **Paclitaxel + topotecan** x2c**→ 70/35 + EP** x3c. PCI for PR or CR.

70 Gy is safe and has a similar OS to BID regimens (22 mo).

* + 63 pts. LS-SCLC.

* **CONVERT**/EORTC 8072 [[Faivre-Finn Lanc Onc '17](https://www.sciencedirect.com/science/article/pii/S1470204517303182?via%3Dihub), [Salem JAMA Onc '18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6439849/)]: **45/30 BID vs. 66/33 with CE x4-6c**.   
  Protocol available in Supplement 1 of the Salem publication.

Powered for superiority (not non-inferiority) and did not show superiority, therefore BID RT remains standard of care.

Recall: Turrisi had 30% G3 esophagitis. This trial looks at Turrisi, but without coverage of bilateral mediastinum.

* + 547 pts. LS-SCLC. PCI recommended if there is no progressive disease (~80%). MFU 45 mo.
    - Concurrent **CDDP 75** and **Etoposide 100** q3w x4-6c.
    - Cord 42 Gy in BID arm, while 48 Gy in qday arm. Lung V20 < 35%.
    - RT starts at the second cycle of CE. Most 3D, some IMRT, and no ENI.
    - GTV: Includes nodes ≥ 1 cm short axis and/or "PET positive nodes"
    - CTV: GTV + 5 mm with manual adjustments. No prophylactic nodal irradiation or field reduction.
    - PTV: CTV + 1 cm CC and 0.8 cm radial.
  + **2y OS ~53%** (~56→ 51% [NS]) and MS ~30→ 25m (p=0.14). 5y OS ~33%.
  + Completion of RT in 98→ 83%, completion in goal time 63→ 48% (19 vs. 45d).
  + G3-4 esophagitis ~20%. G4 neutropenia 49→ 38%.

* **CALGB 30610/RTOG 0538** [[NCT00632853](https://clinicaltrials.gov/ct2/show/NCT00632853)]: **70/35 vs. 45/30 BID** vs. 28.8/16→ BID RT to 61.2 (RTOG 0239 - closed).

Completed accrual January 2020! Return to the [[Future Directions](#_kcsj058yvbh4)] section.

RTOG 02-39 dose escalation dropped at planned interim analysis in 2017 to facilitate accrual.

* + 70/35 (7 weeks) thoracic RT at 3c EP (first two topotecan and paclitaxel).
    - BID arm single phase GTV + ipsi hilum to 45 Gy. Cord **41 Gy** in BID arm, previously **36 Gy** on Turrisi.
    - QD arm with GTV + ipsi hilum to 44 Gy then cone-down to GTV to 70 Gy.
    - GTV: **Post**-chemo GTV + initially involved nodal groups.
      * Includes nodes > 1 cm short axis or pretreatment PET SUV > 3.
    - CTV: ITV ± ipsi hilum + involved subcarinal/bilat mediastinal nodes. No ENI of mediastinum and SCV.
      * CTVp = GTVp + 8mm, CTVn = GTVn + 5mm.
      * OK to include **pre**-chemo volume in CTV.
    - PTV: CTV + 5mm if daily set up imaging. If no 4D or daily imaging, use 1.5 cm CC and 1 cm radial.
    - Limited ENI, as single institution data suggests ~2-3% isolated nodal failure rate without ENI.
    - CDDP 80 d1, etoposide 120 d1-3 q3w x4c.
    - PCI offered to all pts with CR or near CR, given 3-6w after completion of all 4 cycles of chemotherapy.
  + MS 20 mo, 2y OS 35%.

* **NRG-LU005** [[NCT03811002](https://clinicaltrials.gov/ct2/show/NCT03811002)]: **CCRT** (66/33 or 45/30 BID) **± concurrent/adjuvant Atezolizumab** q3w up to 1y.

See NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)] and [[Future Directions](#_kcsj058yvbh4)] for more information.

* + LS-SCLC. Tx, T1-4 N0-3 M0. PCI recommended for CR or near CR.
  + Concurrent CDDP/Etoposide q3w x4c. RT started with C2 of chemotherapy.
  + Tumor and involved lymph nodes (> 1 cm SAD) or SUV >3 at time of planning CT.
* **ADRIATIC** [[NCT03703297](https://clinicaltrials.gov/ct2/show/NCT03703297), [Senan CLC '20](https://www.clinical-lung-cancer.com/article/S1525-7304(19)30374-2/fulltext)]: Phase III. **CCRT→ ± Durvalumab ± Tremelimumab consolidation**.

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| **Prophylactic cranial irradiation in Limited Stage**   * Initiate following completion of CCRT (LS: EP with CDDP 75 d1, etoposide 100 d1-3 q3w x4c). Takes 3 mo. * Consider repeat brain imaging at that time to investigate occult disease progression. * Consider around 4 weeks after completion of chemotherapy prior to initiation (unplanned subset on Auperin demonstrated trend towards less BM if PCI started < 4 mo). * General consensus: 25/10 is recommended. Use of concurrent memantine and hippocampal avoidance is experimental. There has not been a clearly demonstrated decline in mental status after 25/10, but this detriment is clear after 30/10. Two studies in 2019 have demonstrated conflicting results with hippocampal avoidance: The [[Netherlands](#awimct4qrhv4)] trial demonstrated no difference in HVLT-R at 4 and 8 mo, while the [[Spanish PREMER](#y9yq0t2ckhf)] trial demonstrated less decline in free delayed recall at multiple timepoints up to one year. Therefore, enroll your patients on [[NRG CC003](#t1s96574976t)] to help answer this question! |

### [PCI in Limited Stage](#_x7eot2pqwmlq)

* Brain mets in 10-15% at Dx→ 80% autopsy. Up to 30% have BM after chemo! (depends on timing of MRI).
  + 2y incidence of brain mets after CRT of 50-80%.
* **LS-SCLC: Is PCI Necessary?** [[Farris PRO '19](https://www.sciencedirect.com/science/article/abs/pii/S1879850019301857)]: Retro. **Obs vs. PCI**.

Patients with CR in the chest appear to not benefit from PCI, while PR/SD experience improved PFS.

Overall, PCI was associated with improved PFS and reduced early incidence of brain metastasis.

Subsets of the LS-SCLC population such as patients with a CR in the primary may be potentially spared from PCI in the era of modern imaging. *However, the boards answer for LS-SCLC is to favor PCI based on the Auperin meta-analysis below.*

* + 92 patients without intracranial disease at initial staging. MFU ~5y.
  + MS ~31→ 38 mo (p=0.07).
  + MPFS 12→ 26 mo.
  + 2y cumulative incidence of brain mets 29→ 10%, while at 4y was equivalent ~30%.
  + In patients with a negative MRI brain after initial treatment, 1y incidence of brain mets ~10%.
* PCI neurocognitive effects:
  + Prior to PCI, ~25% of pts have abnormal QoL-cognitive functioning scores, increasing to ~40% at 2-3y.
  + Age greater than 60 may be associated with more significant decline in memory.
  + There is a clear short term memory detriment with 30/10.
  + Hippocampal avoidance may lead to [[improvements](#y9yq0t2ckhf)] in free delayed recall.

* **Meta-analysis** [[Auperin NEJM '99](https://www.nejm.org/doi/10.1056/NEJM199908123410703?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov)]: **Meta ± PCI** for pts in CR, only 13% ES.

PCI improves 3y OS by over 5% for those in CR, though some trials defined CR by CXR alone (did not image the brain).   
Unplanned subgroup of time between start of induction and randomization with trend towards less BM if PCI started < 4 mo.

Subsequently, Le Pechoux and Wolfson's QoL subset of this study demonstrated no benefit to doses >25/10.

* + 987 pts, **3y BM 60→ 30%** (59→ 33%), 3y OS 15→ 21%. RR death = 0.84.
    - In some trials, CR was defined by CXR!
  + Time between the start of induction and randomization < 4 / 4-6 / > 6 mo HR for brain mets of 0.3→ 0.5→ 0.7.
  + There was no difference in relative risk of death for differences in start of treatment.

* **RTOG 0212** [[Le Pechoux Lancet '09](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(09)70101-9/fulltext), [Ann Onc '11]](https://academic.oup.com/annonc/article/22/5/1154/178653): **25/10 vs. 36/18 vs. 36/24 BID** for pts in CR.  
  25/10 is the standard of care for PCI. There is more neurologic deterioration in doses higher than 25/10.
  + 720 pts LS-SCLC. All had pretreatment MRI or CT no more than 1 month before study entry.
  + No significant reduction in BM after higher dose, significant increase in mortality.
  + 2y BM ~25%. 2y OS 42→ 37% in higher dose groups likely due to increased CSM.
  + [Wolfson [IJROBP '11]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3024447/): Neurologic deterioration at 1y in at least one of the following regardless of brain mets: HVLT-recall, HVLT-recognition, HVLT-DR, COWAT, TMTA or TMTB.
    - Neurologic deterioration in 62→ 85→ 89%.

* **Netherlands** [[Belderbos ASTRO ‘19](https://www.eventscribe.com/2019/ASTRO/fsPopup.asp?Mode=presInfo&PresentationID=559273)]: Phase III. **PCI** (25/10) **± HA**.   
  There is no significant difference in the rate of brain mets with PCI. No patients developed a single brain met in the HA region. There appears to be no difference in neurocognitive decline with HA.
  + 168 patients. 30% Extensive stage. All patients had baseline MRIs. MFU 2y.
  + Only 13% developed brain metastasis. 70% of these asymptomatic and MRI detected, mostly at 4 mo, some at 1y.
  + There is no difference in HVLT-R at 4 mo, with a rate of ~30% dropping at least 5 points in both arms.
  + 8 mo HVLT-R dropping at least 5 points of ~34→ 26% (p=0.5).

* **Spanish PREMER** [[Rodriguez De Dios ASTRO ‘19](https://www.eventscribe.com/2019/ASTRO/fsPopup.asp?Mode=presInfo&PresentationID=559274)]: Phase III. **PCI** (25/10) **± HA**.  
  There is a significant decline in memory in the PCI group. The incidence of brain metastasis in the hippocampus is very low.
  + 118 patients. LS and ES. Primary: NCF at 3 mo assessed by Free and Cued Selective Reminding Test (memory).
    - RT: PRV = Hippocampus + 5mm.
  + D100 of 8.4 Gy, maximum dose 14.5 Gy.
  + 3 mo decline in free delayed recall of 22→ 5%.
  + 6 mo decline in free delayed recall of 33→ 7%.
  + 12 mo decline in free delayed recall of 19→ 4%.
  + 1y brain metastasis just over 20%. *Only 4 patients developed brain metastasis in the HA region.*
* **SAKK 15/12** [[Vees IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32142869)]: Phase II. **Thoracic CCRT at C2 of chemo + HA-PCI**.

The rate of no NCF decline at 6 and 12 mo after early HA-PCI does not appear to be better than sequential PCI without HA.

TBL [QS](http://www.quadshotnews.com/2020/03/hippocampal-distancing.html): In this phase 2 trial, HA-PCI during definitive thoracic chemoradiation for LS-SCLC did not seem to significantly reduce the rate of neurocognitive failure compared to historical controls of standard sequential PCI.

* + 38 pts. Primary: NCF at 6 mo after HA-PCI, assuming ≤ 30% of pts with no NCF decline as promising. MFU 1y.
    - NCF tests: HVLT-R, COWA, TMTA/B at baseline, 1.5 mo, 3 mo, 6 mo, 12 mo.
  + No NCF decline at 6 / 12 mo of 34→ 49%.
  + 1y BMFS 84%. 1y OS 88%.

* **NRG-CC003** [[NCT02635009](https://clinicaltrials.gov/ct2/show/NCT02635009)]: Phase II/III. **PCI** (25/10) **± HA**.
  + For both limited stage and extensive stage disease.
  + Phase II accrued→ Study held x1y for data analysis. Results not yet available.

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| **Extensive Stage: Clinical Pearls**  See [[What is the role of RT in the immunotherapy era](#snu066265ta7)?].   * ES (70%): 5y OS < 5% with MS 12 mo. * Palliative chemo-immunotherapy *without* chest consolidation is standard of care. * Rationale for RT in ES-SCLC is palliation, while consolidative or prophylactic RT remains controversial. * Symptomatic brain mets at presentation should receive palliative RT. * Extra-cranial sites of symptomatic disease may be reasonably treated with chemo or RT. * Non-symptomatic low volume brain mets should consider initiation of chemo or RT. * Standard of care is 4c of chemo with concurrent and maintenance immunotherapy (or up to 6c chemo alone).   Easy boards answer: CDDP 75 d1, Etoposide 100 d1-3 q3w x4c, add concurrent/adjuvant Durva for ES-SCLC (Atez: CarboE only). |

## [Extensive Stage](#_nruipiivq02s)

Thoracic RT with **10%** OS benefit (25% LC benefit), PCI with **10%** OS benefit (now "disproven" per [[Takahashi](#9gdi4pjk5ixd)]).

See [[Impower133](#a2sv4pgkksn3)] (Atezolizumab) and [[CASPIAN](#myzsvi6f3bt3)] (Durvalumab).

See [[What is the role of RT in the immunotherapy era](#snu066265ta7)?].

### [Role of RT in ES](#_x7eot2pqwmlq)

* **Jeremic** [[JCO '99]](http://ascopubs.org/doi/abs/10.1200/JCO.1999.17.7.2092?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): Single institution. CR distally and at least PR in chest after 3x chemo **± 54/36 BID with CE→ PCI**.  
  Improvement in overall survival with CCRT given after 3c of chemotherapy.
  + 210 pts. CDDP 50/Etop 50 x3c→ at least PR in chest, CR distally.
    - RT fields: (gross dz and ipsi hilum + 2 cm) + (mediastinum + 1 cm) + (bilateral SCN).
  + MS 11→ 17 mo. 3y OS 13→ 22%. 5y OS 4→ 9%.
  + Slight benefit to thoracic RT, but not enough to change in a lot of centers.

* **CREST** [[**Slotman** Lancet '15](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61085-0/fulltext), ['17](https://www.sciencedirect.com/science/article/pii/S0169500217302611?via%3Dihub)]: 4-6c chemo→ PR/CR→ **PCI** (dealers choice) **± Thoracic RT 30/10**.  
  Improvement in 2y OS (not primary endpoint) with consolidative RT delivered after completion of chemo and PCI.

OS significantly worse when liver and/or bone mets present.

There is insufficient data for patients in CR; it may be reasonable to observe.

* + 498 pts. ES, no brain mets or pleural involvement. 12% of patients had CR in the chest. MFU 2y.
    - Before chemo 50% of asx patients were screened, while 20% of asx patients were screened after chemo.
    - PTV = pre and post-chemo nodal stations (even in CR) + 1.5 cm margin.
      * 2D and 3D planning allowed. Lung V20 < 35%.
  + **Did not meet primary 1y OS** ~28→ 33% (p=0.06) **but 2y OS 3→ 13%**. 6m PFS 7→ 24%.
  + MS ~8m, but MS thoracic disease 12 mo, DM 7.5 mo, or both 8.3 mo.
    - This suggests LC (thoracic disease only) may translate to better OS.
  + Only the patients with residual chest disease (88%) appeared to benefit from thoracic RT [[Slotman Lancet '15](https://www.ncbi.nlm.nih.gov/pubmed/25890910)].
  + Intrathoracic progression alone 46→ 20%, but 36% had DM as first progression in thoracic RT arm.
  + Slotman NNT to save one life of 11, but still appears cost effective [QS](http://www.quadshotnews.com/2017/11/a-no-brainer-addition-to-pci.html).
  + Secondary analysis [[Slotman Lung Cancer '17](https://www.sciencedirect.com/science/article/pii/S0169500217302611?via%3Dihub)]: OS and PFS were significantly better in patients with 2 or fewer metastases. OS was significantly worse if the liver and/or bone mets present. Future studies on extrathoracic RT in ES-SCLC should focus on patients with 2 or fewer metastases.

### [Oligometastatic SCLC](#_mr2dodxoiote)

* **RTOG 0937** [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=11137)[, Gore JTO '17]:](https://www.jto.org/article/S1556-0864(17)30468-9/fulltext) Phase II. Up to 4 extracranial mets. **PCI** (25/10) **± thoracic/oligo RT** (45/15, 30/10).

Closed early at interim analysis due to G4/5 toxicity. Midway through, CREST (Slotman) demonstrated 2y OS benefit with thoracic RT therefore the control arm should have been PCI + consolidation to thorax ± residual metastatic disease.

Consolidation may reduce progression, but did not improve OS (underpowered).

Future studies on extrathoracic RT in ES-SCLC should focus on patients with 2 or fewer metastases.

* + 97 pts. ES-SCLC. 1-4 metastatic lesions. Requires CR or PR to initial chemotherapy. MFU 9 mo.
    - RT: > 45 Gy delivered in 70% of the PCI + RT arm. PCI delivered in 95% of patients.
    - Two-thirds of patients had 2-4 metastases. It is unclear how many had 1-2 metastases.
  + 1y OS ~60→ 51% (p=0.21). 12 mo rate of any progression 80→ 75%, 3 mo rate of any progression 53→ 15%.
* **FIRE-SCLC** [[Rusthoven JAMA Onc '20](https://pubmed.ncbi.nlm.nih.gov/32496550/)]: Multicenter cohort. No prior WBRT or PCI. **WBRT vs. SRS**.

The primary trade-offs associated with SRS without WBRT, including a shorter TTCNS progression without a decrease in overall survival, are similar to those observed in settings in which SRS is already established.

TBL QS: The authors conclude upfront SRS for SCLC brain mets is reasonable for “carefully-selected populations” (read: with good performance status and a single brain met).

* + 710 patients. 1994-2018 (88% were year 2000 or later). Median (IQR) brain mets was 2.5 (1-6).
  + MS 8.5 mo. Median TTCNS progression (MTTCNSP) 8 mo. Median CNSPFS 5 mo.
  + MS after SRS for 1 / 2-4 / 5-10 / 11+ lesions of 11→ 9→ 8→ 6 mo.
  + MTTCNSP after SRS for 1 / 2-4 / 5-10 / 11+ lesions of 12→ 7→ 6→ 5 mo.
  + Competing risk estimates of 1y LF of 7%, while 1y distant CNS failures of 42%.
  + Leptomeningeal progression in 11% with neurological mortality in 12%.
  + Propensity score-matched analysis demonstrated improved TTCNSP with WBRT, but not OS or CNSPFS.

### [PCI in Extensive Stage](#_mr2dodxoiote)

Takahashi recently demonstrated a suggested lack of OS benefit with PCI.

Optimal dose remains unresolved (though 25/10 preferred). Who cares though! Rate of extracranial progression is 90%.

* EORTC 08993 [[**Slotman** NEJM '07]](https://www.nejm.org/doi/10.1056/NEJMoa071780?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov) Chemo x4-6c→ SD/PR/CR→ **± 20/5 PCI** (most) or 30/10.   
  In the context of no asymptomatic brain imaging, PCI has an OS benefit at one year and will prevent progression to symptomatic disease. No thoracic RT was given in this study. There was no data on chemo delivered in this study. There was no restaging MRI/CT scan (unless patients were symptomatic). The PCI group was more likely to get chemo at progression. Half of the no PCI group did not get WBRT at progression. Also, 20/5 is used!

Is this *really* a PCI trial when we don’t know who had brain metastasis at baseline?

* + 286 pts. ES-SCLC randomized after "any response" to 4-6c of chemo. Interval from dx to PCI 4 mo.
    - RT varied, commonly 20/5 (most) vs. 30/10.
  + **1y symptomatic BM 40→ 15%**, MDFS 12→ 15 mo, MS 5.4→ 6.7 mo. **1y OS 13→ 27%**.
  + No effect on global QoL at 9mo.

* **Japan** [[**Takahashi** Lancet '17]](https://www.sciencedirect.com/science/article/pii/S1470204517302309?via%3Dihub): **± 25/10 with MRI at baseline**.

Suggestion of no improvement of OS with PCI, but no mention of thoracic RT throughout the paper! Why? 90% fail extracranially. Close MRI follow up required to replicate results, and there was a decreased incidence of MRI brain mets at each time point with PCI.

* + 224 pts with any response to chemo and no brain mets on MRI (CR in 15%). Primary endpoint OS.
    - MRI q3mo x1y, 18 mo and 24 mo.
    - Also, 60% of patients who had no PCI had therapeutic brain RT.
  + 1y BM 69→ 48%. Salvage RT for brain mets of 58→ 22%. MTT brain mets of 193→ 384 days.
  + MS ~13.7→ 11.6 mo (p=0.09).
  + Equivalent MMSE at baseline, 12mo and 24 mo.
* Consider enrollment on [[NRG CC003](#t1s96574976t)], which is investigating the role of hippocampal avoidance in 25/10 WBRT.

## 

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  Contouring   * See protocols for guidance. * Cardiac Contouring Atlas (Supplement) [[Duane RTO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5356506/)] * ARRO: [[Small Cell Lung Cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/ARROCaseSmallCell.pdf)].   Review Articles   * What is the role of RT for ES-SCLC in the immunotherapy era? [QS](http://www.quadshotnews.com/2019/07/chest-bump.html) [[Nesbit TLCR '19](http://tlcr.amegroups.com/article/view/28932)] [RoR](#snu066265ta7) * Start date of any treatment to End of RT (SER) [[De Ruysscher JCO '06]](http://ascopubs.org/doi/abs/10.1200/JCO.2005.02.9793?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): Aim for SER < 30 days! [RoR](#8g80j0b22nvp) * LS-SCLC: Is PCI Necessary? [[Farris PRO '19](https://www.sciencedirect.com/science/article/abs/pii/S1879850019301857)]: Retro. Obs vs. PCI. [RoR](#_6a2wqadfkp6a)   Society Guidelines   * ASCO/ACCP Guideline: [Treatment of Small-Cell Lung Cancer](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/9991) *September 8, 2015* [RoR](#nbv7mkaxnlnw) * ESMO Guidelines for Diagnosis, Treatment and Follow up [[Früh Ann Onc '13](https://www.esmo.org/guidelines/lung-and-chest-tumours/small-cell-lung-cancer)] [RoR](#nbv7mkaxnlnw) * ASTRO Guideline: RT for Small Cell Lung Cancer [[Simone PRO '20](https://www.ncbi.nlm.nih.gov/pubmed/32222430)] [RoR](#_nruipiivq02s)   Relevant Accessible Radiation Protocols   * LS-SCLC   + CONVERT / EORTC 8072 (Supplement 1) [[Salem JAMA Onc '18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6439849/)]: 45/30 BID vs. 66/33 with CE x4-6c. [RoR](#jgrlfoasvoc2) * ES-SCLC   + RTOG 0937 [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=11137)[]:](https://www.jto.org/article/S1556-0864(17)30468-9/fulltext) Phase II. Up to 4 extracranial mets. PCI (25/10) ± thoracic/oligo RT (45/15, 30/10). [RoR](#jgrlfoasvoc2)   Quality of Life/Toxicity   * CONVERT (Table 4) [[Faivre-Finn Lanc Onc '17](https://www.sciencedirect.com/science/article/pii/S1470204517303182?via%3Dihub), [Salem JAMA Onc '18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6439849/)]: 45/30 BID vs. 66/33 with CE x4-6c. [RoR](#g5ydzigdyk9u) * CREST (Table 2) [[Slotman Lancet '15](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61085-0/fulltext)]: 4-6c chemo→ PR/CR→ PCI (dealers choice) ± Thoracic RT 30/10. [RoR](#xm6erzs5c8vp) * RTOG 0212 PCI QoL [[Wolfson IJROBP '11](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3024447/)[]](https://academic.oup.com/annonc/article/22/5/1154/178653): 25/10 vs. 36/18 vs. 36/24 BID for pts in CR. [RoR](#rzv3trcpeyty) |

## [Treatment planning](#_nruipiivq02s)

See the Summary Box above.

What treatment volumes?

* Two RCTs look at **Pre vs. Post-chemo**:

1. SWOG [1979] used wide field vs. limited field 2D planning.
2. Chinese used 3D planning.
   * + No differences in relapse rates or toxicity if using post-CTX volume!

* Two trials looking at **ENI**:
  + If based on CT alone, then isolated nodal recurrence in 5-11%. If PET/CT and CT+, then only 3% isolated nodal recurrence [[De Ruysscher RTO '06](https://www.thegreenjournal.com/article/S0167-8140(06)00309-4/fulltext), [Van Loon IJROBP '10]](https://www.sciencedirect.com/science/article/pii/S0360301609006737?via%3Dihub).
  + These two prospective trials suggest that ENI is not req'd if PET/CT performed, but may be required in the absence of PET as isolated nodal relapse may be > 10%.
  + Older pts: Response rates same as younger pts a/w expense of increased pulmonary or hematologic toxicity.
* Volumes
  + Turrisi treated bilateral mediastinum. CONVERT and CALGB tends to prefer ipsi hilum and will only treat mediastinum and carina if involved. If non-PET based planning or no formal mediastinal interrogation, consider ENI.
  + [**Turrisi**](#ameifz489gnc): Pre-chemo gross tumor on CT and bilateral mediastinal and ipsi hilar lymph nodes. No uninvolved SCV. From thoracic inlet to 5 cm below carina or to a level including ipsi hilar structures, whichever was lower.
    - GTV: **Pre**-chemo GTV.
    - CTV: (GTV + 1.5 cm) + (ipsi hilum + bilat mediastinum + 0.8 cm).
    - AM and PM tx on-cord for w1, then AM dose on-cord and PM off-cord using obliques w2-3.
    - PCI given for all patients with a CR.
  + **CONVERT** [[Protocol](https://bmjopen.bmj.com/content/bmjopen/suppl/2016/01/20/bmjopen-2015-009849.DC1/bmjopen-2015-009849supp4.pdf)]:
    - GTV: Includes nodes > 1 cm short axis or "include PET positive nodes"
    - CTV: GTV + 5 mm with manual adjustments. No prophylactic nodal irradiation*.*
    - PTV: CTV + 8 mm radial and 1 cm CC.
  + [**CALGB 30610/RTOG 0538**](#g5ydzigdyk9u)[[NCT00632853](https://clinicaltrials.gov/ct2/show/NCT00632853)]: 3D (AP/PA, obliques) or IMRT. ITV utilized.
    - GTV: **Post**-chemo GTV + initially involved nodal groups.
      * Includes nodes > 1 cm short axis or pretreatment PET SUV > 3.
    - CTV: ITV ± ipsi hilum + involved subcarinal/bilat mediastinal nodes. No ENI of mediastinum and SCV.
      * CTVp = GTVp + 8mm, CTVn = GTVn + 5mm.
      * OK to include **pre**-chemo volume in CTV.
    - PTV: CTV + 5mm if daily set up imaging. If no 4D or daily imaging, use 1.5 cm CC and 1 cm radial.
* “PCI should be given to all SCLC patients with response to chemo unless poor PS or impaired neurocog function”
  + Give 8-12 wks post-chemo; for pts with CR/near CR [[Auperin](#2iz1ptxc86ic)].
* PTV V93% > 99%. D2cc ≤ 120%.
* Doses
  + LS-SCLC: 45 Gy at 1.5 BID, or 66-70 Gy QD.
  + PCI 25/10.
  + BM: 30-37.5 Gy in 10-15 fx.

## [Follow up](#_nruipiivq02s)

* CT chest q6 mo x2y, then annually. PET/CT should not be used as a surveillance tool [[ASCO Guidelines '19](#x0pt4mmhjq2i)].
* MRI brain q3 mo during year 1, then q6 mo during year 2 [[ASCO Guidelines '19](#x0pt4mmhjq2i)].
* **Molecular subtypes and clinical outcomes to initial systemic treatment in SCLC** [[Lai ASCO '20](https://meetinglibrary.asco.org/record/184549/abstract)]:

Differential expression of the transcription regulators ASCL1 and NeuroD1 can be used to define molecular subtypes of SCLC. Molecular subtypes defined by ASCL1 and NeuroD1 may predict patient outcomes.

* + 281 patients with SCLC. IHC performed to assess ASCL1 and NeuroD1 expression.
  + 6 mo PFS for A-N- (n=4) / A-N+ or A+N- (n=15) / A+N+ of 25→ 60→ 55%.
* H&P, CT C/A

## 

## [Future Directions](#_nruipiivq02s)

See NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)].

* See [[**NRG-LU005**](#9m1slc23c4pm)]: Phase II/III. **CCRT** (66/33 or 45/30 BID) **± concurrent/adjuvant Atezolizumab** q3w up to 1y.
  + LS-SCLC. Tx, T1-4 N0-3 M0. PCI recommended for CR or near CR.
  + Concurrent CDDP/Etoposide q3w x4c. RT started with C2 of chemotherapy.
  + Tumor and involved lymph nodes (> 1 cm SAD) or SUV > 3 at time of planning CT.
* **NRG-LU007** [Not open as of early 2020]: Phase II/III. **Chemo + Atez ± RT**.

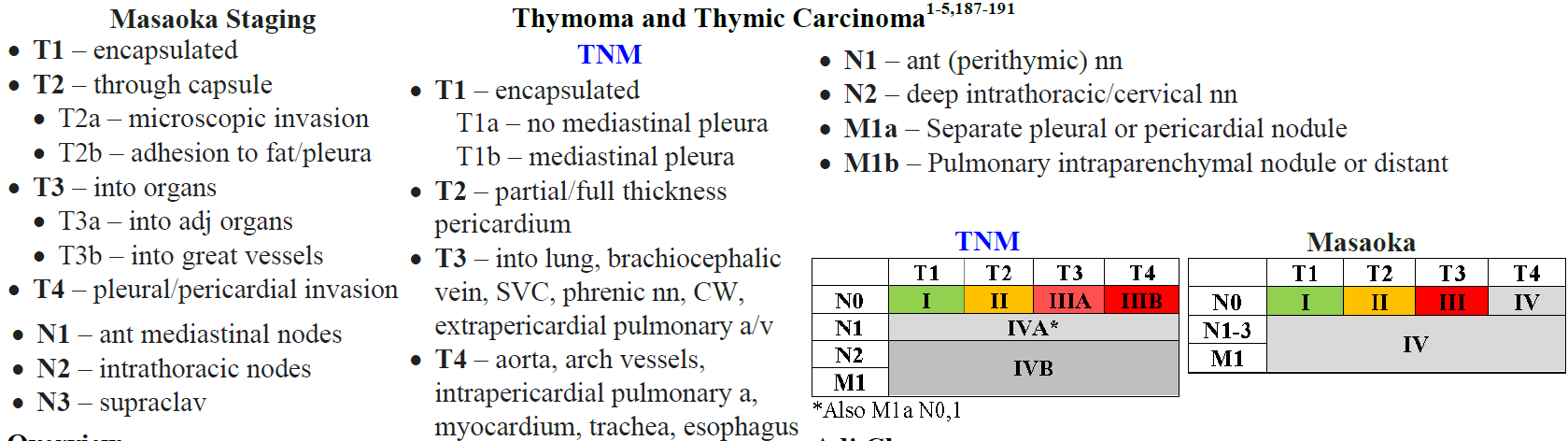
See [[What is the role of RT in the immunotherapy era](#snu066265ta7)?].

* + ES-SCLC.
* See [[**CALGB 30610/RTOG 0538**](#ai573yweolpf)]: **70/35 vs. 45/30 BID** vs. 28.8/16→ BID RT to 61.2 (RTOG 0239 - closed).

Completed accrual January 2020!

* + 70/35 (7 weeks) thoracic RT at 3c EP (first two topotecan and paclitaxel).
    - RTOG 02-39 dose escalation dropped at planned interim analysis in 2017 to facilitate accrual.
    - Limited ENI, as single institution data suggests ~2-3% isolated nodal failure rate without ENI.
    - CDDP 80 d1, etoposide 120 d1-3 q3w x4c.
    - PCI offered to all pts with CR or near CR, given 3-6w after completion of all 4 cycles of chemotherapy.
  + MS 20 mo, 2y OS 35%.
* **S1827** [[NCT04155034](https://clinicaltrials.gov/ct2/show/NCT04155034)]: Phase III. **MRI brain surveillance vs. PCI**.
  + LS or ES-SCLC with no evidence of progression in the opinion of the treating investigator.
  + Thoracic RT or surgery required for limited stage.
  + ES-SCLC does not mandate thoracic consolidation, even for partial response…

# [Thymoma, Thymic Carcinoma](#_6sfwza45y5km)



T2A micro, T2B macro through capsule.

Stage IV: Any lymph nodes.

Masaoka IV is pericardial involvement, while TNM pericardial involvement is II.

ARRO: [[Thymoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Thymoma.pdf)].

* 0.2-1.5 cases per million person-years in the USA. Age = 40-60y.
* 33-50% diagnosed incidentally by CXR.
* Thymoma is **20%** of mediastinal tumors and **50%** of anterior mediastinal masses in adults.
  + **Anterior mediastinal DDx**: Lymphoma, Teratoma, Thymoma, Thyroid (ectopic goiter), carcinoid, GCT.
  + < 1% are thymic carcinoma, with 5y OS 60%.
* Often associated with immune and non-immune mediated paraneoplastic syndromes:
  + **Myasthenia gravis**: **Up to 50% of pts with thymoma have MG**. All MG with abnormal thymus should get thymectomy.
    - 80% of patients with MG have thymic abnormalities, of which **15%** are thymomas.
      * More likely to have MG if thymoma is diagnosed, while only 15% of those w MG get thymoma.
    - Always check serum anti-acetylcholine receptor antibodies to reduce risk of respiratory failure at surgery.
      * 50% need acetylcholine inhibition preop (neostigmine or pyridostigmine).
      * Tensilon test (edrophonium): Ach Esterase inhibitor. If that helps, diagnostic.
  + **Pure red cell aplasia**: 5-10% of pts with thymoma will have PRCA. 50% of pts with PRCA have thymoma.
  + **Hypogammaglobulinemia**: 3-6% of pts w thymoma will have this (e.g. Good's syndrome).
* **Structure of thymus**: **Capsule, cortex, and medulla**.
  + Epithelial cells, epithelioreticular cells (from Hassall's corpuscles), myoid cells, thymocytes, B-lymphocytes.
  + **Medulla**: Coarse network of reticular cells, less lymphoid cells but more **mature** T cells, and Hassall's corpuscles which are concentric layered whorls of epithelial cells that increase in number throughout life.
  + **Cortex**: Early thymocytes, TCR gene rearrangement and positive selection occurs here.
* **WHO Histologic Classification** (10y DFS[[1]](https://www.sciencedirect.com/science/article/pii/S0169500205002503?via%3Dihub)). 10y DFS for Masaoka 94→ 88→ 66% for I/II/III.
  + **A (95%)**: Medullary thymoma. *Mature T-cells.*
    - Bland, **spindle shaped** at least focally with paucity/absence of TdT+.
  + **AB (90%)**: Mixed thymoma.
    - Same but abundance of TdT+.
  + **B1 (85%)**: Predominantly cortical thymoma. *Immature T cells.*
    - Thymus like: lots of TdT+, medullary islands, paucity of dendritic cells.
  + **B2 (71%)**: Cortical thymoma.
    - More polygonal/dendritic epithelial cells.
  + **B3 (40%)**: Well-differentiated thymoma (immature T-cells crowded out).
    - Sheets of polygonal, atypical cells, rare intercellular bridges, paucity/absence of TdT+.
  + **C**: Thymic carcinoma. < 1% of all thymic tumors. 30% DM. 25% long term survival.
* **Workup**
  + Symptoms: Weakness, fatigue, dysphagia.
  + Labs: β hCG, AFP, LDH.
  + Chest CT with contrast, PET/CT as indicated.
  + PFTs.
  + MRI chest as indicated (To determine cyst vs. thymoma).
    - If thymoma is suspected (well defined mass, no nodes involved, negative tumor markers, and **no continuity with thyroid**), then resect without biopsy.
      * At the time of surgery, check for pleural mets.
    - If unresectable, core needle or open biopsy (Don't violate pleural space).
* **Surgery**: Standard of care. Median sternotomy typically, though partial or total pneumonectomy may be required.
  + Avoid resection of both phrenic nerves. Treat MG prior to surgery w AChE inhibitors.
  + **Fox Chase** [[Curran JCO '88](http://ascopubs.org/doi/pdf/10.1200/JCO.1988.6.11.1722)]: **Thymoma s/p surgery**.  
    R0 resections alone appear inadequate for at least microscopic invasion through the capsule.
    - Retro. 103 pts.
    - No recurrences among stage I, R0 without RT.
    - No recurrences for R0 stage II/III who received RT, but 53% local recurrence without RT.
    - 21% recurrence after R2 or biopsy, even when RT given.
  + **Japan** [[Kondo ATS '03](https://www.sciencedirect.com/science/article/pii/S0003497503005551)]: Retro. 1,320 pts. **Stage I→ Obs**. **Stage II/III→ PORT**. **Stage IV→ RT or CTX**.

R0 resections most important, adjuvant therapy may not benefit totally resected patients.

* + - 5y OS for stage III-IV R0 / R1-2 / inoperable of 93→ 64→ 36%.
    - 5y OS for thymic carcinoma for R0 / R1-2 / inoperable of 67→ 30→ 24%.
    - PORT did not affect LR for R0 stage II-III.
    - No benefit w PORT or adjuvant chemo for R0 stage III-IV.
  + **Japan** [Utsumi Cancer '09]: Retro. 324 pts, **R0 thymoma ± PORT** (n=134).
    - 10y DSS ~93%.
    - 10y OS for no PORT in stage I-II and WHO cell type A, AB and B1 of 100%.
    - PORT appears to have no benefit for stage III-IV and WHO B2/B3.
  + **ITMIG** [[Rimner JTO '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5257334/)]: Retro. 1,263 pts, **Stage II-III R0 thymoma ± PORT** (55%). Stage II 70%. CTX 15%.
    - WHO A/AB 30%, B1-B3 70%.
    - 5y OS 90→ 95%, 10y OS 79→ 86%, benefit remains significant for Stage II subgroup.
  + **Japan** [[Haniuda Ann Surg '96](https://oce.ovid.com/article/00000658-199608000-00016/HTML)]: Retro. 80 pts **Stage II R0 thymoma ± PORT**.  
    PORT is effective in macroscopic adhesion to pleura but not microscopic invasion.
    - No recurrences of Stage I thymoma.
    - LR for macroscopic adherence to pleura but no microscopic adherence of 36→ 0%.
    - LR for microscopic pleural invasion 40→ 30% (6/15 and 3/10 pts, respectively).
      * Pleural dissemination observed in 12/13 pts. *PORT does not control pleural dissemination.*
* Chemosensitive with ~66% at least PR, of those 33% CR.
  + Meta of advanced thymic epithelials [[Hamaji Ann Thorac Surg '15]](https://www.sciencedirect.com/science/article/pii/S0003497515000314?via%3Dihub): 12 studies, 266 pts. **NAC + surgery**.
    - At least PR 59%. R0 73%. 5y OS 87%, 10y OS 76%.
* **Chemotherapy** (**Thymic carcinoma**): **Carboplatin**/**Paclitaxel**. *Cisplatin/Etoposide for CCRT.*

See [[S1701](#_wx3ni5l3fmen)] in the Future Directions section.

* **Chemotherapy** (**Thymoma**): Typically **CAP**: Cyclophosphamide, Adriamycin, Cisplatin. *Cisplatin/Etoposide for CCRT.* 
  + **INT** [[Loehrer JCO '97]](http://ascopubs.org/doi/abs/10.1200/JCO.1997.15.9.3093?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): 23 pts. 1983-1995. Unresectable thymoma. **Induction CAP→ PORT** if not PD.
    - 70% PR/CR w 23% CR (n=5). 54 Gy RT converted 80% of pts with SD to PR/CR.
      * Chemo: CDDP, doxorubicin, cyclophosphamide x2-4c q3w
    - 5y FFF 54%. 5y OS 53%, MS 93 mo. MTTF 93 mo.
  + [**MDACC** [Kim Lung Ca '04]](https://www.sciencedirect.com/science/article/pii/S0169500203006263?via%3Dihub): Phase II. 3c **Induction CAP→ resect→ PORT→ 3c consolidation chemo**.
    - Initially unresectable. 22 pts. Induction chemo CR/PR 77%.
      * Cyclophosphamide, doxorubicin, CDDP, prednisone q3-4w.
      * RT to 50 Gy for R0 and 60 Gy for T1 or < 80% tumor necrosis.
    - 76% of pts underwent R0 resection. 5y OS 95%, 7y OS 79%.
* **IMRT CCRT** (Methods) [[Fan IJROBP '20](https://www.redjournal.org/article/S0360-3016(20)30063-8/fulltext)]: Phase II. **60/30 + CE** x2c→ CE x2c.

TBL [QS](http://www.quadshotnews.com/2020/02/bonus-round.html): For the superstars out there who make it to an unresectable thymic tumor case on oral boards, here is a phase 2 trial demonstrating an impressive ORR of 86% with 2 Gy x 30 = 60 Gy using IMRT concurrent to CE.

* + 56 pts. 2011-2018. Limited advanced unresectable thymic epithelial tumors (thymoma/thymic carcinoma). MFU 4y.
    - CCRT: CDDP 25 + Etoposide 75 d1-3, d29-31.
  + ORR 86%.
  + PFS at 1 / 2 / 5y of 66→ 48→ 30%.
  + OS at 1 / 2 / 5y of 91→ 76→ 56%.

## 

## [Treatment planning](#_smffiejkpron)

ARRO: [[Thymoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Thymoma.pdf)]. AVARO [[Normal Thorax Anatomy](http://econtour.org/cases/89)], [[Thoracic nodal levels](http://econtour.org/cases/88)]

RT definitions and reporting guidelines for thymic malignancies [[Gomez JTO '11](https://www.ncbi.nlm.nih.gov/pubmed/21847057)]

IMRT CCRT (Methods) [QS](http://www.quadshotnews.com/2020/02/bonus-round.html) [[Fan IJROBP '20](https://www.redjournal.org/article/S0360-3016(20)30063-8/fulltext)]: Phase II. Thymic Epithelial Tumors. 60/30 + CE x2c→ CE x2c.

* Adjuvant RT: No prospective data.
* **Thymoma**
  + **R0 stage I**: Obs.
    - R0 resection is the mainstay of treatment. 40% will recur usually around 4y, but late recurrences >10y possible.
  + **R0 stage II-IV**: Consider PORT **45-50 Gy** for < 1 mm, gross fibrous adhesions to pleura, or B3 [[Wright CROH '08](https://www.sciencedirect.com/science/article/pii/S1040842807000819)]
    - Stage II: RT reduces LR from 30→ 10%.
    - Stage III: RT reduces LR from >50→ < 25%, OS benefit.
  + **R1**: Obs vs. Adj RT **54 Gy**.
  + **R2**: Adj RT **60 Gy** ± chemo.
  + Unresectable: CAP chemotherapy alone acceptable.
* **Thymic carcinoma**
  + **R0 all stages**→ adj RT.
  + **R1**→ adj RT ± chemo.
  + **R2**→ adj RT and chemo.
* May boost up to **70 Gy** for unresectable.

## [Follow up](#_smffiejkpron)

* 5y OS for I/II/III/IV of 95→ 85→ 70→ 50%.
* CT q6m x2 years, then annually.
* Follow for at least 5-10y for thymic carcinoma and 10y for thymoma. Late recurrences occur.

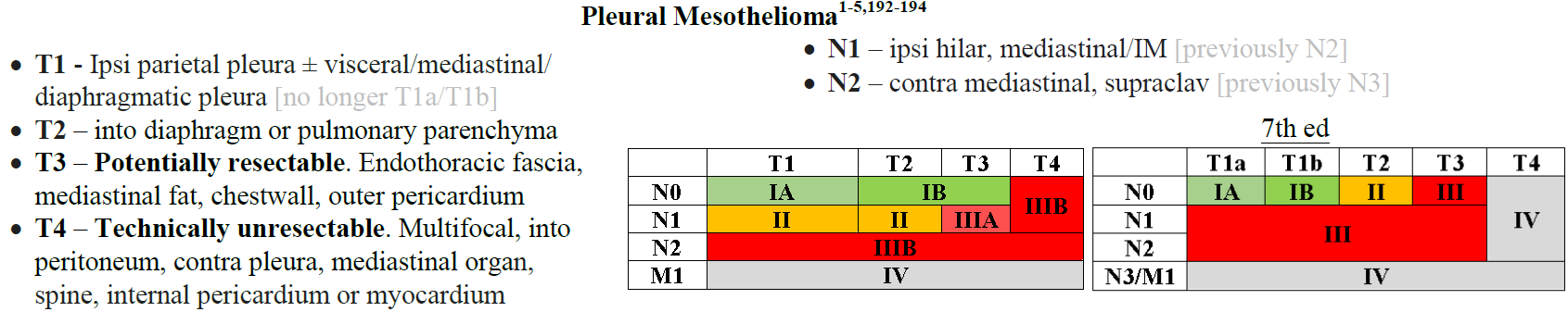
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## Future Directions

See NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)].

* **S1701** [[NCT03694002](https://clinicaltrials.gov/ct2/show/NCT03694002)]: Phase II. **CarboP ± Ramucirumab**.
  + Thymic carcinoma. Unresectable, locally advanced, recurrent, or metastatic.
  + Patients cannot be candidates for curative RT, but may have received palliative RT.

# [Pleural Mesothelioma](#_6sfwza45y5km)



Regional nodes: IMN, intrathoracic, scalene, supraclav

T2: Diaphragm or lung parenchyma (resectable with patch on diaphragm)

T3: Mediastinal fat, CW, outer heart.

T4: Multifocal, into peritoneum, spine, myocardium.

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| **ASCO Guideline:** [**Treatment of Malignant Pleural Mesothelioma**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/29376) *January 18, 2018*   * Prophylactic irradiation of intervention tracts generally not offered. * Give RT to tract if histologically positive. * 8/1, 20/5, and 30/10 are reasonable palliative regimens. * Consider Hemithoracic RT after non-lung sparing surgery (e.g. EPP). * Consider Hemithoracic IMRT after lung-sparing cytoreductive surgery (e.g. P/D or EPD), but toxic. Do on trial! * Do NOT offer NART if lung-sparing surgery is planned, but may be done if EPP and on clinical trial. |

* 2-3k cases per year in the US.
* **Asbestos exposure** 90% of the time. Lifetime risk of asbestos workers up to 10%. Latency of 20-40y.
* **10% seeding of the biopsy tract**, and the tract should be excised at the time of surgery.
  + **Prophylactic tract RT**: usually **7 Gy x 3**, but **no longer favored** [[SMART trial: Clive Lanc Onc '16](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30095-X/fulltext)]. Many institutions rely on surgeons' clinical concern or the length of time a drain has been in place to guide ppx tract RT, or will consider for epithelioid histology or pts who did not receive chemo. Usually ≤ 15% will recur in the biopsy tract.
  + Bayman [[JCO '19](https://ascopubs.org/doi/10.1200/JCO.18.01678)]: 6 mo CW mets for ± 21/3 ppx tract RT of ~10→ 6% (p=0.44).
* **MS 9-17 mo**. May be up to **34 mo** for stage I/II for surgery of choice (most EPP)→ 54 Gy hemithoracic PORT [[1](https://www.sciencedirect.com/science/article/pii/S0022522301367491?via%3Dihub)].
  + Same study with 10 mo OS for stage III/IV disease.
  + Of those who undergo EPP and adjuvant RT, DM is predominant site of progression (not LRF).
  + Trimodality therapy for epithelioid, R0/N0 with 5y OS as high as 50%.
* Can arise from the pleura (80%), peritoneum, pericardium and tunica vaginalis (outpouching of peritoneum).
* **Histology** is important!
  + Epithelioid (60%) does best. Biphasic middle ground, Sarcomatoid does worst (don't even try surgery).
    - Per NCCN: **Only operable if stage I-III epithelial histology**.
  + Often confused with adenocarcinoma.
    - Pleural mesothelioma + for calretinin and WT1, while AC is CEA and TTF-1 positive.
* **Surgery**
  + < 5% are surgically resectable at diagnosis.
  + Require post op FEV > 30%, 1L.
  + **Pleurectomy-decortication (P/D)**: Perioperative mortality of ~2%, but only for T1 tumors confined to the pleura.
    - Radial pleurectomy is removal of pleura and gross tumor (note: decortication is palliative).
    - **Use IMRT after P/D due to high reported toxicity**.
  + **Extrapleural pneumonectomy (EPP)**: Perioperative mortality 4-30%.
    - En bloc resection of entire pleura, lung, diaphragm, pericardium.
    - **No randomized data to support adjuvant RT after EPP**.
  + **Radical pleurectomy**: Becoming more common. Adjuvant RT should be offered only in clinical trial setting.
* **Unresectable disease**: Typically systemic chemotherapy alone.
  + The addition of **pemetrexed to cisplatin** improved OS for malignant pleural effusion.
    - Adding bevacizumab may add 3 months of survival.
* **Workup**:
  + CT chest with contrast, thoracentesis, pleural biopsy (**thoracoscopic biopsy** preferred over open).
    - Cytology from pleural effusion low yield for dx (only ~25%). If symptomatic, perform thoracentesis.
    - Be sure to biopsy the contralateral side if imaging findings are suspicious (not operable candidate).
    - If thoracoscopic or open biopsy cannot be done, then core needle biopsy.
    - Pleural mesothelioma + for calretinin, keratins 5/6, WT1. *While AC is CEA and TTF-1 positive.*
  + Consider MRI C/A to look into diaphragm invasion.
  + Consider VATS and/or laparoscopy if suspicion of contralateral or peritoneal disease.
  + Renal scan: Check contralateral renal function in case RT port encompasses the kidney.
* **MDACC** [[Rice IJROBP '07]](https://www.sciencedirect.com/science/article/pii/S0360301607005056?via%3Dihub): Retro. 63 pts. **EPP and IMRT**.
  + Pulmonary related death (PRD) and non-cancer related death within 6 mo of IMRT.
  + PRD 9.5%.
  + MVA: **Lung V20 ± 7%** with 42x increased risk of PRD than those with lower V20.
    - After EPP, V20 < 20% still w 50% chance of fatal pneumonitis. *Goal V20 < 7%.*
    - MLD 8.5 Gy w no RP.
* **SAKK 17/04** (Methods) [[Stahel Lancet Onc '15]](https://www.sciencedirect.com/science/article/pii/S1470204515002089?via%3Dihub): Phase II. **NAC→ EPP ± 55.9 Gy** (for R0).   
  No routine role for hemithoracic RT after EPP.
  + 52 pts with CR (34%) of 151 pts (75% had EPP). T1-3, N0-2 M0.
    - NAC: CDDP 75 and pemetrexed 500 q3w x3c.
    - RT: entire hemithorax, thoracotomy channel, and mediastinal LNs if positive or violated surgically.
  + R0 resection in 64% of patients
  + MLRRFS ~7.6→ 9.4 mo.

* **IMPRINT** (Methods) [[Rimner JCO '16](https://www.ncbi.nlm.nih.gov/pubmed/27325859)]: Phase II. **NAC→ P/D→ 50.4/28**.

Hemithoracic IMRT is safe and has an acceptable rate of RP. Impetus for [[NRG-LU006](#_cpbqoifbflcb)].

* + 45 pts enrolled. 18 not evaluable, 9 of whom progressed prior to RT. MFU nearly 2y.
    - Pemetrexed + cisplatin or carboplatin.
    - Lung V20 < 37-40%. Contra lung V20 < 7%.
  + 8 patients underwent P/D or extended P/D. 13 underwent partial P/D.
  + 27 patients started IMPRINT. Median 46.8 Gy.
  + G2-3 RP in 30% (n=8), all recovered after corticosteroids.
  + MPFS 12 mo. MS 24 mo.
  + 2y OS for unresectable / resectable of 25→ 59%.

## [Toxicity](#_5m4o063lxb43)

* **Contra Lung V20 ± 7%** with 42x increased risk of PRD than those with lower V20 [[Rice IJROBP '07]](https://www.sciencedirect.com/science/article/pii/S0360301607005056?via%3Dihub).
  + After EPP, V20 < 20% still with 50% chance of fatal pneumonitis. *Goal V20 < 7%.*
  + Contra lung V20 < 7%.
* Kidney V18 < 50%, V15 < 15%, V20 < 30%.
* Heart V45 < 30%, V50 < 20%.
* **Pleurectomy-decortication (P/D)**: Perioperative mortality of ~2%, but only for T1 tumors confined to the pleura.
* **Extrapleural pneumonectomy (EPP)**: Perioperative mortality 4-30%.

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  AVARO [[Normal Thorax Anatomy](http://econtour.org/cases/89)], [[Thoracic nodal levels](http://econtour.org/cases/88)]  Society Guidelines   * ASCO Guideline: [Treatment of Malignant Pleural Mesothelioma](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/thoracic-cancer#/29376) *January 18, 2018*   Relevant Accessible Protocols   * SAKK 17/04 (Methods) [[Stahel Lancet Onc '15]](https://www.sciencedirect.com/science/article/pii/S1470204515002089?via%3Dihub): Phase II. Mesothelioma. NAC→ EPP ± 55.9 Gy (for R0). * IMPRINT (Methods) [[Rimner JCO '16](https://www.ncbi.nlm.nih.gov/pubmed/27325859)]: Phase II. Mesothelioma. NAC→ P/D→ 50.4/28.   Quality of Life/Toxicity   * Mesothelioma. Contra Lung V20 ± 7%with 42x increased risk of PRD than those with lower V20 [[Rice IJROBP '07]](https://www.sciencedirect.com/science/article/pii/S0360301607005056?via%3Dihub). |

## [Treatment planning](#_5m4o063lxb43)

* Induction chemo (pemetrexed and CDDP or carboplatin)→ restage→ surgical exploration.
  + **If resectable**:
    - **EPP→ hemithoracic** RT
    - **P/D→ Observe** vs. RT.
  + **If unresectable**: Chemotherapy alone.
* **Sarcomatoid or mixed or stage IV**: Obs vs. chemo vs. best supportive care. *Never surgery for sarcomatoid.*
* Per NCCN: RT only for PS 0-1, good pulmonary fxn (no supplemental O2), good contra renal function, absence of DM.
  + Per NCCN: Only operable if stage I-III epithelial histology.
* **No randomized data to support adjuvant RT after EPP**. **Use IMRT after P/D due to high reported toxicity**.
  + After EPP, contralateral lung dose constraints:
    - V20 < 20% still with 50% chance of fatal pneumonitis. *Goal V20 < 7%.*
    - MLD 8.5 Gy with no RP.
* **3D technique**
  + Supine with arms akimbo.
  + AP/PA covers the entire hemithorax T1→ L2.
    - Medial = contra VB, add 1.5 cm beyond contra VB if mediastinum is involved.
  + Day 1: Block liver, stomach and kidney.
    - Block heart/humerus after **19.8 Gy** and cord after **41.4 Gy** by moving medial border to ipsi side of VB.
    - **Electron field patch** to supplement dose to pleural space under block (usually 153 cGy per day, as it is assumed ~15% of photon field dose is delivered through scatter).
  + Bolus scars, biopsy, and drain sites.
* **IMRT technique after EPP** (50-54 R0 EPP, 54-60 SM+).
  + CTV: Sup border 5 mm sup to most sup surgically violated space
  + Ant, post, lat margins 5 mm beyond the inside of the thorax or skin if near a surgically violated space.
  + Posteromedial margin is ipsi mediastinum and the subcarinal areas 5 mm medial to the most medial surgical clips.
  + Inf margin is 5 mm inferior to the most inferior surgical clips if left, or per pre op imaging.
  + bCTV: Areas at very high risk for residual disease or positive margins.
  + PTV = CTV + 0.5-1 cm (except into heart).
* **PORT to 54 Gy**. Can boost R2 to 60 Gy if OARs can tolerate.
  + May reduce dose to spare toxicity: must use a minimum of 40 Gy per NCCN.

## [Future Directions](#_5m4o063lxb43)

See NCTN Trial Portfolios by Disease Site: [[Thorax](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Thoracic_Trials.pdf)].

* **S1619** [[NCT03228537](https://clinicaltrials.gov/ct2/show/NCT03228537)]: Phase I. **Neoadjuvant CDDP/Pemetrexed + Atez→ Surgery→ Maintenance Atezolizumab**.
  + Newly diagnosed, stage I-III, resectable (sarcomatoid excluded).
  + PORT mandated for EPP, while not allowed for P/D.
* **NRG-LU006** [[NCT04158141](https://clinicaltrials.gov/ct2/show/NCT04158141)]: Phase III. **P/D + Chemotherapy ± adjuvant hemithoracic IMRT** [[IMPRINT](#9u9p6gsewhdn)].
  + Stage I-IIIA, resectable (sarcomatoid excluded).

# Benign

## Ventricular Tachycardia

* **Noninvasive Cardiac RT for Ablation of Ventricular Tachycardia** [[Cuculich NEJM '17](https://www.nejm.org/doi/full/10.1056/NEJMoa1613773), [Robinson IJROBP '19](https://www.sciencedirect.com/science/article/pii/S0360301619336673?via%3Dihub)]: **24/1**.  
   EPS guided cardiac radioablation is highly effective.
  + 5 pts w HR, refractory VTac. Rx to arrhythmogenic scar region.
    - MRI and SPECT used to ID the arrhythmogenic area.
  + After 6 weeks, the number of VT events dropped by 99.9% with minimal acute toxicity.
  + [[Robinson IJROBP '19](https://www.sciencedirect.com/science/article/pii/S0360301619336673?via%3Dihub)]: Phase I/II. **25/1**.
    - 19 patients. MFU 2y.
    - 6 mo safety profile with 11% serious adverse events.
    - OS at 6 mo / 1y / 2y of 89→ 72→ 58%.
    - 94% reduction in VT episodes.
    - Toxicity: 1 pericarditis and 1 gastropericardial fistula.

## Coronary Restenosis

* **Meta** [[Benjo '15](https://onlinelibrary.wiley.com/doi/full/10.1002/ccd.25998)]: **Vascular BT vs. DES in treatment of in-stent restenosis**.
* Intravascular BT. Sr-90 common (pure β-), also I-125, P-32, Ir-192.
* Rx 15-20/1 to 2 mm depth, 5 cm active length.
* Restenosis ± RT 50→ 15-20%.
* DES (paclitaxel, sirolimus) have better outcomes, but intravascular BT may be an option after failure of DES

1