Evidence Based Radiation Oncology Fact Sheets

Non-Small Cell Lung Cancer 2023

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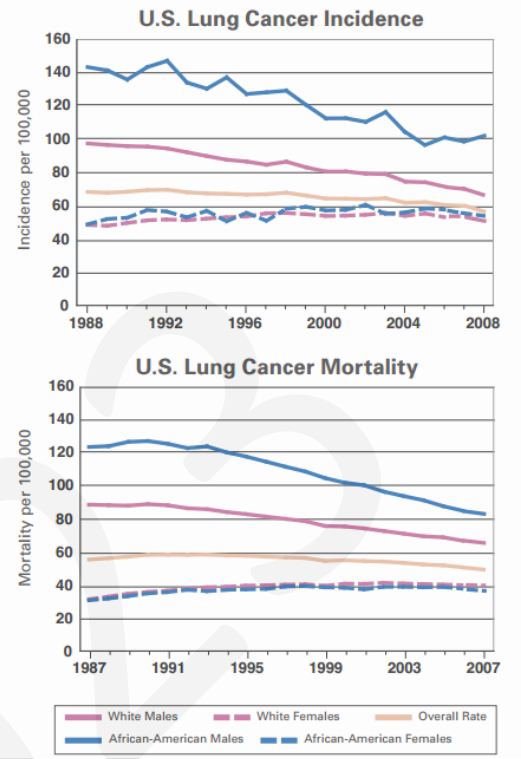
Overview:

Epidemiology[1]

- Lung cancer is the leading cause of cancer death for men and women worldwide.
- Estimated that 127,070 deaths (67,160 men and 59,910 women) from this disease will occur in the United States in 2023.
- In 2020, an estimated 1,796,144 people died worldwide from the disease.
- The 5-year relative survival rate for **all types of lung cancer** in the United States is 23%. For NSCLC, the 5-year relative survival rate is 28%.
- 5-year relative survival rate for NSCLC in women in the United States is 33%.
- 5-year relative survival rate for NSCLC in men is 23%.



Pathology

- Adenocarcinoma - 40% (more common in those that do not smoke)
  - Adenocarcinomas have a worse prognosis stage-for-stage.
  - Bronchoalveolar is a subtype of adenocarcinoma.
  - Arises from type II pneumocytes, is least associated with smoking.
- Squamous cell carcinoma - 30%
  - More common in smokers
- Small cell carcinoma - 15%
  - Smokers 85%, non-smokers 15%[2]
- Large cell – 13%
- Other: Neuroendocrine (carcinoid).

Risk factors

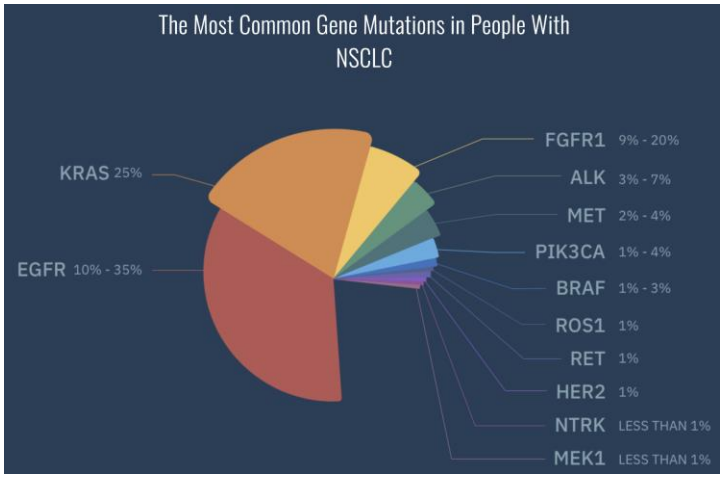
- Smoking, radon, asbestos, Fam Hx, Pulm fibrosis, occupational (silica, cadmium, arsenic, beryllium, diesel exhaust, coal soot).

Genetics

- > 95% of clinically relevant mutations found in ACs.
- EGFR sensitive to AGE DO (afatinib, gefitinib, erlotinib) (Osimertinib Dacomitinib)
- ALK ABC (alectinib, brigatinib, ceritinib/crizotinib). Loratinib.
  A FAT (afat..) ALEC (alectinib)
- ROS-1 Crizotinib.
- BRAF V600E Vermuafenib
- MET (notorious for causing resistance to EGFR-TKIs) Tepotinib, Crizotinib, savolitinib, capmatinib
- RET Cabozantinib, selpercatinib
- PD1 Pembrolizumab Nivo (for young women, non-smokers)

BTW, Nivolumab and pembrolizumab (PD-1 inhibitors), and atezolizumab, durvalumab and avelumab (PD-L1 inhibitors).

SUBSET: Asian Female Non-smoker
Think: Adenocarcinoma with EGFR mutation (63%) cases. All other Δ ALK, KRAS, PIK3CA, ERBB2, BRAF, ROS1, and RET (1-7%).
Thus, 79% of lung adenocarcinomas from never-smoker females harbored well-known oncogenic mutations.
∴ ↑ treatment response rates to EGFR-TKIs (such as gefitinib and erlotinib).
These women could also have EML4-ALK Δ (but this is MUTUALLY EXCLUSIVE vs. EGFR Δ).



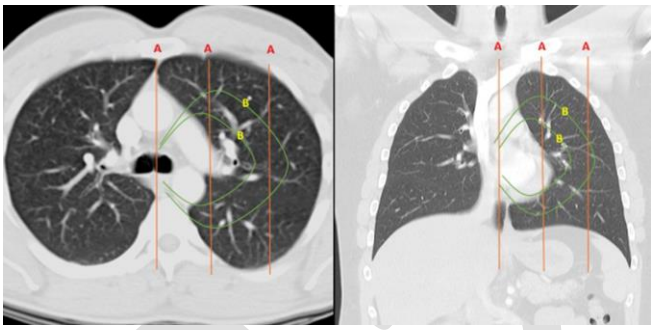
[1] https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8968543/

Central vs. Peripheral

Major Definitions:

NCCN: Methods to delineate the thirds of the hemithorax: A lines (straight lines in sagittal plane) and B lines (concentric lines arising from hilum)

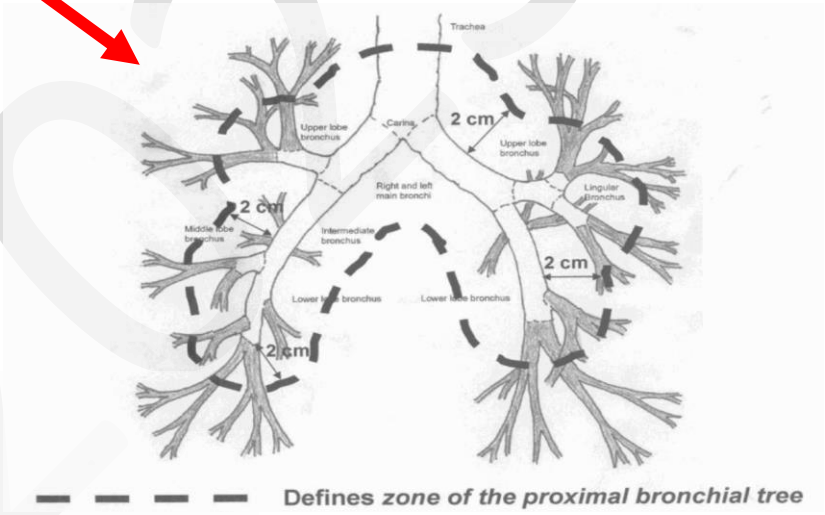
[d] Based on the CT of the chest: Peripheral = outer third of lung; Central = inner two thirds of lung.



RTOG 08-13: Central = "NSCLC tumors that are touching or within the zone of the proximal bronchial tree (Figure 1 below) or are adjacent to mediastinal or pericardial pleura (as these are also dose-limiting organs for high dose SBRT). " = **"2 cm No Fly Zone"** See figure

Canadian LUSTRE Trial
Central NSCLC = "Within 1 cm of mediastinum or 2 cm of the proximal bronchial tree."

Commentary:
Chang, J Thorac Oncol 2015. "The definition of what constitutes a "central lesion" has varied in published studies, and includes (1) a tumor within 2cm in all directions of the proximal bronchial tree (carina, right and left main bronchi, and bronchial tree to the second bifurcation), as in RTOG 0236; (2) a tumor within 2cm in all directions of any mediastinal critical structure, including the bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve (Fig.1); and (3) a tumor within 2cm in all directions around the proximal bronchial tree and immediately adjacent to mediastinal or pericardial pleura ("PTV touching the mediastinal pleura") as in RTOG 0813 (a phase I dose-escalation study of SABR for central lesions). Definition 2 has been used most often in recent studies because of reported toxicity to lung and other critical structures such as esophagus, heart, and nerves etc. after SABR. Therefore, we recommend the definition 2 (Fig.1) in our routing clinical practice."



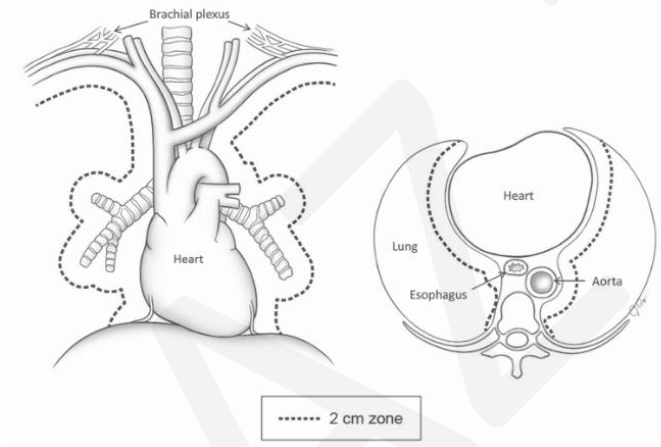


FIGURE 1. Recommended definition of central lesion: a tumor within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve.

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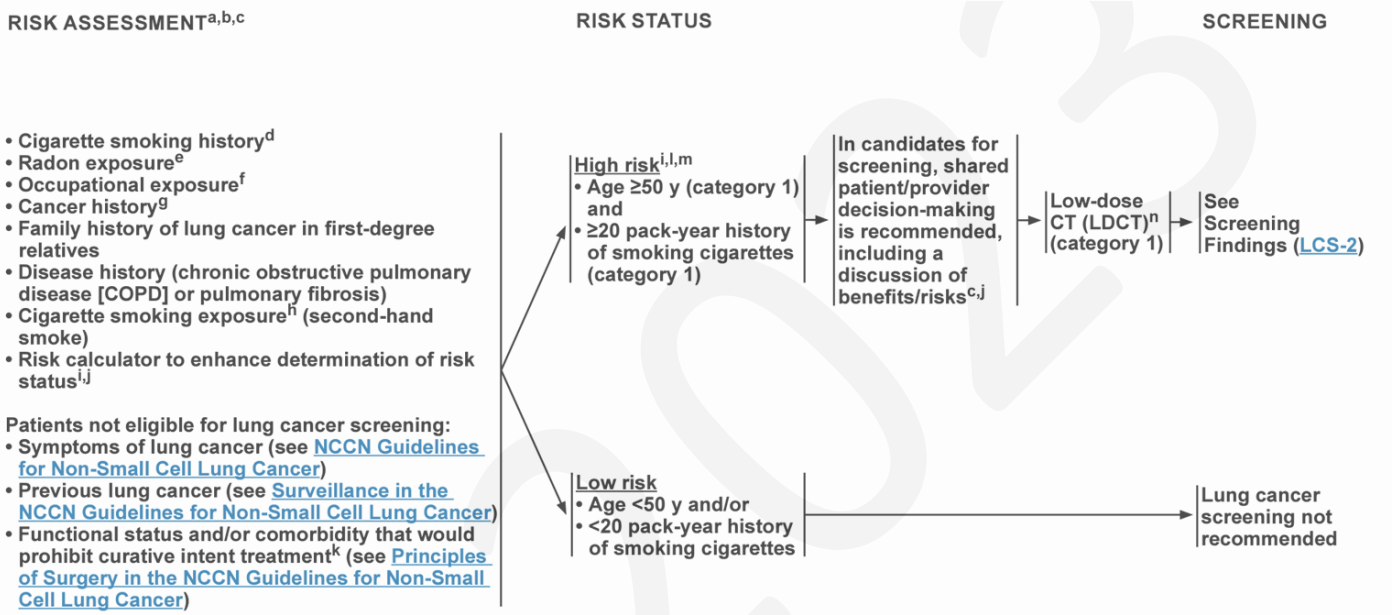
The Term **Ultracentral** has no specific defintion. However a commonly used one → SUNSET trial, which enrolled patients with tumors ≤6 cm whose PTV touches or overlaps the central bronchial tree, esophagus, pulmonary vein, or pulmonary artery.

Screening

Recommendation Summary

Population	Recommendation	Grade
Adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years	The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.	B



Note: LOW DOSE CT is about a 1/8 dose of normal CT.

Reduced Lung Cancer Mortality with Low Dose Computed Tomography Screening (NEJM, 2011)
53,454 persons (55 to 74y) high risk (> 30 pk year), randomly assigned to three annual screenings: low dose CT or PA CXR
Quit < 15 years.
Positive screening tests 24.2% (low dose CT) vs. 6.9% (CXR)
20% relative reduction in mortality from lung cancer
The rate of death from **any cause** was reduced in the low-dose CT group, as compared with the radiography group, **by 6.7%**
There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% vs. 26.7; P = 0.004.
Conclusion: Screening with the use of low-dose CT reduces mortality from lung cancer.

FANSS Study FEMALE ASIAN NON SMOKER
Background: Lung cancer (LC) is the leading cause of cancer death in Asian Americans and unfortunately the majority are diagnosed at advanced or late stages. **In Asia, approximately 60-80% of female LC patients are never smokers**. Current screening in the U.S. with low-dose CT (LDCT) Chest scans is offered only to current or former smokers based on the National Lung Screening Trial (NLST). The LC detection rate in NLST was 1.1%. The TALENT study, a LC screening study for high-risk nonsmokers in Taiwan reported a LC detection rate of 2.6% which included invasive adenocarcinoma (adeno), adeno in situ, minimally invasive adeno and adenosquamous carcinoma. Invasive adeno detection rate was 1.52%. *We are conducting the ongoing FANSS in the U.S. to screen female Asian nonsmokers with LDCT Chest scans to evaluate the feasibility of a LC screening program in this population*.
Inclusion: age between 40-74 years old (yo), never smoked or smoked <100 cigarettes in one's lifetime and identify as from Asian descent.
Prospective 222 patients → 201 had baseline LDCT at NYU. 83 (41%) reported a family history of LC

Shum, ASCO 2023 Abstract.
87 (43%) were Lung-RADS 1, 101 (50%) were Lung-RADS 2, 6 (3%) were Lung-RADS 3 and 7 (3.5%) were Lung-RADS 4.
5 pts with Lung-RADS 3 and 3 pts with Lung-RADS 4 have solid, subsolid or groundglass nodules >6mm that remain in close follow-up.
3 pts were diagnosed with invasive lung adeno for a LC detection rate of 1.5%; 2 are stage IIB and 1 is stage IIIC.
All pts were surgically resected, **EGFR mutation positive** and are **receiving adjuvant osimertinib**. Analysis cfDNA fragmentation ongoing.
Conclusions: Our data shows that LC screening in Asian female nonsmokers is feasible. Preliminary results demonstrate an invasive adeno detection rate comparable with TALENT and higher than in NLST. Early detection brings new meaning with the recent FDA approval for adjuvant targeted therapy in early stage LC. The expansion of LC screening guidelines to other high-risk populations warrants further attention. FANSS is continuing to accrue at additional U.S. sites this year

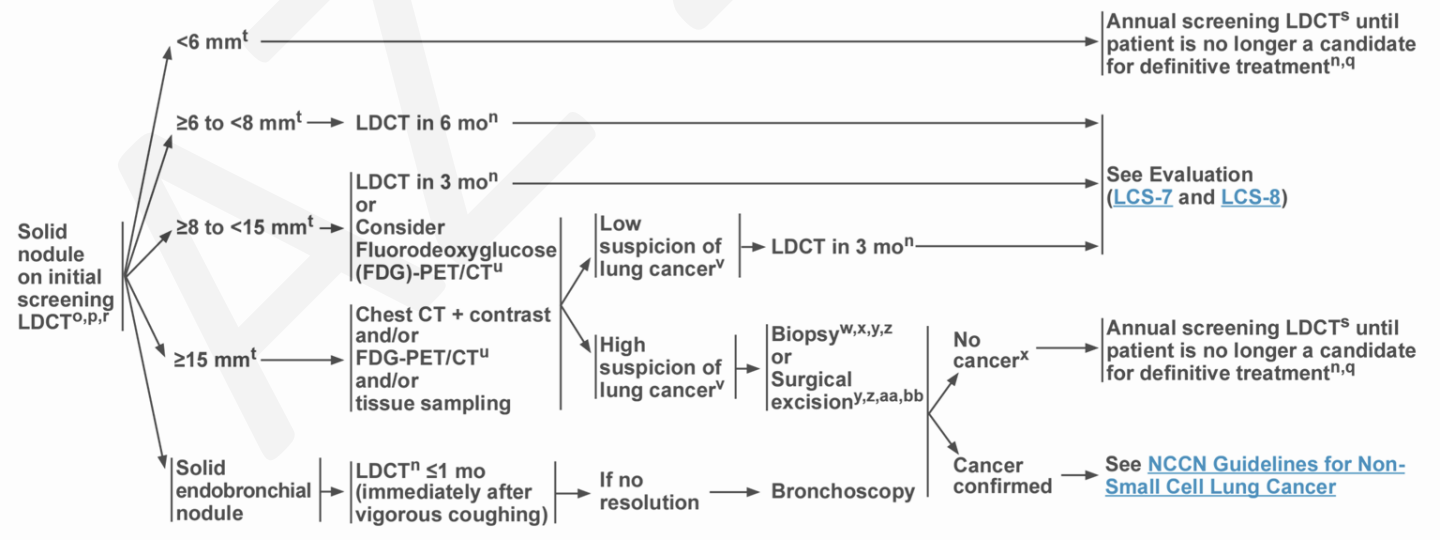
LD-CT Screening ↓ brain mets at 3 years (Su, J Thorac Oncol 2021)
3-year brain mets 11.9% → 6.5% (in the screening diagnosed cohort).

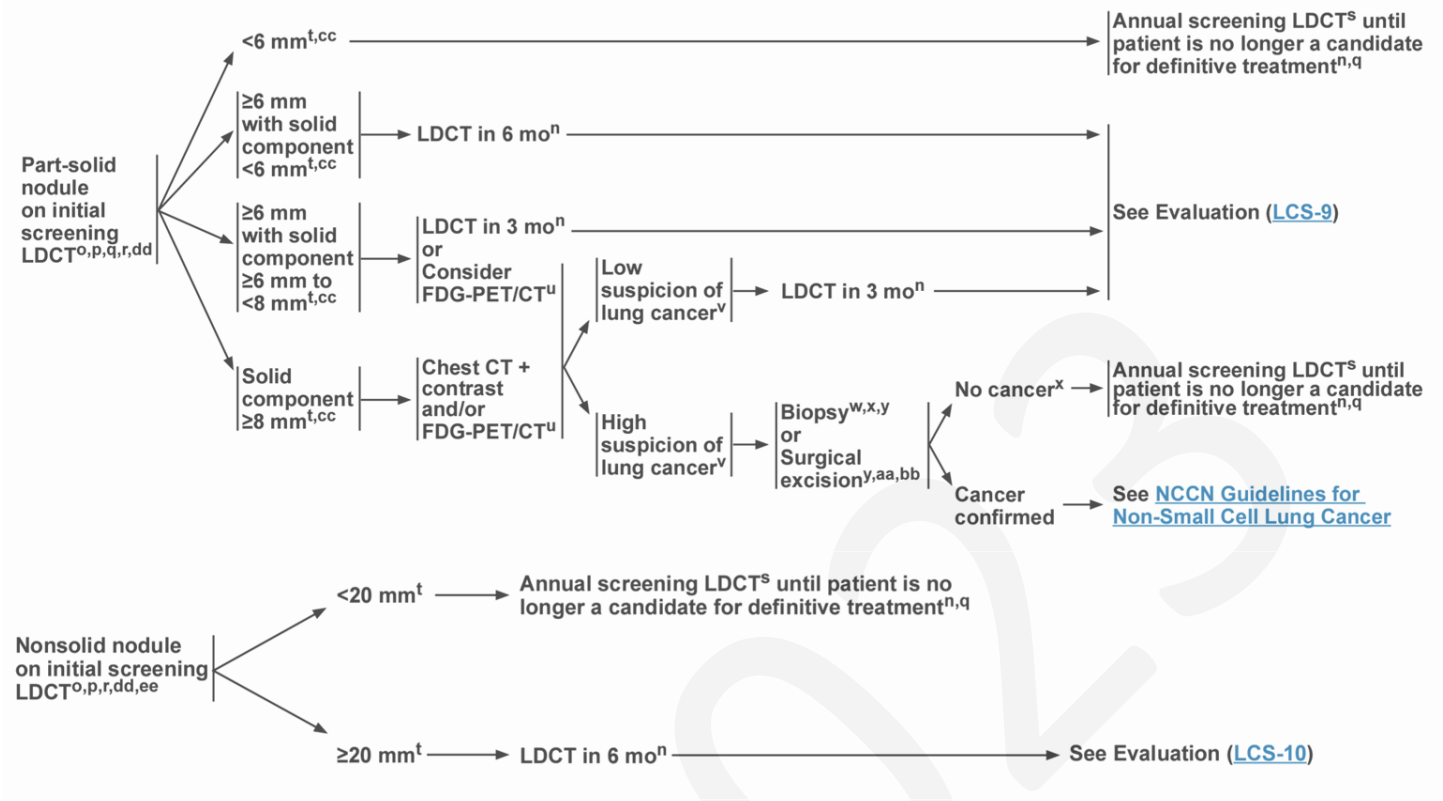
Dutch NELSON Trial
←R→ 13,195 men (and 2594 women 50-74 yo) | 1. CT screening at T0, 1 yr, 3 yr, and 5.5 yr | 2. No screening |.
10-year follow-up. Average adherence to CT screening was 90.0%. Hx ≥ 300 pack years who continued to smoke or quit less than 10 years ago.
9.2% of the screened participants underwent at least one additional CT scan (initially indeterminate)

de Koning, NEJM 2020.
Overall referral rate for suspicious nodules was 2.1%.
10-year incidence of lung cancer was **5.58 cases** per 1000 person-years vs. **4.91 cases** per 1000 person-years in the control group.
10-year lung-cancer mortality was **2.50 deaths** per 1000 person-years vs. **3.30 deaths** per 1000 person-years, respectively.
10-year CI CSM 0.76 (0.61 to 0.94; P=0.01) with screening.
Among women, the rate ratio was 0.67 (95% CI, 0.38 to 1.14) at 10 years of follow-up, with values of 0.41 to 0.52 in years 7 through 9.
CONCLUSIONS In this trial involving high-risk persons, lung-cancer mortality was significantly lower among those who underwent volume CT screening than among those who underwent no screening. There were low rates of follow-up procedures for results suggestive of lung cancer.

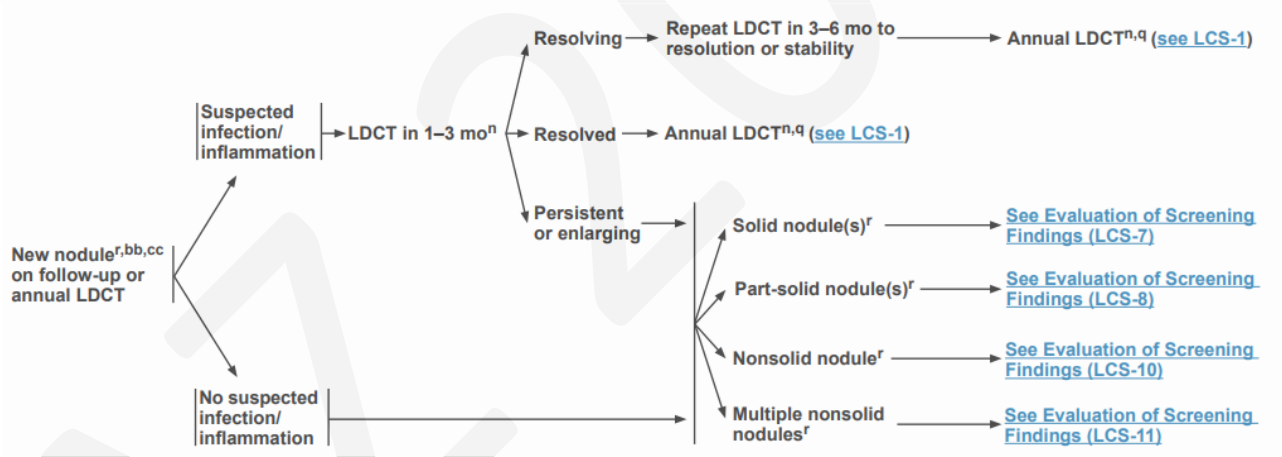
DELUGE "Screening Implementation" Study
Purpose: Lung cancer screening saves lives, but implementation is challenging. We evaluated two approaches to early lung cancer detection-low-dose computed tomography screening (LDCT) and program-based management of incidentally detected lung nodules.
Prospective 22886 → enrolled : 5,659 in LDCT, 15,461 in Lung Nodule, and 1,766 in Multidisciplinary Care.
LDCT = 2013 USPSTF criteria for lung cancer screening.
Lung Nodule Program = suspicious lung nodule on standard diagnostic imaging.
Methods: A prospective observational study enrolled patients in the early detection programs. For context, we compared them with patients managed in a Multidisciplinary Care Program. We compared clinical stage distribution, surgical resection rates, 3- and 5-year survival rates, and eligibility for LDCT screening of patients diagnosed with lung cancer.

Osarogiagbon, JCO 2022
Of 150 (LDCT), 698 (Lung Nodule), and 1,010 (Multidisciplinary care)
61%, 60%, and 44% were diagnosed at clinical stage I or II,
19%, 20%, and 29% were stage IV (P = .0005);
47%, 42%, and 32% had curative-intent surgery (P < .0001)
3-year OS 80% vs. 64% vs. 49%
5-year OS 76% vs. 60% vs. 44% .
Only 46% of 1,858 patients with lung cancer would have been deemed eligible for LDCT by US Preventive Services Task Force (USPSTF) 2013 criteria, and 54% by 2021 criteria. Even if all eligible patients by USPSTF 2021 criteria had been enrolled into LDCT, the Nodule Program would have detected 20% of the stage I-II lung cancer in the entire cohort.
Conclusion: LDCT and Lung Nodule Programs are complementary, expanding access to early lung cancer detection and curative treatment to different-risk populations. Implementing Lung Nodule Programs may alleviate emerging disparities in access to early lung cancer detection



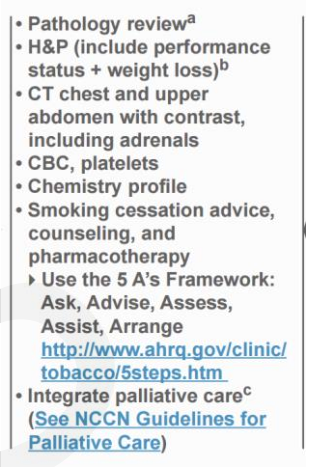

Part-solid nodule on initial screening LDCT[o,p,q,r,dd]
<6 mm[t,cc]
Annual screening LDCT[s] until patient is no longer a candidate for definitive treatment[n,q]
≥6 mm with solid component <6 mm[t,cc]
LDCT in 6 mo[n]
≥6 mm with solid component ≥6 mm to <8 mm[t,cc]
LDCT in 3 mo[n] or Consider FDG-PET/CT[u]
See Evaluation (LCS-9)
Low suspicion of lung cancer[v]
LDCT in 3 mo[n]
Solid component ≥8 mm[t,cc]
Chest CT + contrast and/or FDG-PET/CT[u]
High suspicion of lung cancer[v]
Biopsy[w,x,y] or Surgical excision[y,aa,bb]
No cancer[x]
Annual screening LDCT[s] until patient is no longer a candidate for definitive treatment[n,q]
Cancer confirmed
See NCCN Guidelines for Non-Small Cell Lung Cancer

Nonsolid nodule on initial screening LDCT[o,p,r,dd,ee]
<20 mm[t]
Annual screening LDCT[s] until patient is no longer a candidate for definitive treatment[n,q]
≥20 mm[t]
LDCT in 6 mo[n]
See Evaluation (LCS-10)


New nodule[r,bb,cc] on follow-up or annual LDCT
Suspected infection/ inflammation
LDCT in 1–3 mo[n]
Resolving
Repeat LDCT in 3–6 mo to resolution or stability
Annual LDCT[n,q] (see LCS-1)
Resolved
Annual LDCT[n,q] (see LCS-1)
Persistent or enlarging
No suspected infection/ inflammation
Solid nodule(s)[r]
See Evaluation of Screening Findings (LCS-7)
Part-solid nodule(s)[r]
See Evaluation of Screening Findings (LCS-8)
Nonsolid nodule[r]
See Evaluation of Screening Findings (LCS-10)
Multiple nonsolid nodules[r]
See Evaluation of Screening Findings (LCS-11)

Work-up

- Hx/Physical exam
  - Symptoms: dysphagia, odynophagia, weight loss
  - Advanced disease: present with symptoms of local invasion- hematemesis, hemoptysis, melena, cough from fistula, dysphonia, paralysis of hemidiaphragm
- Labs:
  - CBC, platelets, chemistry, **PFTs**.
- Imaging:
  - CT chest and upper abdomen (include adrenals)
  - PET scan.
  - Pathologic LN > 1 cm.
  - "Bulky" defined as either > 3cm, multiple matted nodes, cECE, or ≥ 3 stations involved.
  - MRI brain:
    - **EVERYTIME except peripheral IA……..(IB is optional).**
- Biopsy:
  - Bronchoscopy with biopsy
  - Pathologic Mediastinal LN Evaluation **(SEE PATHOLOGY BELOW)**
    - **EVERYTIME optional peripheral IA……..**
- Other
  - Smoking cessation advice, counseling, pharmacotherapy



Prognostic factors

- clinical stage
- KPS cutoff 90.
- Age cutoff 70.
- Weight loss > 5% in 6 months (50% present with weight loss).
- sex (males: worse survival)
- squamous: better prognosis in stage III (not others)
- stage IIIB/IV: WBC, hypercalcemia
- stage I: high pre-op CEA poor prognosis (esp if levels remain elevated post-op)
- Biologic features:
  - bcl-2, EFGR mutation (favorable)
  - EGFR overexpression, TTF1, Cox2, ras, Ki67, HER2, VEGF, p53, aneuploidy, microvascular density (adverse)

Maybe to differentiate between metastatic disease and primary lung, you use TTF1 and napsin.

LN drainage

For primary tumor in a lobe, which lymph nodes does it drain to?

- Right upper lobe - ipsilateral mediastinum
- Left upper lobe - ipsilateral and contralateral mediastinum
- Right lower lobe - Subcarinal nodes -> right superior mediastinum -> right inferior mediastinum
- Left lower lobe - Subcarinal nodes -> right or left superior mediastinum -> right or left inferior mediastinum

Paraneoplastic syndromes

- Gynecomastia - most commonly with large-cell
- Hypercalcemia - most commonly with squamous cell (think PTHrP)
- Hypertrophic pulmonary osteoarthropathy - presents as bilateral pain and tenderness in the legs, especially over the tibias. Bone scan positive. X-rays show elevated periosteum without cortical involvement. - most commonly with **adenocarcinoma** (secondary to PTHrp)
- Clubbing of digits

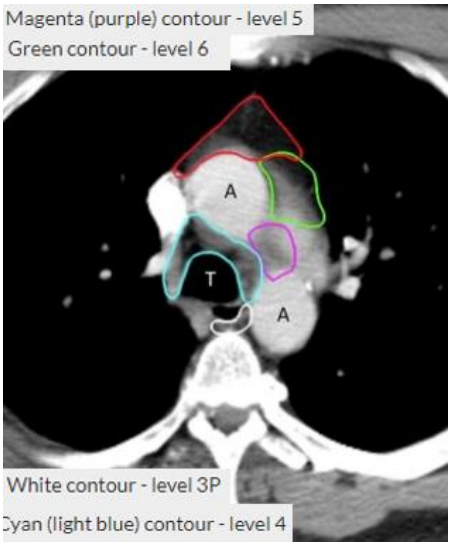
Syndromes according to tumor location:

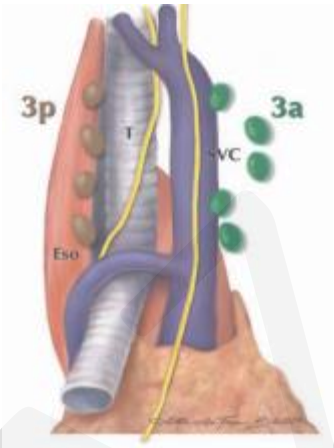
- Pancoast syndrome (superior sulcus tumor) - **lower brachial plexopathy, Horner's syndrome, shoulder/ulnar distribution of pain**.
- Horner's syndrome - **enophthalmos, ptosis, miosis, ipsilateral loss of sweating, hoarseness due to recurrent laryngeal nerve involvement**

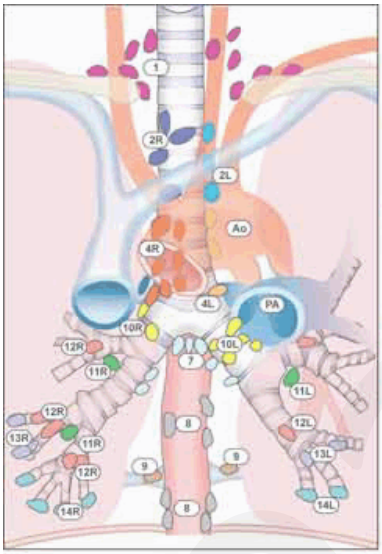
Second primary: Patients treated for upper aerodigestive tract tumors (lung, H&N, esophagus) have a 3%/year risk of developing a subsequent cancer.

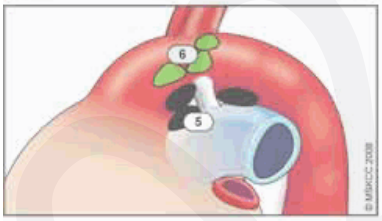
Anatomy: IASLC LN Map

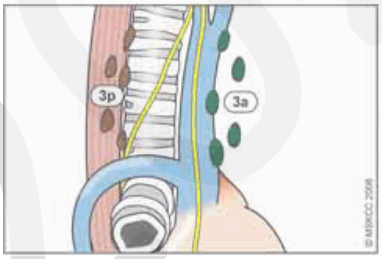
Notes:
Lv 2 is L and R of the trachea.
Lv 3 is anterior and posterior of trachea.
Carina T5
Trachea starts C3-4











Supraclavicular zone
- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone
- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

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

Inferior Mediastinal Nodes

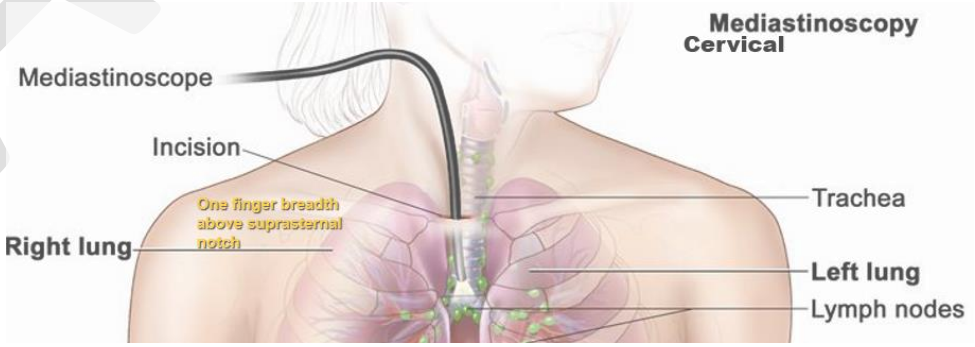
Subcarinal zone
- **7** Subcarinal

Lower zone
- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament

N_1 Nodes

Hilar/Interlobar zone
- **10** Hilar
- **11** Interlobar

Peripheral zone
- **12** Lobar
- **13** Segmental
- **14** Subsegmental



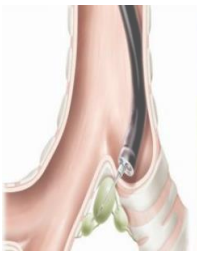
Pathology

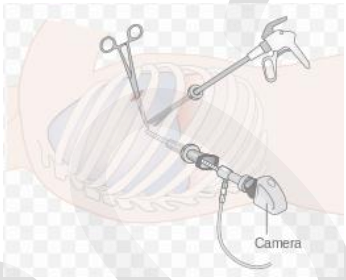
Minimally invasive: EBUS-TBNA, EUS-FNA.
Surgically Invasive: Mediastinoscopy (Anterior vs. Cervical)

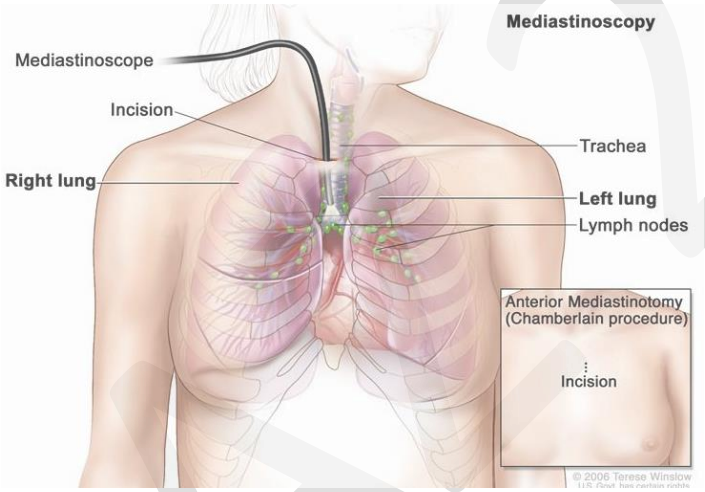
- EBUS-TBNA 2,4,7 **10-12**
- EUS-FNA 2,4,7 **8,9** L Adrenal Gland
- Anterior Mediastinoscopy (Chamberlain) 4,**5,6**,7
- Cervical Mediastinoscopy 2,3,4, **(NO 5 or 6)** 7, **(NO 8 or 9),** 10

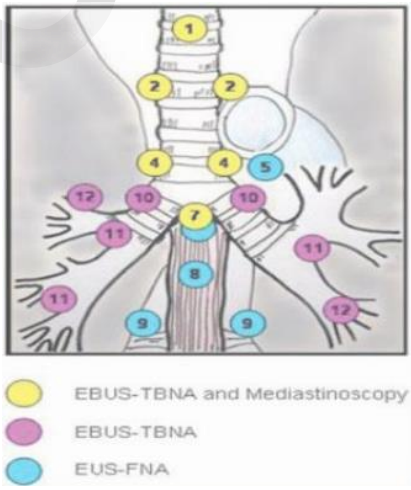
ASTER Trial
←R→ 241 resectable NSCLC 1. mediastinoscopy 2. EBUS → mediastinoscopy. All received PET/CT upfront, known N2-3 patients excluded.
1^{O} sensitivity for N2/N3 metastases.

Annema, JAMA 2010.
Sensitivity of mediastinoscopy 79% vs. EBUS 85% vs. **EBUS→med 94%.**
Unnecessary thoracotomies 18% (med) vs. 7% (EBUS).
Conclusions: EBUS → med is better than med or EBUS alone.









PRINCIPLES OF DIAGNOSTIC EVALUATION

- **The least invasive biopsy with the highest yield is preferred as the first diagnostic study.**
  - ◊ **Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.**
  - ◊ **Patients with peripheral (outer one-third) nodules may benefit from navigational bronchoscopy, radial EBUS, or transthoracic needle aspiration (TTNA).**
  - ◊ **Patients with suspected nodal disease should be biopsied by EBUS, EUS, navigational bronchoscopy, or mediastinoscopy.**
    - **– EBUS provides access to nodal stations 2R/2L, 3P, 4R/4L, 7, 10R/10L, 11–13, and other hilar nodal stations if necessary.**
    - **– An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.**
    - **– EUS–guided biopsy provides additional access to stations 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.**
    - **– TTNA and anterior mediastinotomy (ie, Chamberlain procedure) provide additional access to anterior mediastinal (stations 5 and 6) lymph nodes if these are clinically suspicious. If TTNA is not possible due to proximity to aorta, VATS biopsy is also an option.**
  - ◊ **EUS also provides reliable access to the left adrenal gland.**
  - ◊ **Rapid on-site evaluation (ROSE), when available, helps to increase diagnostic and molecular yield.**
  - ◊ **Patients with lung cancer with an associated pleural effusion should undergo thoracentesis and cytology. A negative cytology result on initial thoracentesis does not exclude pleural involvement. An additional thoracentesis and/or thoracoscopic evaluation of the pleura should be considered before starting curative intent therapy.**
  - ◊ **Patients suspected of having a solitary site of metastatic disease should have tissue confirmation of that site if feasible.**
  - ◊ **Patients suspected of having metastatic disease should have confirmation from one of the metastatic sites if feasible.**
  - ◊ **Patients who may have multiple sites of metastatic disease—based on a strong clinical suspicion—should have biopsy of the primary lung lesion or mediastinal lymph nodes if it is technically difficult or very risky to biopsy a metastatic site.**

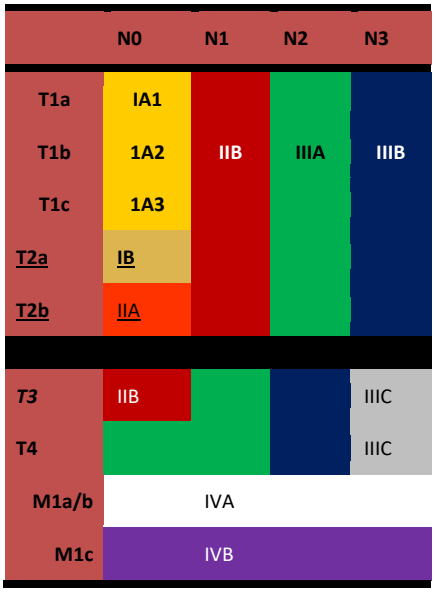
Staging 8th EDITION

T-stage:

	Size (cm)	Location	Invasion	Satellite	Other
Tis **STAGE 0**	In situ ≤ 3 cm. **PURE LEPIDIC**				
Tmi **STAGE 1**	≤ 3 cm ≤ 5 mm invasion **Mostly Lepidic**				
T1a	≤ 1	Lobar bronchus			Surrounded by lung or visceral pleura
T1b	> 1, ≤ 2				
T1c	> 2, ≤ 3				
T2a	> 3, ≤ 4	Main bronch (no limit from carina)	Visceral pleura		Atelectasis/pneumonitis
T2b	> 4, ≤ 5				
T3	> 5, ≤ 7		Chest wall, diaphragm, phrenic N, mediast pleura, parietal pericardium	Same lobe	
T4	> 7 cm	Carina, trachea	Mediast, heart, gr v, rec laryngeal N, eso, vert body	Different ipsilateral lobe	
M1a				Contralat lobe, pleural nodules	Malignant effusion (lung or heart)
M1b				Single extrathoracic met	SINGLE NONREGIONAL LN
M1c				Multiple extrathoracic mets	

T3 = PPP Phrenic, Parietal Pericardium, Pleura (mediastinal) + Chest wall Diaphragm
T4 =Think more structures. Like nerve, vertebra, heart, mediastinum, esophagus.

N-staging:
N1 = Ispsilateral peribronchial and/or ipsilateral hilar LN or intrapeulmonary LN.
N2 = ipsilateral mediastinal and/or subcarinal LN.
N3 = Contralateral anything. OR **supraclavicular nodes** OR ipsilateral or contralateral scalene.
NOTE: Lv 5 and 6 are L sided nodes. SO IF YOU HAVE Lv 5+ and a L sided cancer, it is N2. BUT if you have a R sided cancer, it is N3 if you have Lv 5/6+.



Survival Estimates:

Stage	5 Yr Survival	Median Survival
IA	50-70%	5-10 Yrs
IB	40-60	3-7
IIA	55	3-4
IIB	40	1.5-3
IIIA	20-25	1-2
IIIB	7-9	1-1.5
IV	2-13	0.5-1.5*

* Best supportive care is 3-6 months, or 8-10 months with chemo.

Radiation Practice

RT Dosing

ESTRO-ASTRO Recommendations Guckenberger, Radio Oncol 2020

Case	Description	Dose Recommended
Stage I NSCLC	Stage I, inoperable, peripherally located NSCLC	**SBRT**: 3-4 Fx total dose 45 – 54 Gy
Stage III NSCLC	Locally advanced stage IIIA (bulky N2) NSCLC	**STD CRT** 30-33 Fx over 6-6.5 weeks, total dose 60-66 Gy
PORT NSCLC	Resected N2 (multi-station and extra nodal spread) NSCLC	**STD RT:** 27 Fx over 5.5 weeks, total dose 54 Gy (MY NOTE: 60 Gy ECE or gross disease) Should Not Hypofx
LS SCLC	SCLC, limited stage	**CRT option 1:** 30 Fx over 3.0 weeks, total dose 45 Gy (BID) **CRT option 2:** 33 Fx over 6.5 weeks, total dose 66 Gy (daily)
PCI LS SCLC	PCI for SCLC limited stage after good response to radiochemotherapy	**STD RT:** 10 Fx over 2 weeks, total dose 25 Gy
Palliative NSCLC	Palliative metastatic NSCLC with failure after first-line chemo-IO combination and symptoms due to mediastinal/hilar disease progression and severe cough and moderate dyspnea. y	**STD RT:** 10 Fx over 2 weeks, total dose 30 G

PRINCIPLES OF RADIATION THERAPY

Conventionally Fractionated RT for Locally Advanced NSCLC (continued)

- **Dosing Regimens**
  - **Doses of 45 to 54 Gy in 1.8 to 2 Gy fractions are standard preoperative doses.[86] Definitive RT doses delivered as preoperative chemoRT can safely be administered and achieve promising nodal clearance and survival rates,[87-90] but require experience in thoracic surgical techniques to minimize the risk of surgical complications after high-dose RT.**
  - **In PORT, the CTV includes the bronchial stump and high-risk draining lymph node stations.[91] Standard doses after complete resection are 50 to 54 Gy in 1.8 to 2 Gy fractions, but a boost may be administered to high-risk regions including areas of nodal extracapsular extension or microscopic positive margins.[60,61,92] Lung dose constraints should be more conservative, because tolerance appears to be reduced after surgery. The ongoing European LungART trial provides useful guidelines for PORT technique.[93]**

Case 2 stage III NSCLC Hypofractionate?	Response	Maximum degree of hypofractionation supported
Radiotherapy only	**Yes: 97% (strong consensus)**No: 3%	60 Gy in 15 Fx (33%) 60 Gy in 20 Fx (27%) 60-66 Gy in 24-30 Fx (2.2-2.75 Gy/day) (23%) 55 Gy in 20 Fx (13%) None (3%)
Sequential radiochemotherapy	**Yes: 97% (strong consensus)**No: 3%	60-66 Gy in 24-30 Fx (2.2-2.75 Gy/day) (27%) 55 Gy in 20 Fx (27%) 60 Gy in 15 Fx (23%) 60 Gy in 20 Fx (20%) None (3%)
Concomitant radiochemotherapy	Yes: 27% **No: 73% (consensus)**	See footnote*

*Although there was consensus not to recommend hypofractionation, the respondents supportive of hypofractionation (n=11) were asked which fractionation(s) they would support, with multiple answers allowed. The favored options were 60-66 Gy in 22-30 Fx, given at 2.2-2.75 Gy/day, (75%) and 55 Gy in 20 Fx (63%)

SABR Planning

"How 3 Academic Centers Prescribe Stereotactic Body Radiation Therapy for Primary Lung Cancer"[3] De Leo, PRO 2022

	Institution A	Institution B	Institution C
Simulation			
Body position	Supine, arms above head	Supine, arms up	Supine
Immobilization	Vacuum bag/indexed upper body mold	Vacuum bag	Alpha cradle (arms up) or aquaplast mask (if arms down)
IV contrast desired for simulation? (yes/no)	No (unless tumor location is such that IV contrast would be helpful)	No	Yes
Oral contrast desired for simulation? (yes/no)	No	No	Peripheral tumors: No
			Central tumors: Yes
Respiratory motion management (None vs specify type)	4DCT, free breathing ABC-DIBH considered if ≥1 cm of motion	4DCT, free breathing Gating if motion >1 cm	4DCT, free breathing DIBH if tumor near diaphragm Consider gating if motion >1 cm and DIBH is not tolerable
Contouring			
Fusion imaging desired? (none vs specify type)	No	No	PET/CT
iGTV delineation approach (4DCT)	GTV contoured on all 4DCT phases to account for respiratory motion	GTV contoured on MIP and verified in all phases of 4DCT	GTV contoured on MIP and verified in all phases of 4DCT
CTV definition	No CTV	No CTV	iGTV + 2-3 mm (carve out adjacent fixed structures)
PTV definition	iGTV + 5 mm	iGTV + 5 mm	CTV + 5 mm
RT prescription			
Total dose (Gy), no. of fractions (fx)	48 Gy, 4 fx	Peripheral tumors[†]: 50 Gy with SIB GTV to 60 Gy, 4 fx	Peripheral tumors[†]: 1. 54 Gy, 3 fx 2. If abutting chest wall: 48 Gy, 4 fx 3. If abutting diaphragm: 50 Gy, 5 fx
		Central tumors[‡]: 1. 50 Gy with SIB GTV to 60 GY, 4 fx (12.5 Gy with SIB GTV 15 Gy/fx) or 2. 70 Gy with SIB GTV 80 Gy, 10 fx (7 Gy with SIB GTV 8 Gy/fx)	Central tumors: 50 Gy, 5 fx (10 Gy/fx)
Dosimetry planning			
Image sequence used for planning	Average CT	Average CT	Average CT
Forward or inverse planning?	Forward preferred (conformal arc) If OAR constraints cannot be met, inverse planning (VMAT)	Both	Inverse planning
If using IMRT: what percentage of dose/MUs must be delivered through an open arc/field?	No specific requirement	No specific requirement	25% (cGy/MU)
Dose calculation algorithm	Pinnacle adaptive convolution	AAA	AAA
Plan evaluation			
Primary target coverage goal	PTV $D_{95\%}$ ≥100% Rx	PTV $D_{95\%}$ ≥100% Rx GTV $D_{100\%}$ ≥110%-120% Rx	PTV $D_{95\%}$ ≥100% Rx
Maximum dose no greater than	0.03 cc ≤150% Rx	No specific requirement	D_{max} <115%
			(*Continued*)
Maximum dose no less than	0.03 cc ≥115% Rx	No specific requirement	Not used
CI[§] goal	≤1.5	No specific requirement	Not used
$R_{50\%}$[‖] goal	Varies, depends on PTV volume (ref RTOG 0915)	No specific requirement	Not used
Major OAR constraints (ie, hard constraints)	4 fractions: Spinal canal $D_{0.1cc}$ <26 Gy Trachea $D_{0.1cc}$ <34.8 Gy Esophagus $D_{0.1cc}$ <34 Gy	4 fractions: Esophageal D_{max} <35 Gy Bronchial tree D_{max} <40 Gy Brachial plexus D_{max} <35 Gy 10 fractions: Esophageal D_{max} <50 Gy Bronchial tree D_{max} <60 Gy Brachial plexus D_{max} <55 Gy	3 fractions: Spinal cord D_{max} <26 Gy Aorta D_{max} <45 Gy Stomach/small bowel D_{5cc} < 21 Gy Large bowel D_{5cc} <25 Gy 4 fractions: Spinal cord D_{max} <28 Gy Aorta D_{max} <49 Gy Stomach/small bowel D_{5cc} <23 Gy Large bowel D_{5cc} <27.5 Gy 5 fractions: Spinal cord D_{max} <30 Gy Aorta D_{max} <52.5 Gy Stomach/small bowel D_{5cc} <25 Gy Large bowel D_{5cc} <30 Gy Any fractionation: Lung V_{20} <25 %(Lungs - iGTV) V_{20} <12 %Liver V_{15} <700 cc (Liver: iGTV) D_{mean} <16 Gy
Priority ranking for plan evaluation	1. Major OAR sparing 2. Target coverage 3. Maximum dose no less than objective 4. CI	1. Esophageal and bronchial tree sparing 2. Target coverage	1. Major OAR sparing 2. Target coverage (iGTV > CTV > PTV) 3. Nonmajor OAR sparing
Treatment			
Image guided RT technique	Daily CBCT	Daily CBCT	Daily CBCT
6DOF image registration required?	No	No	Yes
Comments			Look to keep BED_{10} ≥100

[3] Florida, MSK, MDACC

	VALOR[2]	PACIFIC-4/RTOG 3515[3]	RTOG 0813[4]	RTOG 0915[5,6]
Eligibility				
Tumor size	≤5 cm	≤7 cm	≤5 cm	≤5 cm
Tumor location	Central or peripheral Not ultracentral Central = GTV or iGTV within 2 cm of spinal canal, bronchus, trachea, brachial plexus, esophagus, heart, or great vessels Ultracentral = tumors within 1cm of trachea, esophagus, brachial plexus, first bifurcation of PBT, or spinal cord	Central or peripheral Not ultracentral Central = tumor within zone of PBT* Includes tumors immediately adjacent to mediastinal or pericardial pleura Ultracentral = tumors abutting trachea, mainstem bronchus, or esophagus	Central Central = tumors within or touching the zone of the PBT or adjacent to mediastinal or pericardial pleura	Peripheral Not central Central = tumor within zone of PBT
Simulation				
Immobilization	Various types permitted (as long as risk that iGTV deviates beyond PTV is <5%)			
4DCT required?	Yes (unless breath-hold or tracking employed)	Yes (unless real time fluoroscopy used)	No (permitted)	No (permitted)
IV contrast desired for simulation?	Yes (unless the patient has a contrast allergy or renal insufficiency)	Yes	Yes (unless the patient has a contrast allergy or renal insufficiency)	No (unless no IV contrast in diagnostic CT within 8 weeks of registration)
Respiratory motion management	Various types permitted Consider if tumor motion is >1 cm in any	Various types permitted Recommended if motion >1 cm in any	Various types permitted	Various types permitted
Contouring				
Fusion imaging desired?	No (permitted)	PET-CT	Not specified	Not specified
iGTV delineation approach (if using 4DCT)	Boolean union of GTV defined on all phases of 4DCT Acceptable to use MIP as starting point and validate against all phases of breathing May add 2-5 mm margin to account for uncertainty to the Boolean union to create iGTV	Boolean union of GTV defined on all phases of 4DCT or a MIP (unless tumor located near soft tissue density) If MIP used, must verify tumor is defined in iGTV in each individual phase	(If used): ICRU 62	(If used): GTV + tumor motion from 4DCT
CTV definition	Not defined (GTV = CTV)			
PTV definition	iGTV + 5-7 mm	iGTV + 5-7 mm	ITV + 5 mm, or GTV + 5 mm axial + 10 mm cranio-caudal (if no 4DCT)	ITV + 5 mm, or GTV + 5 mm axial + 10 mm cranio-caudal (if no 4DCT)
RT prescription				
Total dose (Gy), no. of fractions (dose/fraction)	*Central:* 50 Gy, 5 fx (10 Gy/fx)	*Central* (any): - 60 Gy, 8 fx (7.5 Gy/fx) - 50 Gy, 8 fx (6.25 Gy/fx) - 55 Gy, 5 fx (11 Gy/fx) - 50 Gy, 5 fx (10 Gy/fx)	Starting dose 50 Gy, 5 fx (10 Gy/fx) increased in 2.5 Gy increments to 60 Gy, 5 fx (12 Gy/fx)	Randomized: - 48 Gy, 4 fx (12 Gy/fx) vs - 34 Gy, 1 fx (34 Gy/fx)
	Peripheral (any): - 54 Gy, 3 fx (18 Gy/fx) - 56 Gy, 4fx (14 Gy/fx) - 57.5 Gy, 5 fx (11.5 Gy/fx)	*Peripheral* (any): - 54 Gy, 3 fx (18 Gy/fx) - 42 Gy, 4 fx (10.5 Gy/fx) - 48 Gy, 4 fx (12 Gy/fx) - 55 Gy, 5 fx (11 Gy/fx) - 50 Gy, 5 fx (10 Gy/fx)		
Minimum interfraction interval	Every other day	1 day	40 hours	1 day
Dosimetry planning				
Forward or inverse planning?	Either If IMRT/VMAT used, optimize to provide a similar distribution as 3DCRT	Either	Either Consider IMRT when target coverage, OAR dose limits, or dose spillage are not achievable with 3DCRT	Either
Addressing interplay effect with modulated fields	At least 2 arcs in VMAT and restricting the modulation or dose rate in fixed-field IMRT deliveries	Not specified	Avoid excessive segments (control points) and complex beam fluences	Not specified
Dose calculation algorithm	Various ones permitted (must account for scatter): - Superposition/convolution - Linear Boltzmann transport equation solvers - Monte Carlo	Modern algorithms that accurately handle tissue heterogeneity and scatter should be used	Various ones permitted: superposition/convolution dose calculation or alternative algorithms, such as Clarkson or pencil beam	Superposition/convolution or Monte Carlo-based
Plan evaluation				
Primary target coverage goal	PTV $V_{100\%}$ >94%	PTV $D_{95\%}$ ≥100% Rx	PTV $D_{95\%}$ ≥100% Rx	PTV $V_{95\%Rx}$ = 100%
Secondary target coverage goal	PTV $V_{90\%}$ ≥99%	PTV $D_{99\%}$ ≥90% Rx	PTV $D_{99\%}$ ≥90% Rx	PTV $V_{90\%Rx}$ > 99%
Maximum dose no greater than	167%			
Maximum dose no less than	111%			
CI[†] goal	<1.2 (minor deviation < 1.5)	<1.2 Desired	<1.2 (minor deviation <1.5)	<1.2 (minor deviation < 1.5)
$R_{50\%}$[‡] goal	Varies, depending on PTV volume			
Major OARs (ie, normal structures with "hard constraints")	- Spinal canal - Esophagus - Brachial plexus	- Spinal canal - Esophagus - Brachial plexus - Stomach	- Spinal canal - Brachial plexus - Skin - Bilateral lung	- Spinal canal - Esophagus - Brachial plexus - Heart/pericardium - Great vessels - Trachea and large bronchus - Skin - Stomach - Bilateral lungs
Priority ranking for plan evaluation	Major OAR constraints > target coverage	Major OAR constraints > target coverage > minor OAR constraints	Major OAR constraints > target coverage	Major OAR constraints > Target coverage
Treatment				
Image-guided RT technique	Daily volumetric imaging strongly recommended	Volumetric Imaging (ie, CBCT or CT on rails) is strongly recommended repeat imaging during treatment recommended to verify that the tumor is in the iGTV	AP and lateral images to ensure alignment with isocenter or reference point immediately before each treatment Verification CT scans are permitted but not required	Various types permitted: - Planar kV imaging - In-room helical CT device - Tomotherapy helical CT - CBCT

Summary

MOST Peripheral SBRT PROTOCOLS:
GTV = CTV
CTV without 4DCT max 10mm CC + 5mm radial = PTV
CTV WITH 4DCT max 5mm spherical = PTV

4D-CT. Supine Vac Lok arms up. 2.5 mm slices.
Consider fluoroscopy first to see sup inf tumor motion, if tumor moves > 1 cm sup/inf, consider abdominal compression. If < 1 cm can do free breathing.

Central SBRT RTOG 08-13

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)		Percent of Lung Receiving 20 Gy Total or More, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0	<10	<15

NCCN Clinical Practice Guidelines in Oncology → Based on constraints used in recent and ongoing RTOG SBRT trials (0618, 0813, and 0915). Less than 14 Gy for single fraction, 18 Gy for 3 fractions, 26 Gy for 4 fractions and 30 Gy for 5 fractions of SBRT.

Table 2

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Spinal Cord	<0.25 cc <0.5 cc	22.5 Gy (4.5 Gy/fx) 13.5 Gy (2.7 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Ipsilateral Brachial Plexus	<3 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	neuropathy
Skin	<10 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Parallel Tissue	**Critical Volume**	**Critical Volume Dose Max (Gy)**		**Avoidance Endpoint**
Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)		Pneumonitis

Table 3

Serial Tissue*	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Esophagus, non-adjacent wall	<5 cc	27.5 Gy (5.5 Gy/fx)	105% of PTV prescription	stenosis/fistula
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	105% of PTV prescription	pericarditis
Great vessels, non-adjacent wall	<10 cc	47 Gy (9.4 Gy/fx)	105% of PTV prescription	aneurysm
Trachea and ipsilateral bronchus, non-adjacent wall	<4 cc	18 Gy (3.6 Gy/fx)	105% of PTV prescription	stenosis/fistula

*The volume maximum column shows suggested limits for these structures for planning purposes. Exceeded these limits is not a protocol violation. However, exceeding the Maximum Point Dose column is a violation per Section 6.7.2.

NOTE: SABR Toxicity

Brachial Plexus Injury Model 5% if Dmax 50 Gy EQD2(3Gy) and 10% risk if 85-90 Gy EQD2(3Gy).[4]
SABR Dose = 40-60 Gy in 3-5 fractions (majority 50 Gy in 5 fractions).

Esophageal Injury <20% G2 esophagitis if Dmax (BED10) <62 Gy, a D1cc (BED10) <48 Gy, D2cc (BED10) <43 Gy, Dmax ≤85% prescription[5]
Palliative RT generally is AP/PA, but IMRT may spare esophageal toxicity (30 Gy in 10 fx – G2 Tox – IMRT 0% vs. 3D-CRT 30%)[6]

[4] https://www.practicalradonc.org/article/S1879-8500(21)00341-6/fulltext
[5] https://www.practicalradonc.org/article/S1879-8500(21)00341-6/fulltext
[6] https://jamanetwork.com/journals/jamaoncology/fullarticle/2789387

NCCN Constraints

TO MEMORIZE

	3 fx	5 fx
Bronchial Tracheal Tree / Ribs	30 Gy	105%
Heart / pericardium	30 Gy	105%
Esophagus	27 Gy	105%
Brachial Plexus / Skin	24 Gy	32 Gy
Spinal Cord	18 Gy	30 Gy

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small (<2 cm) tumors, esp. >1 cm from chest wall
45–60 Gy	3	Peripheral tumors and >1 cm from chest wall
48–50 Gy	4	Central or peripheral tumors <4–5 cm, especially <1 cm from chest wall
50–55 Gy	5	Central or peripheral tumors, especially <1 cm from chest wall
60–70 Gy	8–10	Central tumors

Please note - Tables 2–4 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).
^For central tumor location. NS = not specified.

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60–70 Gy	2 Gy	6–7 weeks
Preoperative RT	45–54 Gy	1.8–2 Gy	5 weeks
Postoperative RT			
• Negative margins	50–54 Gy	1.8–2 Gy	5–6 weeks
• Extracapsular nodal extension or microscopic positive margins	54–60 Gy	1.8–2 Gy	6 weeks
• Gross residual tumor	60–70 Gy	2 Gy	6–7 weeks
Palliative RT			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30–45 Gy	3 Gy	2–3 weeks
• Bone metastases with soft tissue mass	20–30 Gy	4–3 Gy	1–2 weeks
• Bone metastases without soft tissue mass	8–30 Gy	8–3 Gy	1 day–2 weeks
• Brain metastases	CNS GLs*	CNS GLs*	CNS GLs*
• Symptomatic chest disease in patients with poor PS	17 Gy	8.5 Gy	1–2 weeks
• Any metastasis in patients with poor PS	8–20 Gy	8–4 Gy	1 day–1 week

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT with Concurrent Chemotherapy*,‡

OAR	Constraints in 30–35 fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%–40%†; MLD ≤20 Gy
Heart	V50 ≤25%; Mean ≤20 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose; V60 ≤17%; contralateral sparing is desirable
Brachial plexus	Median dose ≤69 Gy

Other Constraints

Suggested Maximum Doses to Critically Sensitive Normal Structures
Organ Maximum Dose

Brachial Plexus	Dmax < 66 Gy
Spinal Cord	Dmax < 45 Gy
Kidney	Mean < 18 Gy, V20 < 32% (bilateral)
Total lung	Mean < 20 Gy, V20 < 37%, V5 < 65%
Heart	Mean < 26 Gy, V30 < 45%
Liver / Larynx	Mean < 30 Gy, V30 < 45%
Esophagus	Mean < 34 Gy, Dmax 105%. Consider contralateral sparing.

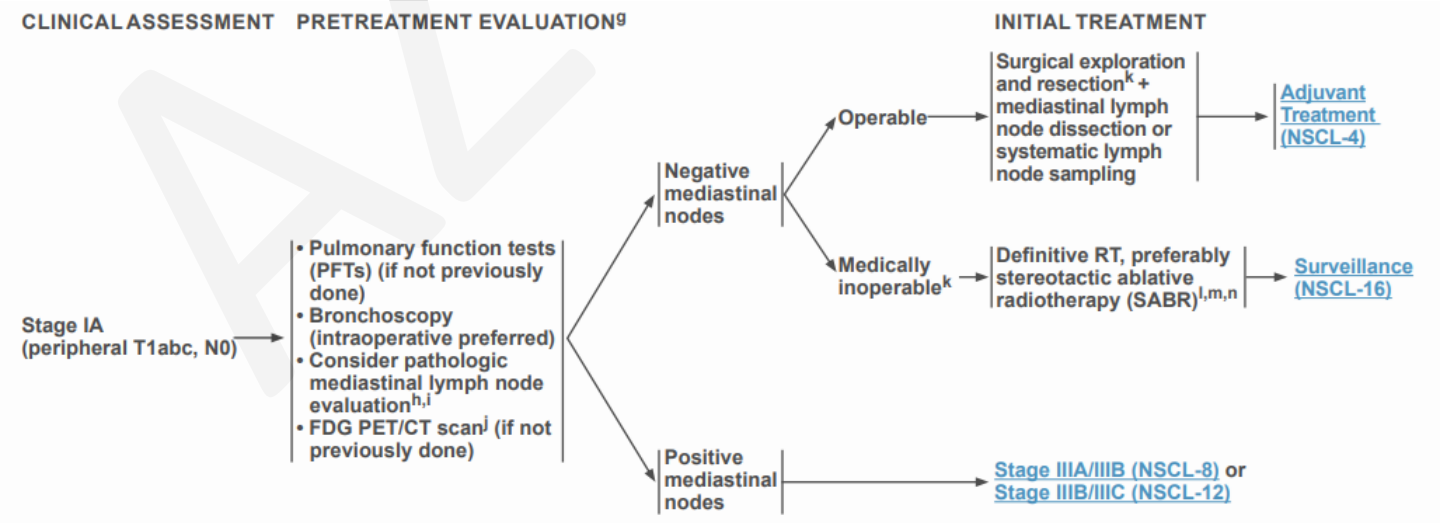
CHEST WALL (Retrospective MSKCC Mutter IJROBP 2012)
D70cc < 30 Gy Other institutions: 30 Gy < 30 cc or 60 Gy < 1 cc.

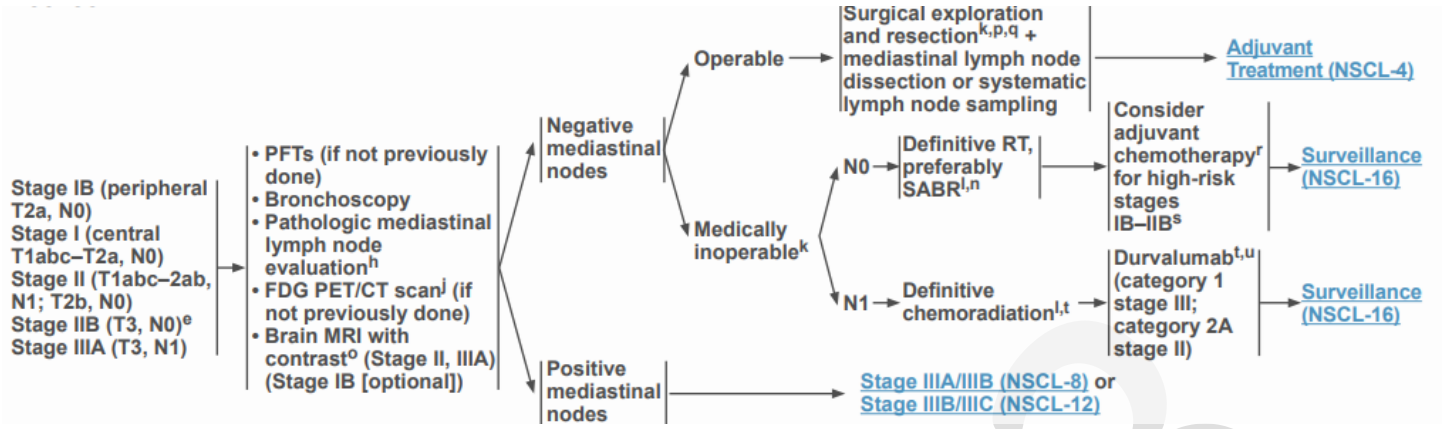
V20 Gy	Grade 2+ Pneumonitis (Cumulative Incidence)
< 22%	0/12 (0%)
22-31%	4/42 (9.6%)
32-40%	4/28 (14.3%)
>40%	8/17 (47.1%)

"In this retrospective review of 99 patients treated with definitive 3DCRT, the lung V20, Veff and mean dose, and location of primary tumor (upper vs lower lobe) predicted for Grade ≥2 radiation pneumonitis on univariate analysis. A lung V20 > 40% was associated with an actuarial incidence of Grade ≥ 2 pneumonitis of 36% while a lung V20 < 22% resulted in no incidences of Grade ≥2 pneumonitis. On multivariate analysis, only the lung V20 predicted for radiation pneumonitis (P=0.001)."
References: Graham MV et al. Int J Radiat Oncol Biol Phys., 1999 Sep; 1; 45(2):323-9.

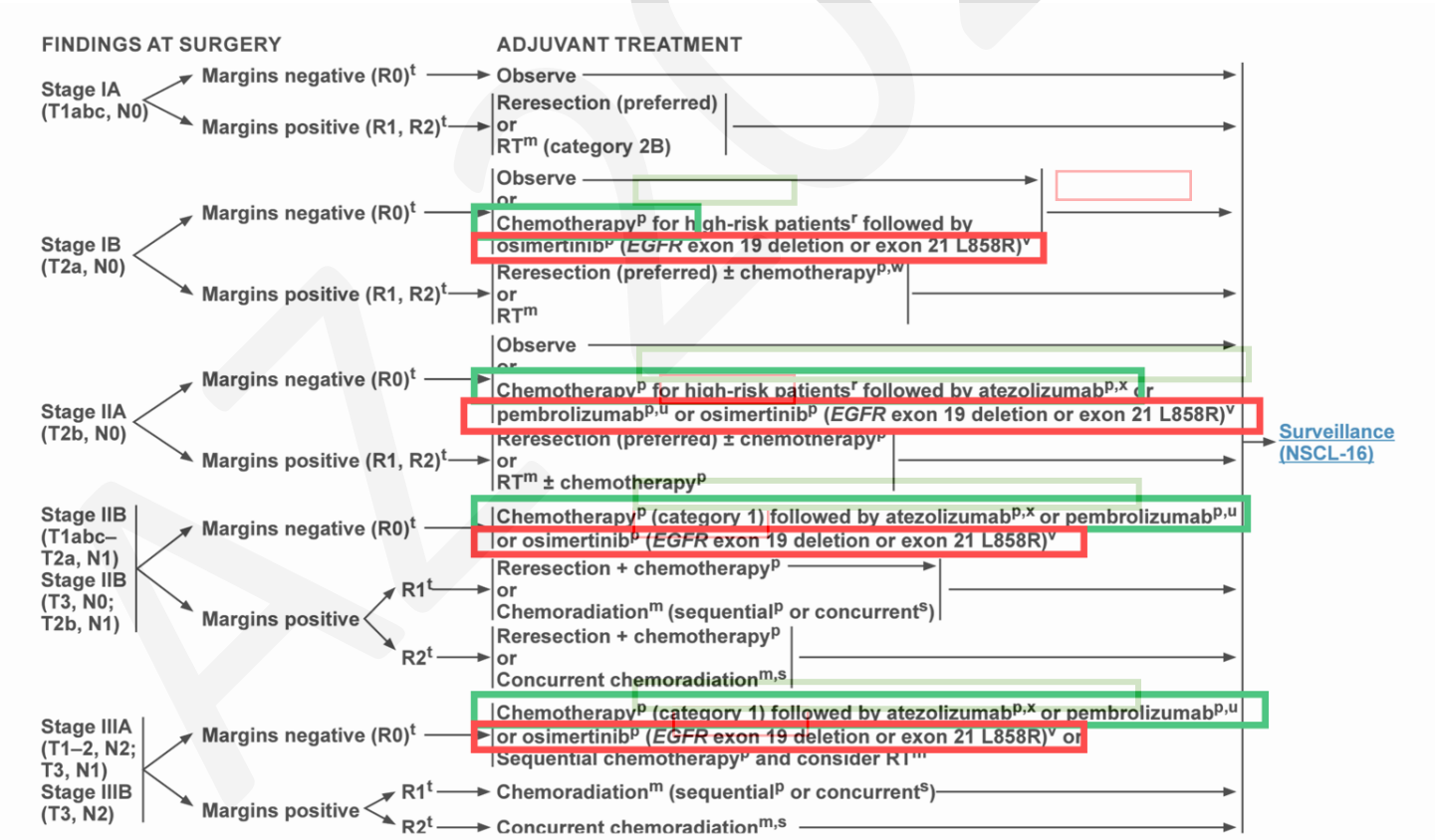
Early-Stage Disease: Operable Disease

- **NCCN guidelines**:
  - Workup: see above.
  - Recommended treatments:
    - Operable I-II — **Lobectomy (2-3% mortality)** > pneumonectomy (5-7% mortality) >> wedge. LRF lobe 6%, wedge 18%. Must do LN sampling since 15% of cT1-2N0 disease have LN+.
      If N1, must give chemo (CNIC BR.10). But if N0, consider chemo for T2, especially if > 4cm (CALGB).
      For T3N0, give adjuvant chemo (IALT).
      For close margins / + margins, re-resect or consider post-op RT.
    - Inoperable I-II — **Definitive RT to primary and + LN** (SBRT, conventional fractionation, hypofractionation).
      SBRT 2-3 yr LC 85-95%, OS 55%. **Std** 5 yr OS T1N0 30-50%, T2N0 15-20%. **Hypofx** 2-3 yr OS 40-50%.
      Conventional RT is 2 Gy to 66 Gy (Dosoretz 1996, Sibley 1998)
      If peripheral tumor or ↓ PS, may hypofrx 4 Gy/fx to 1^{O} tumor only (Slotman 1996, Cheung 2002).
      Dose escalation > 70 Gy and SBRT technique (60 Gy in 3 fx) >> conventional in LC.
      If patient can tolerate it, give chemo (induction, concurrent, an/or consolidation) if T3N0, or N1.
      Off trial, patients should not get chemo concurrently with dose-escalated RT or SBRT.





h Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.



m Principles of Radiation Therapy (NSCL-C).
p Perioperative Systemic Therapy (NSCL-E).
r Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.
s Concurrent Chemoradiation Regimens (NSCL-F).
t R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
u For patients whose tumors are negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy. The benefit for patients with PD-L1 <1% is unclear.
v For patients with *EGFR* exon 19 deletion or exon 21 L858R mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
w Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.
x For patients with PD-L1 ≥1% and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy

Surgery:

Eligibility

- PFTs
  - Lobectomy: FEV1 > 70% and > 1.2 L
  - DLCO > 60%
  - Wedge: FEV1 > 0.6L
  - SBRT/RFA: FEV1 > 0.2L
  - Post-op predictive FEV1 > 0.7 to 0.8 L

- Medically inoperable: FEV1 < 1.2 L or 40%, DLCO < 60%, FVC < 70%.
  - DLCO 60% for pneumonectomy, 40% for lobectomy

Type of Resection

Lobar resection:
- Overall 5-year OS for Stage I is ~65%, for Stage II is ~45%
- Tumor size is a prognostic factor, independent of T-stage, with smaller tumors having better survival
- Selected patients with tumors <1.5 cm may have 5-year OS as high as 95%

LCSG 821 - **North American Lung Cancer Study Group 821** (1982-88) -- sublobar resection vs **lobectomy**.
←R→, 247/276 patients with pathologic peripheral pT1N0 (defined on PA and lateral CXR). Middle lobe tumors excluded. Frozen section of LN (at least one node from bronchopulmonary, hilar, and mediastinal) had to be negative, otherwise completion lobectomy prior to randomization.
1. Lobectomy **2.** Limited resection (segmental resection or large wedge with 2 cm margin).

Ginsberg, Ann Thorac Surg 1995)
Results: **LRR**: limited resection 17% vs. lobectomy 6% (SS, 3x higher). RFS 69% vs. 82% (NS, p=0.06 in one-sided test with p<0.1);
OS 61% vs. 70% (SS, p=0.09 in one-sided test with p<0.1); Deaths due to cancer 62% vs. 55%.
No difference in DM. By tumor volume: lobectomy better, regardless of tumor size (<3 cm^3, 3-8 cm^3, 8-27 cm^3).
Toxicity: perioperative morbidity, mortality (1%) comparable. Early post-op pulmonary function significantly better for sublobar resection at 6 months, but no difference at 1 year and 1.5 years.
Conclusion: Lobectomy is the surgery of choice.

Lederle, Ann Thorac Surg 1996. Update
12 new recurrences identified (7 on sublobar arm and 5 on lobectomy arm). New survival curves
Results: Overall death-rate-increase improved from 47% in original report to 26% (NS); death due to cancer-rate-increase improved from 47% to 28% (NS); recurrence rate-increase improved from 60% to 39% (NS)
Conclusion: Modest corrections, but overall conclusions hold, with local recurrence rate difference essentially unchanged.

When should you use sublobar resection?
- If you can achieve parenchymal resection margins ≥ 2 cm or ≥ size of nodule
- If you can sample N1, N2 stations.
- Appropriate in:
  - Poor pulmonary reserve, other co-morbidity
  - Peripheral nodule < 2cm with at least one of:
    - Pure adeno CA in situ histology
    - Nodule has ≥ 50% ground glass appearance
    - Long doubling time (≥ 400 days)

JCOG0802/WJOG4607L Stage IA "Sub-Lobectomy" Trial **COMMENT: Results perhaps singular exception, not rule…**
←R→ 1106 patients clinical IA NSCLC (tumour diameter ≤2 cm; consolidation-to-tumour ratio >0·5) | 1. lobectomy | 2. Segmentectomy |.
1^{o} OS.

Saji, Lancet 2022 7.3 years
5-year OS 91.1% vs. 94·3% (HR 0·663; 95% CI 0·474–0·927; one-sided p<0·0001 for non-inferiority; p=0·0082 for superiority).
↑ OS observed **consistently across all predefined subgroups** in the segmentectomy group.
1 year follow-up, the SS Δ in ↓ of median forced expiratory volume in 1 sec between the two groups was 3·5% (p<0·0001), which did not reach the predefined threshold for clinical significance of 10%.
5-year RFS 88% NS.
The proportions of patients with local relapse were 10·5% for segmentectomy and 5·4% for lobectomy (p=0·0018).
52 (63%) of 83 patients and 27 (47%) of 58 patients died of other diseases after lobectomy and segmentectomy, respectively.
No 30-day or 90-day mortality was observed. One or more postoperative complications of grade 2 or worse occurred at similar frequencies in both groups (142 [26%] patients who received lobectomy, 148 [27%] who received segmentectomy).
Interpretation To our knowledge, this study was the first phase 3 trial to show the benefits of segmentectomy versus lobectomy in overall survival of patients with small-peripheral NSCLC. The findings suggest that segmentectomy should be the standard surgical procedure for this population of patients.

ACOSOG Z4032 (Negative study).
←R→ 244 wedge resection ± I-125 mesh brachytherapy for medically high-risk patients. MODERN STUDY (vs. Ginsberg).
Med age 71. high-risk operable patients with NSCLC ≤ 3 cm were randomly assigned to SR or SRB (sub-lobar w/ brachy).
1^{o} time to LR (defined as staple line, primary tumor lobe, ipsilateral hilar nodes).

Fernando, JCO 2014. Med f/u 4.38 years.
Same time to LR and same types of LR → Local progression occurred in only 7.7% of 222 patients.
SRB did NOT ↓ LR (but did trend…) even in those with potentially compromised margins (margin < 1 cm, margin-to-tumor ratio < 1, positive staple line cytology, wedge resection, nodule size > 2.0 cm).
This was most marked in 14 patients with positive staple line cytology (HR, 0.22; *P* = .24).
Three-year overall survival rates were similar for patients in the SR (71%) and SRB (71%) arms (*P* = .97).
Conclusion Brachytherapy did not reduce LR after SR. This finding may have been related to closer attention to parenchymal margins by surgeons participating in this study.

VA Recurrence RISK Study (Heiden, Jama Net 2021): For Stage I NSCLC patients, factors associated with ↑ risk of recurrence…
Younger age HR 0.992 for every 1-year increase in age (SS), ↑ Charlson Comorbidity Index score HR 1.055 (SS) for every 1-unit increase in composite score, segmentectomy (HR vs lobectomy, 1.352; SS) or wedge resection (HR vs lobectomy, 1.282; SS), ↑ tumor size (eg, 31-40 mm vs <10 mm; HR, 1.209; SS), ↑ tumor grade (eg, II vs I; HR, 1.210; SS), ↓ number of lymph nodes examined (eg, ≥10 vs <10; HR, 0.866; SS), ↑ pathologic stage (III vs I; HR, 1.571; SS), and **longer TTS (time to surgery)**, with ↑ risk per week after 12 weeks. For each week of surgical delay beyond 12 weeks, the HR ↑ by 0.4% (SS).

RT → Surgery

Nijmengen (Dutch) – Preoperative mediastinal RT vs Surgery alone.
←R→ 33 patient, cT1-2N0 NSCLC, mediastinoscopy LN-. R0 resection in pre-op 57% vs surgery only 28%.
1. Pre-op RT 20/5 to hilar, subcarinal, tracheo-bronchial, and paraesophageal LNs → surgery following Monday 2 . Surgery (lobe or pneumo).
Kazem, IJROBP 1984.
Results: 5-year OS **pre-op RT 58%** vs. surgery alone 43%; DSS 78% vs. 67% (NS); median OS 6 years vs. 2.5 years.
Subgroup analysis: If lobectomy, RT beneficial ONLY during first year, then no Δ. If pneumonectomy, RT beneficial during entire follow-up (5-year OS 66% vs. 42%). **Toxicity**: 9% operative mortality (all patients in surgery only arm); delayed wound healing comparable.
Conclusion: Pre-op RT well tolerated, and results are encouraging

NCI Trial (1963-1966) -- Pre-op RT vs. Surgery only
←R→. 17 institutions. 568 pt operable (no carina, no mediastinum/SCV, no chest wall invasion). 1. surgery vs. 2. Pre-op RT, >40 Gy supravoltage.
Warram, Cancer 1975.
Outcome: 5-year OS pre-op RT 13% vs. surgery 16% (NS); 5-year RFS 11% vs. 14% (NS).
Toxicity: Post-op mortality in surgery alone 11%, not estimated for pre-op RT group
Conclusion: No difference!

Overall, 1 study supports, and the other is no difference. Conflicted results.

Surgery → RT

Italian Trial.
←R→ 104 pIa pIb all with R0 (GTR) surgery NSCLC . 1. Surg → RT 2. Surg → obs.
RT target volumes included bronchial stump and ipsilateral hilum. RT = 50.40 Gy in 28 fx.

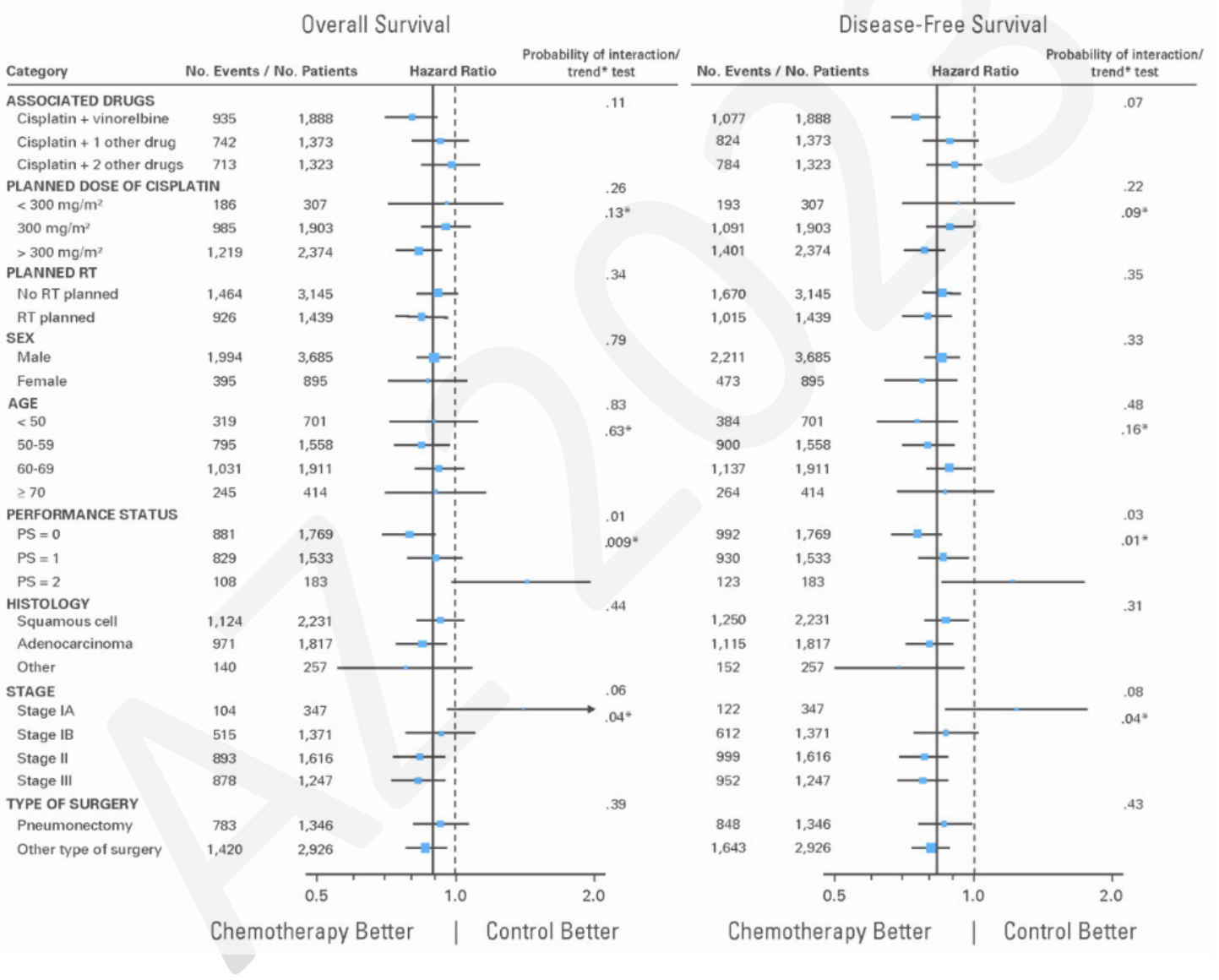
Trodella, Radiother Oncol 2002.
RESULTS: 5-year LR 2.2% vs. 23%. 5-year DFS 71% vs. 60% (P=0.039). 5-year OS 67% vs. 58% (P=0.048).
Regarding toxicity in G1, six patients experienced a grade 1 acute toxicity. Radiological evidence of long-term lung toxicity, with no significant impairment of the respiratory function, has been detected in 18 of the 19 patients who have been diagnosed as having a post-radiation lung fibrosis.
CONCLUSIONS: Adjuvant radiotherapy gave good results in terms of local control in patients with completely resected NSCLC with pathological Stage I. Overall 5-year survival and disease-free survival good too.

Surgery → Chemo

LACE Meta-analysis.
←M→ Completely resected patients that were conducted after the 1995 NSCLC meta-analysis. Median follow-up time of 5.2 years

Pignon, JCO 2008.
Overall HR of death was 0.89 (P = .005) → 5-year absolute benefit of 5.4% from chemotherapy.
HR benefit varied with stage: **stage IA = 1.40; 95% CI, 0.95 to 2.06** stage IB = 0.93; 95% CI, 0.78 to 1.10
stage II = 0.83; 95% CI, 0.73 to 0.95 stage III = 0.83; 95% CI, 0.72 to 0.94).
Chemotherapy effect was higher in patients with better performance status. There was no interaction between chemotherapy effect and sex, age, histology, type of surgery, planned radiotherapy, or planned total dose of cisplatin.

CONCLUSION: IA definite not. IB unsure. II-III chemo works.
See below for Japanese trial (**Kato, NEJM 2004)** for IA benefit!



CALGB 9633 (1996-2003) -- Surgery +/- paclitaxel and carboplatin
←R→ *Stopped early after interim analysis showed survival benefit.* 344 patients (target 500). NSCLC, T2, pN0 by mediastinoscopy **(STAGE IB)**, resected with lobectomy/pneumonectomy. **1.** adjuvant paclitaxel 200 mg/m2 + carboplatin AUC 6 Q3W x4 cycles vs. **2.** observation.
Primary endpoint OS.

Strauss, JCO 2008. **Outcome**: median OS chemo 7.9 years vs. observation 6.5 years (NS); 5-year OS 60% vs. 58% (NS); DFS 52% vs. 48% (NS).
Subgroup analysis: survival difference for tumors **≥ 4cm**. DFS 96 vs 63 months. OS 99 vs 73 months.
Toxicity: Grade 3/4 neutropenia in 35%
Conclusion: Negative trial, adjuvant chemo should not be standard of care in Stage IB. **Survival advantage for large tumors on subset analysis.**

NSCLC Collaborative Group 2010.
Meta-analysis. 34 trials and 8447 patients, individual data.

Outcome: Benefit of adding chemotherapy after surgery (HR 0.86, SS) with absolute OS benefit at 5 years of 4% (60% to 64%). Benefit of adding chemotherapy after surgery + PORT (HR 0.88, SS), absolute OS benefit at 5 years of 4% (29% to 33%)
Conclusion: **Addition of adjuvant chemotherapy after surgery improves survival, regardless if post-op RT was used.**

CHEST (Chemotherapy for Early Stages Trial) (2000-2004) -- ***NEOADJUVANT*** gemcitabine + cisplatin.
Phase III. 270 pts. Stages I (excluding T1N0), II, or IIIA (T3N1 only).
1. 3 cycles of **preoperative** gemicitabine + cisplatin followed by surgery or **2.** surgery alone.

Scagliotti, JCO 2012. Closed early (closed in 2004 after results of 3 randomized trials of adjuvant chemotherapy were released.)
Median f/u 3.3 yrs. HR of PFS 0.70 and for OS 0.63, both SS.
Results:
PFS: 3-yr PFS 52.9% vs 47.9%. No significant benefit for Stages IB/IIA.
PFS benefit for Stages IIB/IIIA (HR 0.51), median PFS 4.0 yrs vs 1.1 yr; 3-yr PFS 55.4% vs 36.1%.
OS: MS 7.8 yr vs 3.8 yr. 3-yr OS 67.6% vs 59.8%. No benefit for Stages IB/IIA. OS benefit for Stages IIB/IIIA (HR 0.42).
Conclusion: although the study was terminated early, preop chemotherapy improved OS for stages IIB and IIIA.

International Adjuvant Lung Trial (IALT) (1995-2000) -- Surgery +/- cisplatin and vinca alkaloids
←R→. *Terminated early due to slow accrual.* 1867 patients (target 3300). Stages I-III (Stage I 36%, Stage II 24%, Stage III 40%), complete resection.
1. Adjuvant cisplatin with either etoposide (in 56%) **2.** vinca alkaloid (vinorelbine, vinblastine, vindesine) x3-4 cycles. ~25% also received RT based on institutional preference.

Arriagada, NEJM 2004. Median F/U 4.7 years.
Outcome: 5-year OS chemo 44% vs. 40% control (SS); DFS 39% vs. 34% (SS). Also benefit for local control, distant control.
However, no OS benefit on Stage I subset analysis (HR 0.95, NS).
Toxicity: 1% died due to chemo effects
Conclusion: Cisplatin-based adjuvant chemo improves survival

Olauusen, NEJM 2006. Expression of ERCC1. 761 tumors analyzed. 44% positive, 56% negative.
ERCC1 negative: 5-year OS 47% chemo vs. 39% control (SS). Median OS 56 months chemo vs. 40 months control (14 month benefit)
ERCC1 positive: 5-year OS 40% chemo vs. 46% control (NS). Median OS 50 months chemo vs. 55 months control (NS)

NCI-Canada JBR.10 / INT (1994-2001) -- Surgery +/- cisplatin and vinorelbine
←R→. 482 patients with Stage IB-II (T3 excluded), complete resection.
1. Adjuvant cisplatin 50 mg/m2 and vinorelbine 25 mg/m2 Q4W x4 cycles **2.** observation. No RT given.

Winton, NEJM 2005. Median F/U 5 years.
Outcome: Median OS chemo 7.8 years vs 6.1 years (SS); 5-year OS 69% vs 54%. Median RFS 61% vs. 49% (SS).
Subgroup analysis showed no benefit for chemotherapy for Stage IB.
Conclusion: Improvement in overall survival.

Japan JLCRG (1994-1997) -- Surgery +/- uracil-tegafur (UFT).
←R→. 999 patients, pathologic Stage I adenocarcinoma. **1.** adjuvant oral uracil-tegafur (tegafur 250 mg/m2) x2 years **2.** observation.
Primary end point OS.

Kato, NEJM 2004. Median F/U 6.1 years.
Outcome: **5-year OS UFT 88% vs. observation 85% (p=0.047).** Stage IA 89% vs. 90% (NS), Stage IB 85% vs. 74% (SS).
Toxicity: Grade 3 in 2%
Conclusion: Adjuvant chemotherapy improves survival. **THIS CHEMO IS NOT USED IN US.**

Surg → C vs CRT

CALGB 9734 - post-op chemo +/- RT.
←R→. 37/44 patients. Completely resected Stage IIIA. Adjuvant paclitaxel x4 cycles, then 2-4 weeks later +/- RT. *Closed early due to slow accrual.*

Perry, Clinical Lung cancer 2007.
Outcome: Median DFS no RT 1.4 years vs. RT 2.8 years (NS); 1-year OS 72% vs. 74% (NS)
Conclusion: Small study, no improvement in outcome

INT 0115 ECOG EST 3590 / RTOG 91-05 - chemo/RT vs RT.
←R→ 488 patients. Stage II-IIIA. **1.** Cisplatin/etoposide x4 cycles + concurrent RT **2.** RT alone. Cis 60 mg/m2, etop 120 mg/m2. RT 50.4/28.

Keller, NEJM 2000.
Outcome: median OS 3.2 years vs. 3.2 years (NS). In-field recurrence 13% vs. 12% (NS).
Toxicity: treatment-related mortality RT 1.2% vs. CRT 1.6%
Conclusion: No difference in recurrence or survival.

RT vs. Surgery

Pooled Prospective (International Early Lung Cancer Action Program(I-ELCAP) and Initiative for Early Lung Cancer Research on Treatment(IELCART))
1115 patients clinical T1a-bN0M0 NSCLCs (1003 surgery and 112 SBRT) 525 in I-ELCAP in 1992-2021, 590 in IELCART in 2016-2021.
Surgery = lobectomy (56%) or sublobar mostly wedge resection (44%).
Patient selection = Surgery ↓ comorbidities and ↓ age (vs. SABR group)

Henschke, Journal of Thoracic Oncology 2023 Median follow-up was 57.6 months.
10-year Lung Ca SpSurvival Surgery 90% vs. SABR 88% (NS)
10-year All Cause Survival Surgery 75% vs. SABR 45% (p<.0001).
BUT after propensity score matching, **all-cause-survival using Cox regression was no longer different** for the combined cohorts(p=0.74), or separately for I-ELCAP(p=1.00) and IELCART(p=0.62).

Conclusions This first prospectively collected cohort analysis of long-term survival of small, early NSCLCs demonstrated that lung-cancer-specific-survival was high for both treatments and not significantly different and **also that all-cause-survival after propensity matching was not significantly differen**t. This supports SBRT as an alternative treatment option for small, early NSCLCs which is especially important with their increasing frequency due to low-dose CT screening. Also treatment decisions are influenced by many different factors and should be personalized based on the unique circumstances of each patient.

Commentary: Despite a skewed patients selection favoring the surgery group (better age and less comorbidities), all cause survival was not different between the 2 groups. This suggests that if the patient population would be equally balanced between the two groups, SABR might provide improved survival endpoints.

Pooled analysis of STARS (MD Anderson CC) and ROSEL (Dutch) trials; 2015 "Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials" (Chang J et al., Lancet Oncology. 2015 Jun;16(6):630-7).

Chang, Lancet 2015. Median F/U 3.4 years.
Pooled analysis of 2 Phase III studies that both did not meet accrural goals.
58 patients, operable T1-T2a N0 M0 NSCLC, <4 cm diameter, 1:1 randomization SBRT vs surgery.
STARS: SBRT 54/3 Gy peripheral, 50/4 Gy central over 5 days; **ROSEL**: SBRT 54/3 Gy peripheral (5 -8 days), 60/5 Gy central lesions (10-14 days).
Outcome: 3-year OS **SABR** 95% vs. **Surgery** 79% (Surgery) (p<0.05).
3-year RFS SABR 86% vs. surgery 80% (HR 0·69 log-rank p=0·54).
Toxicity: SBRT: Grade 3 in 10%, no grade 4/5; Surgery: grade 3/4 44%; 1pt Grade 5
Conclusion: SBRT is better tolerated than surgery, SBRT might lead to better OAS; SBRT could be an option for operable Stage I NSCLC.

STARS Prospective
80 patient single Arm prospective > 18 yo, PS 0-2, NSCLC with N0M0 (SCC, AC, Large Cell) with size < 3 cm.
This trial did NOT include patients from the previous pooled analysis.
SABR Peripheral 54 Gy in three fractions or Central 50 Gy in four fractions (SIB GTV → 60 Gy).
1º 3-year OS.
For the propensity-matching analysis, we used a surgical cohort from the MD Anderson Department of Thoracic and Cardiovascular Surgery's prospectively registered, institutional review board-approved database of all patients with clinical stage I NSCLC who underwent VATS L-MLND during the period of enrolment in this trial.
Patients between 2015 – 2017.

Chang, Lancet 2021
3 / 5 year OS = 91% / 87%.
SABR was tolerated well, with no grade 4–5 toxicity. Only 1 case each of grade 3 dyspnoea, grade 2 pneumonitis, and grade 2 lung fibrosis.
3 / 5 year OS in the propensity-matched VATS L-MLND cohort = 91% / 84%.
Non-inferiority was claimed since the 3-year overall survival after SABR was not lower than that observed in the VATS L-MLND group.
Interpretation Long-term survival after SABR is non-inferior to VATS L-MLND for operable stage IA NSCLC. SABR remains promising for such cases but multidisciplinary management is strongly recommended.

Meta-analysis.
←M→ Forty SBRT studies (4850 patients) and 23 surgery studies (7071 patients) published in the same period were eligible.
Median age and MFU **SBRT**: 74 years and 28.0 months vs. **Surg**: 66 years and 37 months. ALL PATIENTS SBRT BED ≥ 100.

Zheng, IJROBP 2014.

Mean OS 1, 3, and 5 years	SBRT	83.4%, 56.6%, 41.2%
	Lobectomy	92.5%, 77.9%, 66.1%
	Limited resection	93.2%, 80.7%, 71.7%

In SBRT studies, overall survival improved with increasing proportion of operable patients. After we adjusted for proportion of operable patients and age, SBRT and surgery had similar estimated overall and disease-free survival.
CONCLUSIONS: Patients treated with SBRT differ substantially from patients treated with surgery in age and operability. After adjustment for these differences, OS and DFS do not differ significantly between SBRT and surgery in patients with operable stage I NSCLC. A randomized prospective trial is warranted to compare the efficacy of SBRT and surgery.

SoCal (City of Hope / Hoag) SBRT Retrospective Selection Bias.
RR 346 patients early-stage NSCLC.

Liu, Clinical Lung Cancer 2021.

Univariate	↓ death	age < 65 years (P = .040)	surgical candidate (P = .010).
Multivariate	↓ death		surgical candidate (HR 0.360, P = .019).

Median OS was SS ↑ for surgical candidates versus nonsurgical candidates (83 vs 53 months, P = .017).
Local failure rate was 9.1%, the locoregional failure rate was 12.7%, and the distant failure rate was 10.7%.
Conclusion Patients who are deemed to be candidates for surgery have improved OS compared to those who are not when treated with SBRT. This raises the question of selection bias in trials comparing surgery with SBRT in NSCLC, as patients who are deemed to be surgical candidates and then go on to undergo surgery may have an inherent OS benefit.

Washington University; 2010 (2000-2007) PMID 20400121 -- "Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer." (Crabtree TD, J Thorac Cardiovasc Surg. 2010 Apr 16. [Epub ahead of print]).
RR. 462 patients with surgery (2000-2006) and 76 patients with SBRT (2004-2007), clinical Stage IA-IB NSCLC, staged with CT and PET. Surgical patients younger (SS), lower comorbidity (SS), better pulmonary function (SS), but higher stage (IA 63% vs 79%). Final path upstaging in 35%.

Crabtree, J Thorac Cardiovasc Surg 2010. Outcome: Unmatched OS surgery 5-years 55% vs SBRT 3-years 32%. 3-year local control IA surgery 96% vs SBRT 89% (SS); no difference in IB local control. No difference in DSS. No difference in LC on propensity analysis 3 yr 88% vs 90% (NS).
Conclusion: Similar rates of local recurrence and disease specific survival on propensity analysis between surgery and SBRT.

Early-Stage Disease: Inoperable Disease

California Cancer Registry. -- Natural history of stage I non-small cell lung cancer. implications for early detection.

Raz, Chest 2007. Registry study.
19,702 patients with Stage I NSCLC, 1432 did not undergo surgery, chemotherapy or RT (Stage IA 40%, Stage IB 60%). Surgery refused in 32%.
Outcome: Median OS 9 months, Stage IA 13 months, Stage IB 8 months.
5-year OS 7%, Stage IA 9%, Stage IB 5%. Median lung CSS Stage IA 2.1 years, Stage IB 10 months. 5-year lung CSS Stage IA 23%, Stage IB 12%.
"Refused" subgroup analysis: median OS 1.2 years, 5-year OS 6%; median CSS 1.7 years, 5-year CSS 22%.
Conclusion: Long-term survival with untreated Stage I NSCLC is uncommon, and vast majority die of lung cancer. Therapy shouldn't be delayed even in patients with small lung cancers.

SEER data; 2005 (1988-2001). -- "Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer."

Wisnivesky, Chest 2005. Population analysis. 4,357 patients with Stage I-II, who did not undergo surgery. Stage I 88%, Stage II 12%. RT delivered in 63%, no RT in 27% (chemotherapy not tracked).
Outcome: 75% died from cancer. On multivariate analysis, RT significantly associated with improved lung cancer survival.
Stage I: median OS RT 1.7 years vs. no RT 1.2; 5-year OS 15% vs. 14% (NS).
Stage II: median OS RT 1.2 years vs. no RT 9 months; 5-year OS 11% vs. 10% (NS).
Conclusion: RT is associated with improved survival in unresected Stage I-II NSCLC, benefit 5-7 months. RT not curative, since 5-year OS same.

Radiation alone (Historical)

NCIC CTG BR.25
Phase II. 80 T1-T3 N0. NSCLC were enrolled. RT 60 Gy in 15 fractions 3D CRT without inhomogeneity correction. Median age 76 years.
GTV → PTV margin was 1.0 to 1.5cm. The primary endpoint was the 2-year primary tumor control rate. CTCAE v3.

Cheung, JNCI 2014.
2-year LC 87.4%. 2-year OS 68.7%. 2-year regional relapse 8.8%. 2-year distant relapse 21.6%.
Tumor size ≥ 3cm ↑ DM HR 3.1
The most common grade 3+ toxicities were fatigue (6.3%), cough (7.5%), dyspnea (13.8%), and pneumonitis (10.0%)
CONCLUSIONS: Conformal radiotherapy to a dose of 60 Gy in 15 fractions resulted in favorable primary tumor control and overall survival rates in patients with T1-3 N0 M0 NSCLC. Severe toxicities were uncommon with this relatively simple treatment technique.

SPACE trial.
←R→ Phase II. 102 stage I medically inoperable NSCLC **1. SBRT to 66Gy in 3 fractions (one week)** 2. 3DCRT to 70Gy (7weeks).
Mean age 74 (57-86), 60% women, the vast majority (92%) had COPD or cardiovascular comorbidity.
NOTE: The SBRT arm included more patients with T2-tumors (p=0.02) and male gender (p=0.35). 3-year median f/u.

Nyman, Radiother Oncol 2016.
1-, 2- and 3-year PFS of: SBRT: 76%, 53%, 42% 3DCRT: 87%, 54% 42%. NS. OS NS.
At the end of the study 70% of SBRT patients had not progressed compared to 59% (3DCRT, p=0.26). Toxicity was low with no grade 5 events.
Pneumonitis of any grade was observed in 19% (SBRT) and 34% (3DCRT, p=0.26), and esophagitis in 8% and 30% respectively (p=0.006).
HRQL was evaluated with the EORTC QLQ 30 and LC14 module and patients treated with 3DCRT experienced worse dyspnea (p=0.01), chest pain (p=0.02) and cough (>10 points difference).
INTERPRETATION: PFS OS both NS. But better chance that you don't progress with SBRT.

MD Anderson; 2006. -- Medically inoperable Stage I non-small-cell lung cancer treated with 2D vs. 3D RT.

Fang, IJORBP 2006. Retrospective. 200 patients with Stage I NSCLC, treated with RT alone. 2D planning (n=115), or 3D planning (n=85).
Median RT dose 64 Gy vs. 66 Gy (NS). Age 69 vs 73 (SS). Median F/U 1.7 years vs. 1.6 years (NS).
Outcome: 5-year OS 2D 10% vs. 3D 36% (SS); 5-year DSS 29% vs. 68% (SS). 5-year LC 34% vs. 70% (SS).
Negative predictors: male, age ≥ 70, weight loss ≥ 5%, tumor ≥ 4 cm.
Conclusion: 3D conformal RT improves outcomes compared with 2D treatment

SEER data; 2005. – RT for unresected stage I-II non-small cell lung cancer

Wisnivesky, Chest 2005. Population analysis. 4,357 patients with Stage I-II, who did not undergo surgery. Stage I 88%, Stage II 12%.
RT delivered in 63%, no RT in 27% (chemotherapy not tracked).
Outcome: 75% died from cancer. On multivariate analysis, RT significantly associated with improved lung cancer survival.
Stage I: median OS RT 1.7 years vs. no RT 1.2; 5-year OS 15% vs. 14% (NS).
Stage II: median OS RT 1.2 years vs. no RT 9 months; 5-year OS 11% vs. 10% (NS)
Conclusion: RT is associated with improved survival in unresected Stage I-II NSCLC, benefit 5-7 months. RT not curative, since 5-year OS same.

Dose Escalation

RTOG 11-17
Phase I-II17 patients. I-III Staged with concurrent carboplatin and paclitaxel. RT = sequentially intensified by ↑ daily fx size, starting from 75.25 Gy/35.
8 patients → dose limiting toxicity (acute Grade 5 pneumonitis, acute Grade 3 pneumonitis; also late Grade 3 pneumonitis and Grade 4 pain)
Dose was de-escalated to 74/37 (Arm II; 9 pts) + concurrent carbo/taxol. Phase II accrued at 74/37 dose level.
Rx at ICRU pt; PTV must be covered by 93% isodose. Calculations without heterogeneity corrections.

Bradley, JCO 2010
53 patients at 74 Gy.
Median OS 25.9 months. 1-year OS 75.5%
Stage III median OS 21.6 mo. Stage III median PFS 10.8 months. Stage III 1-year OS 72.7% and 1-year PFS 50%.
Twelve patients experienced grade >or= 3 lung toxicity (two patients had grade 5 lung toxicity).
Conclusion: The median survival time and OS rate at 12 months for this regimen are encouraging. These results serve as projection expectations for the high-dose radiation arms of the current RTOG 0617 phase III intergroup trial.

Bradley, IJROBP 2010.
Conclusions: The maximum tolerated dose was determined to be 74 Gy/37 fractions (2.0 Gy per fraction) using three-dimensional conformal radiation therapy with concurrent paclitaxel and carboplatin therapy. This dose level in the Phase II portion has been well tolerated, with low rates of acute and late lung toxicities.

RTOG 93-11 Radiation alone (no chemo) Dose escalation
Phase I/II. Stage I-III NSCLC, SCV LN+ excluded (Prior chemotherapy allowed, concurrent chemotherapy not allowed). 3DCRT.
GTV = primary tumor and enlarged LN. **No ENI.** PTV = GTV + 1 cm minimum; verified on fluoroscopy because of breathing motion.
Dose prescribed to ICRU reference point within GTV, 93% isodose line to cover PTV, maximum PTV dose <=107%, no heterogeneity correction.
Patients grouped based on V20 value using 2.15 Gy/fx:

Group 1 (V20 <25%):	70.9/33 → 77.4/36 → 83.8/39 → 90.3/42	(Stage I 53%, Stage III 38%)
Group 2 (V20 25-36%):	70.9/33 → 77.4/36 → 83.8/39 (Stage I 21%, Stage III 75%)	(*accrual stopped after 77.4 Gy due to opening of RTOG 0117*)
Group 3 (V20 >36%):	64.5/30 → 70.9/33 → 77.4/36	(*accrual stopped after 2 patients*)

Bradley, IJROBP 2015.
Acute toxicity: minimal. Group 1 had 9% Grade 3 pneumonitis at 90.3 Gy; Group 2 had 8% Grade 3 pneumonitis at 77.4 Gy. Acute dose-limiting toxicity not reached
Late toxicity. Predictors for pulmonary toxicity: mean lung dose, V20
Group 1 had 13% Grade 3-5 lung and 6% Grade 3-5 esophageal toxicity (1 death of hemoptysis, 1 death of tracheoesophageal fistula) at 90.3 Gy; tolerable otherwise. Late dose-limiting toxicity at 90.3 Gy level.
Group 2 had 16% Grade 3-4 lung toxicity, and 4% esophagus toxicity. Late dose-limiting toxicity not reached.
Outcome: 2-year LR 50-78% (but small individual group sizes); LR sole site 18%, component 38%. **Elective nodal failure <8%**.
Conclusion: For Group 1 (V20 <25%), 83.8 Gy safe; for Group 2 (V20 25-36%), 77.4 Gy safe using 2.15 Gy/fx

CALGB 39904 Radiation 3DCRT Trial
Phase I, 39 patients medially inoperable (Stage I < 4 cm in size), Eligibility clinical stage T1N0 or T2N0 NSCLC. (< 4 cm) and pulmonary dysfunction. The nominal total radiotherapy dose remained at 70 Gy, while the number of daily fractions in each successive cohort was reduced.
Eligibility: FEV1 <40%, DLCO <50%, PCO >45 mmHg, VO2max <15 mL, or O2 dependent (28%).
Radiation: 3D-CRT, nominal dose 70 Gy, accelerated stepwise: 70/29 (@2.41) → 70/26 (@2.69) → 70/23 (@3.04) → 70/20 (@3.5) → 70/17 (@4.11).
Median age 75, 28% on supplemental O2. Median F/U 4.4 years

Bogart, JCO 2010.
1 G3 nonhematologic toxicity observed in both cohort 3 (dyspnea) and cohort 4 (pain).
The major response rate was 77%.
After a median follow-up time of 53 months, the actuarial median survival time of all eligible patients was 38.5 months.
Local relapse was observed in three patients.
Conclusion: Accelerated conformal radiotherapy was well tolerated in a high-risk population with clinical stage I NSCLC. Outcomes are comparable to prospective reports of alternative therapies, including stereotactic body radiation therapy and limited resection, with less apparent severe toxicity. Further investigation of this approach is warranted.

Slotman Postage Stamp Trial "Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer."
Retrospective 31 patients operable T1-2N0 NSCLC received radiotherapy (48 Gy in 12 fractions) to a limited ('postage stamp') field. The hilum and mediastinum were not included in the radiation portals.

Slotman, Radiother Oncol 1996.
3-year OS was 42%. 3-year DSS was 76%.
Failures: One patient developed an isolated regional failure, one had a combined local and distant failure, one had a combined local, regional and distant failure, while three patients failed at distant sites only. Thus, only two patients (6%) recurred regionally.
Conclusions: This study shows that 'postage stamp' irradiation is an effective alternative to surgery. Radiation of the hilar and mediastinal lymph nodes can be omitted in these pulmonary compromised patients.

Tough Cases: https://www.jto.org/article/S1556-0864(21)02112-2/fulltext
Excellent SBRT Commentary: https://www.clinicaloncologyonline.net/article/S0936-6555(22)00025-5/fulltext
Single Fraction SBRT: https://www.clinicaloncologyonline.net/article/S0936-6555(22)00088-7/fulltext
Review ←M→ Ultra-Central: Guidelines[7]
SABR + Mediastinal CRT for LA Phase 3 NRG Oncology LU-008 Trial[8]
FFF saves 30-50% beam-on time https://www.tandfonline.com/doi/abs/10.1080/07357907.2022.2103705

"BED > 100"

BED_{20} Dose and Control Study

Background: A series of radiobiological models were developed to study tumor control probability (TCP) for stereotactic body radiation therapy (SBRT) of early-stage non-small cell lung cancer (NSCLC) per the Hypofractionated Treatment Effects in the Clinic (HyTEC) working group. This study was conducted to further validate 3 representative models with the recent clinical TCP data ranging from conventional radiation therapy to SBRT of early-stage NSCLC and to determine systematic optimal fractionation regimens in 1 to 30 fractions for radiation therapy of early-stage NSCLC that were found to be model-independent.
RR from 9808 patients from 56 papers regarding SBRT doses 2 to 4 Gy, α/β ~20 Gy.

Liu, IJROBP 2023
Linear Tumor Control ↑ from BED_{20} 50 Gy → 100 Gy.
Conclusions The HyTEC radiobiological models with α/β ratios of about 20 Gy determined from the fits to the clinical TCP data for SBRT of early-stage NSCLC describe the recent TCP data well for both radiation therapy of 2 to 4 Gy per fraction and SBRT dose and fractionation schemes of early-stage NSCLC. A steep dose response exists between TCP and biologically effective dose, and TCP reaches an asymptotic maximum. This feature results in model-independent optimal fractionation regimens determined whenever safe for SBRT and hypofractionated radiation therapy of early-stage NSCLC in 1 to 30 fractions to achieve asymptotic maximal tumor control, and T2 tumors require slightly higher optimal doses than T1 tumors. The proposed optimal fractionation schemes are consistent with clinical practice for SBRT of early-stage NSCLC.

Japanese SBRT Dose in Peripheral Tumors
RR 433 patients early stage (ES)-NSCLC patients treated with SBRT between 2005 and 2019.
SBRT = 50 to 60 Gy in 5 fractions with maximum doses of 62.5 to 100 Gy.
Categorized into HighBED (n=262) and LowBED (n=171) groups
Patients were categorized by maximum BED within the planning target volume with a threshold dose of 200 Gy.

Tateishi, IJROBP 2021
Median follow-up times for the HighBED and LowBED groups were 52.3 months and 121.6 months, respectively.
5-year LR High BED vs. Low 1.3% vs. 7.2% (HR 0.15; P = .011).
5-year any recurrence 18.1% vs. 32.1% (HR, 0.52; P = .0058)
5-year CSD 9.5% vs. 21.8% (HR, 0.38; P = .002),
5-year OS 61.7% and 51.8% (HR, 0.71; P = .047).
Conclusion
In patients with peripheral ES-NSCLC, SBRT with a high maximum dose may improve not only local control, but also any recurrence, CSD, and OS rates without increased toxicity. Further trials designed to evaluate whether higher intensity SBRT increases local control rates and contributes to improved CSD and OS outcomes are anticipated.
Note: RT dose prescription: 2005-2011, 50 Gy in 5 fractions to the PTV at the 80% isodose line (Dmax 62.5 Gy, BEDmax 140.6 Gy, BEDavg 119.5 Gy). After 2011 either 50 or 60 Gy in 5 fractions (by location) to the PTV at the 60% isodose line (Dmax 83.3 Gy/100 Gy, BEDmax 222 Gy/300Gy, BEDavg 155.5 Gy/187.5 Gy).

Japanese Society of Radiation Oncology

RR. 245 patients with Stage I NSCLC (T1N0 n=155, T2N0 n=90), tumor diameter < 6 cm, 65% inoperable/35% refused or chose RT. Hypofractionated SBRT (3-12 Gy dose/fx; 1-25 fractions; total dose 18-75 Gy; median BED10 108 Gy; BED10 range 57-180 Gy). Median F/U 2 years

Onishi, Cancer 2004.
Outcome: LF 14%, LF if BED10 <100 26% vs. BED10 >100 8% (SS). 3-year OS 69% vs. 88% (SS)
Toxicity: Grade 3 in 2%
Conclusion: Hypofractionated SBRT with BED10 <150 Gy feasible and beneficial; local control and survival better with BED10 ≥100

Onishi, J Thorac Oncol. 2007. 3 year.
Retrospective. 275 patients, Stage I NSCLC (T1N0 n=164, T2N0 n=93). Hypofractionated SBRT, median BED10 = 111 Gy (57-180 Gy). Median F/U 3.2 years
ALL-COMERS: Overall LF 14% LF if BED10 <100 **43%** vs. BED10 >100 **8%** (SS)
*****IF MEDICALLY OPERABLE*** : 5-year OS if BED10 <100 30% vs. BED10 >100 71% (SS)**
Toxicity: Grade 3 pulmonary 5%
Conclusion: Hypofractionated SRT feasible for curative treatment of Stage I NSCLC; superior to conventional RT. Outcomes in operable patients are excellent
RECALL HOW SIMILAR TO LOBECTOMY 70% OS → Ginsberg, 1995 (LCSG 821)

[7] https://www.sciencedirect.com/science/article/pii/S016950022300819X#:~:text=SBRT%20for%20ultra%2Dcentral%20lung,SBRT%20at%20an%20acceptable%20level
[8] https://www.practicalradonc.org/article/S1879-8500(23)00173-X/fulltext

Older Single Institution

Timmerman, Indiana (Chest 2003).
Phase I dose-escalation trial. 37 patients T1-2 N0 NSCLC. Initial dose was 8 Gy x 3 and increased to tolerated dose 20 Gy x 3. MFU 15.2 mo.
CT simulation with abdominal compression.
Results: pCR 27% Total response 87%. 6 patients failed, but they all received < 18 Gy x 3 fx dosage.
Only 1 patient treated at 14 Gy x 3 developed symptomatic pneumonitis.
Conclusion: Good response and able to be done.

Timmerman, Indiana (JCO 2006).
Phase II medically inoperable 70 patients. T1-2 N0 NSCLC. SBRT 60-66 Gy in 3 fractions 1-2 weeks. MFU 17.5 mo.
Results: 2-year LC 95%. 2 year-OS 54.7%. 6/70 patients treatment related deaths. Median time to toxicity 10.5 mo.
2-year Freedom from Severe Toxicity PERIPHERAL tumor 83% vs. CENTRAL tumor 54%.
Conclusion: **Local control high, but central tumors toxic**.

Fakiris, Indiana (Phase II update IJROBP 2009) MFU 4 years.
Results: 3-year LC 88%. 3-year OS 43%. Nodal recurrence 8.5%. Distal recurrence 13%.
Median Survival 32.4 mo (3-years) → but if T1 39 mo. vs. T2 24.5 mo. Local control is NOT dependent on location.
G3-5 toxicity PERIPHERAL 10% vs. CENTRAL 27%.
Conclusion: same as above. If they are going to fail, 1/3 fail locally, 1/3 regional, 1/3 distally.

Important Dose Studies

CHISEL (TROG 09.02) **SBRT vs. EBRT** **Phase 3**
←R→ 101 biopsy-confirmed stage 1 (T1–T2aN0M0) NSCLC diagnosed by PET 2:1 | 1. SABR | 2. EBRT. Medically inoperable or refused surgery.
SABR = 54 Gy in three 18 Gy fractions, or 48 Gy in four 12 Gy fractions if the tumour was <2 cm from the chest wall.
EBRT = 66 Gy in 33 daily 2 Gy fractions or 50 Gy in 20 daily 2·5 Gy fractions, depending on institutional preference.
1O time to local treatment failure.

Ball, Lancet 2019.
Median time to local treatment failure was not reached in either group.
20 (20%) of 101 patients had progressed locally: nine (14%) of 66 patients in the SABR group and 11 (31%) of 35 patients in EBRT.
FFLF ↑ in the SABR group (HR 0·32, 95%, p=0·0077).
SABR → one grade 4 adverse event (dyspnoea) and seven grade 3 adverse events (two cough, one hypoxia, one lung infection, one weight loss, one dyspnoea, and one fatigue) related to treatment compared with two grade 3 events (chest pain) in the standard treatment group.
Interpretation: In patients with inoperable peripherally located stage 1 NSCLC, compared with standard radiotherapy, SABR resulted in superior local control of the primary disease without an increase in major toxicity. The findings of this trial suggest that SABR should be the treatment of choice for this patient group.

Canadian LUSTRE Trial
←R→ 233 patients (154 SBRT, 79 CRT) medically inoperable histo confirmed stage I (≤5cm) NSCLC or a suspicious growing FDG-PET avid lesion.
Ratio 2:1 | 1. SBRT of 48 Gy/4 fractions (peripheral NSCLC) or 60 Gy/8 fractions (central) | 2. CRT of 60 Gy/15 fractions |.
"Central NSCLC" - within 1 cm of mediastinum or 2 cm of the proximal bronchial tree.
Central tumor (27%), biopsy-proven NSCLC (49%); ≤3cm lesions (71%); mean tumor diameter was 2.5 cm.
Stratification was by tumor size (≤3cm vs >3-5 cm), location: central vs peripheral, and clinical center.
Median Age 75
1^{O} LC Trial closed early due to slow accrual.

Swaminath, IJROBP 2022 **36 months.**
3-year LC rate was 87.6% for SBRT vs. 81.2% for CRT (HR=0.61, p=0.15).
Only one patient in each arm experienced grade 3 acute toxicity (no grade 4/5 toxicities were observed).
Late grade 3/4 toxicities occurred in 7 patients: SBRT - central 3/45 (6.6%), peripheral 2/109 (1.8%), CRT - central 1/19 (5.2%), peripheral 1/60 (1.6%). One patient who received 60 Gy/8 fractions for a central NSCLC experienced a possible RTRD (hemoptysis).
Conclusion This is the largest reported RCT of lung SBRT compared to a contemporary CRT control arm, with mature follow-up and the inclusion of patients with central tumors. There was an observed improvement of LC with SBRT compared to CRT, however, the trial was underpowered to confirm this. No evidence of differences were observed in DFS and OS. Very few patients experienced severe late toxicities, including those with central tumors. This study confirms the efficacy and safety of SBRT for both central and peripheral Stage I NSCLC (NCT01968941).

RTOG 08-13 Central Lung tumors

Impetus for RTOG 08-13 was that ≥ G3 toxicity was **46%** central tumor vs. 20% peripheral tumor in Phase II Timmerman, JCO 2006
Phase 2 60-66 in 3 fractions.

Phase I/II. 120 patients MEDICALLY INOPERABLE
Designed to determine maximum tolerated dose and efficacy of SBRT for PET staged cT1-2 (< 5 cm tumors).
Central tumors designed to be < 2cm from tracheal-bronchial or immediately adjacent to mediastinal or pericardial pleura (aka PTV touches pleura).
Most cancers were T1 (65%) and squamous cell (45%).
SBRT was started at 50 Gy in 5 fractions and escalated by 0.5 Gy / fx → 60 Gy in 5 fractions.
Max Tolerated Dose (MTD) was defined as the SBRT dose at which the probability of Dose Limiting Tox (DLT) was closest to 20% without exceeding it.
N=33 → 12 Gy/fx. N=38 → 11.5 Gy/fx. **7% dose-limiting toxicities in the 12 Gy x 5 arm**.

Abstract 16; Table 1

Dose level	11.5 Gy x 5fr	12 Gy x 5fr
Number (n) of eligible patients	38	33
Pts w Toxicity G3+ (at any time)	6	7
Pts w Early Toxicity G3+ (within 1st yr)	5	4
Pts with Late Toxicity G3+ (beyond 1st yr)	2	5
Pts with primary tumor failure	4	6
Pts with involved lobe failure	2	2
Pts with regional (lymph node) failure	2	4
Pts with distant failure	6	5
2-year local control	89.4% (81.6-97.4%)*	87.7% (78.3-97%)*
2-yr progression free survival	52.2% (35.3-66.6%)*	54.5% (36.3-69.6%)*
2-year overall survival (OS)	70.2% (52.6-82.3%)*	72.7% (54.1-84.8%)*

*90% confidence interval.

Bezjak, ASTRO 2015 LBA10. ASTRO 2016 #16.
2-year LC 88%, PFS 53%, OS 70%.
7/33 patients with ≥ 3 Grade toxicity.
Grade 5 toxicity attributed to SBRT was seen in 3 out of 71 patients

Observed local control at 2 yrs in 71 pts treated with the two highest doses levels (11.5-12 Gy/fr x 5 fr) in this multicenter trial was high, and G3+ toxicity rates were acceptable. Two-year OS rates of 70% in this medically inoperable group of elderly pts with comorbidities were comparable to pts with peripheral early stage tumors.

Bezjak, JCO 2019 (Toxicity Profile) Median follow-up was 37.9 months
Five patients experienced DLTs; MTD was 12.0 Gy/fx, which had a probability of a DLT of 7.2% (95% CI, 2.8% to 14.5%).
71 evaluable patients in the 11.5 and 12.0 Gy/fx cohorts:
2-year LC 89.4% and 87.9%
2-year OS 67.9% and 72.7%
2-year PFS 52.2% and 54.5%
Conclusion: The MTD for this study was 12.0 Gy/fx; it was associated with 7.2% DLTs and high rates of tumor control. Outcomes in this medically inoperable group of mostly elderly patients with comorbidities were comparable with that of patients with peripheral early-stage tumors.

RTOG 02-36 PERIPHERAL Lung tumors.
Phase II. 59 non-surgical patients all with medical comorbidities. Median follow-up 4 years (7.2 years for survivors).
Biopsy-proven peripheral T1-T2 < 5 cm) N0M0 non-small cell lung cancer.
Prescription was 20 Gy x 3…but on later analysis, it was accounting for heterogeneity, 18 Gy x 3 fractions = 54 Gy total of SBRT, lasting 1.5 -2 weeks.
GTV = CTV (NO EXPANSION). GTV → PTV max 10 mm CC and 5 radial. If 4DCT, 5mm uniform.

	Initial results 3-years	Long term results 5-years
OS	56%	40%
MS	48 mo	48 mo.
LC	98%	93%
Lobar control	91%	80%
LRC	87%	62%
Distant Failure	22%	31%

Timmerman, JAMA 2010. Phase II. 55 patients, peripheral T1-T2N0 NSCLC, <5 cm diameter, not surgical candidate. SBRT 54/3 over 1.5-2 weeks. Median F/U 2.9 years.
Outcome: 3-year tumor control 98% (1 1° tumor failure); 3-year LC (tumor+lobe) 91%; 3-year LRC 87%; 3-year DM 22%. Median OS 48 months.
Toxicity: Grade 3 in 13%, Grade 4 in 4%, no Grade 5
Conclusion: Patients with inoperable NSCLC have high rates of local tumor control and moderate treatment-related morbidity.

Note: No EBUS was required in RTOG 02-36. Local failure is a bigger problem in comparison to lobectomy and would require EBRT-alone salvage as many of these patients are not chemo candidates up-front or salvage setting. Lobar recurrence is more easily salvaged with SBRT.

Conclusions: Medically inoperable NSCLC with SBRT had modest survival, high rates of tumor control, and moderate treatment related morbidity. There are noticeable lobar and regional failures, however.

SAFRON II / TROG 13.01
←R→ Phase II 90 patients SBRT 1-3 oligomets to lung ≤ 5cm in size and > 2cm from central structures | 1. 48 Gy in 4 fx | 2. 29 Gy in 1 fx |. BED_{10} 106 Gy. Concurrent systemic or targeted therapy was not allowed.
63% were male and PET staging was used in 72%. Colorectal was the commonest primary (47%), followed by lung (11%) and kidney (10%).
1^{O} CTCAE V4.0 grade 3 within 1 year of treatment.

Siva, IJROBP 2020
1-year ≥G3 toxicity 2 vs. 1.
1-year LC at 93% vs. 95%.
1-year DFS 59% vs. 60%.
Conclusion The pre-specified primary endpoint was met both 28Gy/1 fraction and 48Gy/4 fractions of SABR; therefore, comparison of both arms for secondary endpoints will be performed at trial maturation. These findings may have implications for treatment selection in resource-constrained or bundled payment environments.

RTOG 06-18
Phase II Single SBRT arm operable stage I/II NSCLC (peripheral lesions only, T1-3 N0 < 5cm) treated with 60 Gy in 3 fractions.

Timmerman, ASCO 2013.
2-year LF 19.2% (involve lobe), 11.7 % (regional failure), 15.4% (distant failure).
2-year PFS 65.4% 2-year OS 84.4%.

RTOG 09-15 Single Fraction study.
←R→ Phase 2. 94 patients biopsy-proven peripheral (≥2 cm from the central bronchial tree) T1 or T2, cN0 (PET/CT), M0 tumors were eligible.
1. 34 Gy in 1 fraction (arm 1) 2. 48 Gy in 4 consecutive daily fractions (arm 2).

Videtic, IJROBP 2015. The median follow-up time was 30.2 months.
1-year LC 97% vs 92.7%. 2-year OS 61.3% vs. 77.7%. 2-year DFS 56.4% vs. 71.1%
Adverse Events 10.3% vs. 13.3%.
CONCLUSIONS:
34 Gy in 1 fraction met the prespecified criteria and, of the 2 schedules, warrants further clinical research
NOTE: Based on most SBRT lesions, the R50% ranges from 5 to 3 for volumes 7cc to 126cc, respectively.

Cleveland Clinic -- IMRT-Based SBRT
Videtic, IJROBP 2009. Retrospective. 26 patients with 28 lesions. T1 in 79%, T2 in 21%, no tissue diagnosis in 27%. SBRT IMRT 50/5. Heterogeneity corrected. PTV = ITV + 3-5 mm. Median F/U 2.6 years
Outcome: Actuarial 3-year LC 94%, 3-year OS 52%.
Toxicity: Acute Grade 3 dyspnea in 1 patient (4%), late Grade 2 chest wall pain 1 patient (4%)
Conclusion: SBRT excellent local control and favorable survival.

Indiana University. **Phase II** SBRT, 4 year prospective Phase II.
Fakiris, IJORBP 2009. Phase II. 70 medically inoperable patients, cT1 (n=34) or cT2 (n=36), diameter ≤ 7 cm, biopsy proven NSCLC. Dose 60-66 Gy to 80% isodose in 3 fractions. Median F/U 4.2 years
Outcome: 3-year LC 88%, nodal failure 9%, DM 13%. 3-year OS 43%, CSS 82%. No difference in outcome between T1 and T2, by tumor volume, or by peripheral vs central location.
Toxicity: Grade 3+ toxicity in peripheral 10% vs. central 27% (p=0.09).
Conclusion: SBRT results in high local control in medically inoperable Stage I patients.

Timing, Technique, and Location

NOTE RTOG: RTOG 08-13 it was EOD and on 09-15 it was daily. So even within RTOG in the same era, there was no specific consensus.
NOTE Yale: For peripheral T1 lesions → 54 Gy in 3 fractions based on the results of the RTOG 02-36. When adjacent normal structures are a concern → 50 Gy in 5 fraction, or for larger lesions 55 Gy in 5 fractions (Ohri et al[9]). Do not treat on consecutive days, but this is simply Yale bias.

50 Gy in 5 Cleveland Clinic Experience
Background: American Radiation Oncologist started with RTOG protocols (02-36 and 08-13) which stated QoD SBRT Txs.
Cleveland Clinic started with Japanese data of consecutive daily SBRT treatments: ie 50 Gy in 5 fractions M-F w/o interruption and irrespective of location.
Retrospective 340 lesions in 300 patients (15% multiple treatments). All medically inoperable NSCLC treated with 50 Gy in 5 fractions from 2003-2012 with vacuum-bag based for immobilization and abdominal compression. PTV=ITV + 5 mm margin. SBRT 7-9 IMRT beams **over consecutive days.**
Median Age 74 KPS 80. Median FEV1 and DLCO (as % predicted) were 59 and 52. By RTOG 0813, 115 lesions (33.8%) were "central."
Median tumor diameter was 2.4 cm (range 0.1-10); median PET SUV max was 7.6 (range 1-59); 36.2% of tumors had no or non-diagnostic biopsies.

Videtic, IJROBP 2014. Median FU 17.4 months.
The principal co-morbidity for medical inoperability was pulmonary in 62.0% of patients, with 18.3% smoking at SBRT.
Any grade toxicity was 13.0 % (with no grades 4 or 5) and chest wall symptoms constituted 7.7%.
Central vs. peripheral lesions = the toxicity rate was 15.5% vs 11.7% (chest wall 5.8% vs 8.6%, pneumonitis 5.8% vs 3.0%).
Central vs. peripheral lesions = 5-year LC 79 vs. 75.4, 5-year DMFS 49.5 vs. 56.7, 5-year DFFS 37.2 vs. 34.3, 5-year OS 18.3 vs. 20.3.
At analysis, crude rates by lesion of local, lobar and regional nodal failure (in %) were 11.2, 4.1 and 13.5, respectively.
There were no statistically significant differences in the failure rates between central and non-central lesions for all parameters.
Conclusions A decade's experience with Lung SBRT using 50 Gy in 5 fractions reveals excellent local control. Patterns of cancer failure are mainly distant. Co-morbidities drive mortality in this population. This schedule is effective independent of tumor location in the lung, with minimal toxicities that are location-dependent.

Timing Study.
RR 107 patients T1-2 N0 linac based SBRT (50-60 Gy/fraction). consecutive daily fractions vs. in non-consecutive fractions

Alite, Radiother Oncol, 2016.
RESULTS:
3-year LC 63.6% (consecutive) vs 93.3% (non-consecutive), SS.
Multivariate analysis and propensity score matching showed that consecutive fractionation was an independent predictor of local failure.
OS trended towards non-consecutive group (NS)
CONCLUSION: Five-fraction SBRT delivered over non-consecutive days imparts superior LC and similar toxicity compared to consecutive fractionation. These results should be validated in independent datasets and in a prospective fashion.

Notes: CK vs. Linac Based VMAT SBRT Review[10]
Notes: Margins based on Histo?[11]

Post-op SBRT

Retrospective Post-op SBRT
48 patients (44, 83% were stage I-II) → surgical approaches were 47.9% wedge resection, 4.2% segmentectomy, 43.8% lobectomy, and 4.2% bilobectomy.

Sittenfeld, Clin Lung Cancer 2020.
Surgery → median time LR to local recurrence = 26.4 months → 36 (75%) recurrences were biopsy-proven.
Surgical salvage was not possible owing to un-resectability or underlying comorbidities in 45 (93.8%) patients.
Most (68.8%) patients received 50 Gy in 5 fractions. The median follow-up after sSBRT was 22.6 months (range, 3.8-108.8 months).
1-year Patterns of Failures: Eight (16.7%) local or lobar failure, and 9 (19.1%) nodal failure.
1-year Distant Failure Rates: Nineteen (39.6%).
Median OS sSBRT was 29.3 months.
Toxicity: NONE 72.9%, 3 (6.3%) patients developed grade III toxicity (cough, atelectasis, or soft tissue necrosis) following sSBRT.
Conclusions: Similar to SBRT for primary early stage NSCLC, sSBRT for local relapse following surgical resection of NSCLC offers high rates of local control with limited toxicity. Distant failure remains the primary pattern of failure.

[9] https://pubmed.ncbi.nlm.nih.gov/22999272/
[10] https://www.practicalradonc.org/article/S1879-8500(22)00001-7/fulltext
[11] https://www.mdpi.com/2072-6694/14/5/1282

Patterns of Recurrence

3 cm SBRT Shell → UPMC Retrospective
RR 304 patients and 325 lesions. Dosimetric parameters → prescribed dose, minimum and mean doses to the PTV, conformity index, and the mean EQD2 to a 30 mm shell around the PTV.

Lalonde, Radiother Oncol 2022
"There was no significant correlation between the mean EQD2 dose to a 30 mm shell around the PTV and the rate of distant metastases."
UVA → predictors of ↓ incidence of DM = PTV <22 cc (vs. ≥22 cc, p = 0.01) and GTV <10 cc (vs. ≥10 cc, p < 0.01).
Of note: GTV <10 cc also being a positive predictor of reduced incidence of regional nodal relapse (p < 0.01).
In the subset of patients treated with 4-5 fractions, mean EQD2 dose to the 30 mm shell around the PTV ≥21 Gy was associated with increased incidence of distant metastases (HR 2.42, 95% CI 1.06-5.53, p = 0.04), differing from prior data from Diamant et al.[12]
CONCLUSIONS: We did not observe a correlation between the rate of distant metastases and dose outside the PTV, as reported by other groups; rather, we noted an opposite trend in patients treated with 4-5 fractions. Our data show additional correlations between distant metastases and tumor size.

Korean SBRT → LN Recurrence
RR 114 patients SBRT with regional LN recurrence as the first recurrence.

Lee, Radiother Oncol 2023
Half of the patients had regional LN recurrence only.
The most common simultaneous recurrence was distant metastasis (38.6 %).
Common sites of regional recurrence were ipsilateral hilar (47.2 %), ipsilateral upper mediastinal (40.6 %), and subcarinal (42.5 %) LN stations.
24 (21.1 %) patients underwent salvage radiation therapy (RT), and 44 (38.6 %) patients underwent palliative treatment.
Better OS was observed in the salvage RT group (p = 0.025).
1-year PFS 27.7% Salvage RT vs. 22.8% no RT.
1-year OS 55.2% Salvage RT vs. 39.9% no RT.
MVA showed that salvage RT (PFS, HR 0.463, p = 0.050; OS, HR 0.312, p = 0.002), palliative treatment (PFS, HR 0.436, p = 0.013; OS, HR 0.553, p = 0.050), and simultaneous distant metastasis (PFS, HR 2.335, p = 0.005; OS, HR 1.726, p = 0.054) affected clinical outcomes.
Conclusion: Many cases of regional LN recurrence are confined to the locoregional area of patients, and appropriate treatment can improve the prognosis of these patients.

Salvage and RFA

CRT Salvage
RR 342 patients stage T1-3N0M0 NSCLC treated with definitive SABR from 2003 to 2018.
We evaluated the incidence of isolated hilar or mediastinal nodal recurrence (INR) and baseline factors between patients who did and did not have INR.
34 patients with INR were treated with radiation therapy alone (26.7%), concurrent chemoradiation therapy (43.3%), chemotherapy alone (13.3%), or observation (16.7%).

Devine, PRO 2023 3.3 years
3-year INR rate was 10.6% (95% CI, 6.6%-13.4%).
Among the 34 patients experiencing INR, 3-year rates of OS and PFS were 39.3% (24.4%-63.3%) and 26.7% (14.1%-0.3%), respectively.
INR with → concurrent chemoradiation therapy salvage = **best survival outcomes**
3-year OS and PFS of 81.5% (61.1%-100.0%) and 63.9% (40.7%-100.0%), respectively.
Of the patients treated with salvage radiation therapy or concurrent chemoradiation therapy, 14.3% experienced grade 3 toxic effects, and no patients had grade ≥4 toxic effects.
Conclusions In this study, INR occurred in approximately 10% of patients treated with SABR for early-stage NSCLC. The highest rates of OS and PFS among patients with INR were observed in those treated with salvage chemoradiation therapy.

Commentary: Patient population of those who were treated with salvage CRT also were the best performers.

RAPTURE "Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial."
Lencioni, Lancet Oncology 2008. Multinational prospective trial (Europe, USA, Australia). 106 patients, 183 lung tumors, <3.5cm diameter. Unsuitable for surgery, RT or chemo. NSCLC (n=33), CRC mets (n=53), other mets (n=20).
Outcome: Technical success 99%. 1-year CR 88%. 1-year OS NSCLC 70%, CRC mets 89%, other mets 92%. 2-year OS Stage I NSCLC 72%
Toxicity: Pneumothorax 1%; no SS ↓ of pulmonary function.
Conclusion: Percutaneous RFA high sustained CR, acceptable morbidity

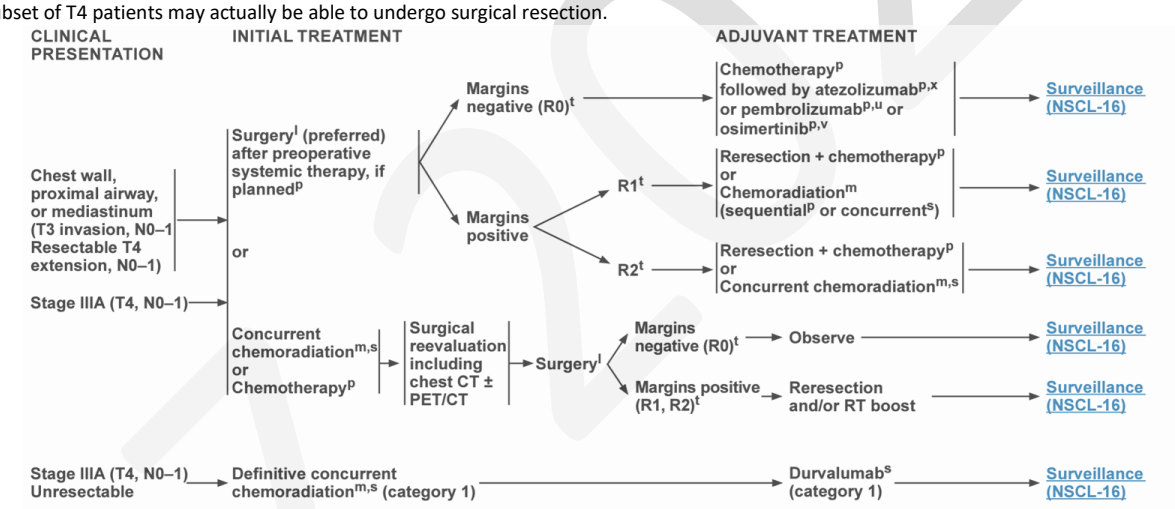
[12] https://pubmed.ncbi.nlm.nih.gov/29801721/

Advanced: Operable NSCLC (IIIA and IIIB)

Guidelines

Resectable	**Surgery → Adjuvant treatment (including Osimertinib ADAURA)** ≥ Stage II R0 → NO RT → Adjuvant Chemo + **Osimertinib** R1-2 → re-resection or radiation	PORT for N2 (50-54 Gy) CRT for R1-2/ECE (R1 54 Gy, R2/ECE 60 Gy)
	Neoadjuvant Chemo + NIVO (Checkmate-816) → surgery → ± PORT NAC Abs Survival ↑ 5% (←M→, Lancet 2014) … but perhaps subpar vs. preop-CRT Albain (see below). NAI (immunotherapy) is much better! (Checkmate-816). NAI pCR 2.2% → 24%. If persistent N2 residual disease after NAC, RR shows PORT benefit (Komiya, Radiother Oncol 2022).	
	Neoadjuvant CRT → surgery Albain Trial = 5-year OS 18% (definitive CRT) → 36% (trimodality ONLY LOBECTOMY). May reduce tumor size to decrease extent of surgery. Not a preferred option in patients who would undergo pneumonectomy.	45 Gy (25) with concurrent cisplatin and etoposide (MANY OTHER CHEMO options)
Resectable or Unresectable	**Definitive CRT → CT restaging 2 weeks after → adjuvant durvalumab start 6 weeks after.** Consider RT alone in elderly patients or poor PS	60 Gy (30) with concurrent cisplatin/etoposide or carboplatin/paclitaxel
Superior Sulcus	**Neoadjuvant CRT → surgery / completion CRT if unresectable** Preferred approach for borderline resectable T3-4 N0-1 SWOG 9416	
	Surgery → CRT Consideration for upfront resectable tumor especially for resectable tumors with significant symptoms.	

Note: Generally, stage IIIA and lower is considered resectable, since all sites of disease can be removed by extended surgery.
In contrast, stage IIIB disease (N3 or T4) is generally considered unresectable due to contralateral LN+ or extensive local tumor.
However, a subset of T4 patients may actually be able to undergo surgical resection.



Patterns of Failure

Duke Patterns of failure after resection of non-small-cell lung cancer.
Kelsey, IJORBP 2006. Retrospective, 61 pts s/p resection with neg margins, no RT, with 1st recurrence at a locoregional site (+/- distant metastasis). Surgery was lobectomy in 69%, wedge in 23%, pneumonectomy in 8%. Most did not receive neoadj/adj chemo (13%).
Most pts presented with pathologic Stage I disease (i.e. not PORT candidates).
Results: 44% presented with LRR without DM. Site of failure was brochial stump / staple line (44%), more common after a wedge resection (79% vs 34%). Mediastinum 70%, ipsi hilum 23%, supraclav 8%. Supraclav involvement more common in those who were pN1-2 vs pN0, whereas mediastinal and hilar involvement did not vary based on pN status.

Patterns of failure demonstrate a fairly predictable pattern based on the involved lobe.
Left-sided tumors: more frequent involvement of contralateral mediastinum.
Small RT fields that cover the surgical stump, ipsi hilum, and lower ipsi mediastinum would encompass at least 60% of failure sites.

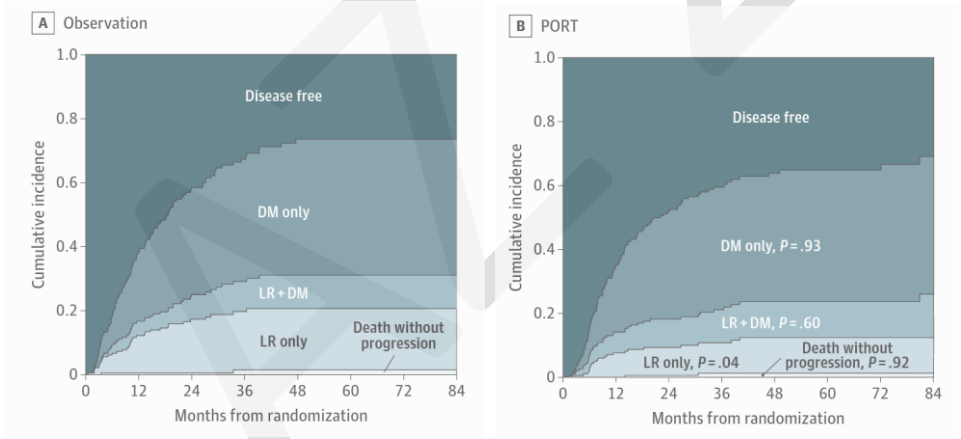
Conclusion: "These data may help clinicians construct postoperative RT volumes that are smaller than ones traditionally utilized, which may improve the therapeutic ratio."

PORT (RT Sequencing)

LungART **pN2**
←R→ Phase III 501 Pet-staged NSCLC s/p R0 resection + nodal exploration + **pN2** | 1. PORT | 2. No PORT |. AdjC or NAC allowed.
PORT = 54 Gy in 2 Gy or 1.8 Gy / fx. 3DCRT mandatory with IMRT permitted.
1O DFS.

Le Pechoux, Lancet 2021. 4.8 years.
3-year DFS 47% vs. 44% (NS). Median DFS 30·5 mo vs. 22·8 mo (HR 0.86, NS).
G3–4 Adverse Pneumonitis 13 (5%) vs. one (<1%), lymphopenia 9 (4%) vs. 0, fatigue 6 (3%) vs one (<1%).
Late G3–4 Cardiopulmonary toxicity 26 (11%) vs. 12 (5%) in the control group.
Two patients died from pneumonitis, partly related to radiotherapy and infection, and one patient died due to chemotherapy toxicity (sepsis) that was deemed to be treatment-related, all of whom were in the PORT group.
Interpretation Lung ART evaluated 3D conformal PORT after complete resection in patients who predominantly had been staged using (18F-FDG PET-CT and received neoadjuvant or adjuvant chemotherapy. 3-year disease-free survival was higher than expected in both groups, but PORT was not associated with an increased disease-free survival compared with no PORT. Conformal PORT cannot be recommended as the standard of care in patients with stage IIIAN2 NSCLC.

PORT-C Trial **pN2**
←R→ 364 patients pIIIA-**N2** NSCLC s/p complete resection → 4 cycles of platinum-based chemotherapy between January 2009 and December 2017.
| 1. PORT | 2. Obs. PORT = 50 Gy.
Surgery = lobectomy + LND (Right Lobe: 4, 7, and 10 or Left Lobe: 4, 5, 6, 7, and 10)
22% of patients assigned to PORT refused treatment.



Hui, JAMA Oncol 2021 **46 months**
3-year DFS rates 40.5% vs. 32.7%, NS.
Median DFS 22.1 vs. 18.6 months, NS.
BUT it was significant with preplanned yet exploratory analysis (stratified analysis by the # detected LN and +LN, HR, 0.75; P = .04).
In the per-protocol analysis, 3-year DFS 43% vs, 31% (SS).
3-year OS 78.3% vs 82.8% (HR, 1.02; P = .93)
3-year LRFS 66.5% vs 59.7% (HR, 0.71; P = .03).
310 per-protocol patients, PORT ↑ SS DFS (42.8% vs 30.6%; P = .05) but not OS (HR, 0.83; P = .41).
3-year LR 9.5% and 18.3% in the 2 arms, respectively (Fine-Gray HR, 0.55; Gray test P = .04).
No radiotherapy-related grade 4 or 5 adverse event was observed.

Conclusions and Relevance In this phase 3 randomized clinical trial of patients with pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy, PORT did not improve DFS. Further studies exploring patients who might best benefit from PORT are needed.

Table 2. Summary of Efficacy Results

	mITT analysis		PP analysis		AT analysis	
Outcome	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
DFS	0.84 (0.65-1.09)	.20	0.75 (0.57-1.00)	.05	0.73 (0.56-0.96)	.02
OS	1.02 (0.68-1.52)	.93	0.83 (0.53-1.30)	.41	0.72 (0.48-1.09)	.12
LRFS	0.71 (0.51-0.97)	.03	0.56 (0.39-0.80)	.002	0.52 (0.37-0.74)	<.001
DMFS	0.94 (0.72-1.22)	.62	0.85 (0.63-1.14)	.28	0.82 (0.62-1.08)	.15

Abbreviations: AT, as-treated; DFS, disease-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, locoregional recurrence-free survival; mITT, modified intent-to-treat; OS, overall survival; PP, per-protocol.

NCDB NAC → Residual Disease N2 Study **pN2 vs. downstaged pN0-1**
RR 1855 NSCLC s/p NAC → surgery R0 but with residual N2 disease (vs. downstaged N 0-1) → adjuvant radiation (≥ 45 Gy+ versus none).
Those who have received neoadjuvant radiation with any dose or adjuvant radiation with less than 45 Gy total dose were excluded.

Komiya, Radiother Oncol 2022
Overall survival Δ persistent N2 median 50.7 months vs. and downstaged N median 82.7 months.
54% total downstaged to pN0-1.
Overall survival Δ adjuvant radiation showed a non-significant detrimental effect in overall survival in the overall and downstaged cohort (univariate p-values 0.27 and 0.077, respectively); however, both univariate and multivariate analyses demonstrated a significant improvement in overall survival in persistent N2 disease cohort (p = 0.004 and 0.028, respectively). These findings are also verified by propensity-score matching analysis (p = 0.0347).
Conclusions
This large-scale retrospective analysis suggests that adjuvant radiation may still have a role in persistent N2 disease after neoadjuvant chemotherapy. Further investigations are warranted.

Francis S, et al. J Clin Oncol. 2018.
Purpose: Although several feasibility studies have demonstrated the safety of adjuvant concur. CRT for locally advanced or incompletely resected. NSCLC, it remains uncertain whether this approach is superior to sequential (C → PORT). We sought to determine the most effective treatment sequence.
Patients and Methods: NCDB, two cohorts of patients with nonmetastatic NSCLC w/ at least a lobectomy → multiagent C and RT.
Cohort 1: R0 resection and pN2 disease. Cohort 2: R1-2 resection regardless of nodal status.

Results:
COHORT 1: Median OS was 58.8 mo. if C→PORT vs. 40.4 mo if concurrent CRT, log-rank P < .001.
COHORT 2: Median OS was 42.6 mo. if C→PORT vs. 38.5 mo if concurrent CRT, log-rank P = 0.42.
Conclusion: Patients with NSCLC who undergo R0 resection and are found to have pN2 disease have improved outcomes when adjuvant chemotherapy is administered before, rather than concurrently with, radiotherapy. **For patients with positive margins after surgery, there is not a clear association between treatment sequencing and survival**.

PORT meta-analysis (Post-operative RT).
10 trials (after 1965), 2232 patients. (Added 1 trial to prior analysis). Median F/U 4.25 years
Significant adverse effect of PORT on survival; 3-year OS reduced from 58% to 52% (18% relative increase in risk of death)
Subset analysis: adverse effect in Stage I-II, N0-1 disease. No evidence of adverse effect in Stage III, N2 patients
Conclusion: PORT is detrimental. Role in N2 tumors may justify further research.

Lancet 1998
2128 pts in 9 randomized trials. Stages I-III.
Local control: 24% reduction in local recurrences
Survival: Increase in relative risk of death by 21% which corresponds to absolute 7% decrease in 2-year OS with PORT. Detrimental effect confined to Stage I-II. No difference in survival for Stage III.
Conclusion: PORT is detrimental and should not be used.
Criticism: ~25% patients had T1N0 disease; initial staging inadequate by today's standards; Co-60 used in 4 trials **(5-year OS for cobalt 8% vs. 30% for MeV)**; old techniques including lateral beams (huge fields like 12 x 12); mix of low doses (30-40 Gy) and high doses (60 Gy) and fractions (up to 3.0 Gy/fx, like 30 Gy in 10 fx), 2D planning. **Excess mortality**: Pneumonitis (outdated techniques) radiation doses varied (some did 3 gy/day and not very conformal therapy). Late effects fraction size. Doses may be too high. **No survival stage III since toxicity >>> benefit.**

Reasons for death:	PORT	Surg Alone
NSCLC related	81%	89%
Tx related	4	2
Other	15	9

Burdett, Lung Cancer 2005
Results continue to show PORT to be detrimental, with an 18% relative increase in the risk of death. Similar detriments were observed for local recurrence-free survival, distant recurrence-free survival and overall recurrence-free survival. There continues to be evidence that the effects of PORT are more harmful in those patients with stage I disease than those with stage II disease.

Adjuvant Navelbine International Trialist Association (ANITA) (1994-2000) -- Surgery +/- cisplatin and vinorelbine. PORT.
←R→ 840 patients. Stage IB-IIIA (36% IB, 24% II, 39% IIIA), complete resection.
1. Adjuvant Cisplatin 100mg/m2 + Vinorelbine 30mg/m2 x4 cycles **2.** observation. Post-op RT not mandatory → each center's policy **(given to 28%)**.
No data on fields, dose, fractions, and % of patients who completed the prescribed course.

Douillard, Lancet 2006. Median F/U 6.3 years
Outcome: 5-year OS chemo 51% vs observation 43% (SS); ↓ death by 21%. Median OS 5.5 yr vs 3.6 yr (SS). Median RFS 3.0 yr vs 1.7 yr (SS).
By Stage: No benefit for Stage IB on subgroup analysis (5-year OS 62% vs 64%, NS). For Stage II, 52% vs. 39%; Stage IIIA 42% vs. 26%.
By N status: If N0, 58% vs. 61% (NS); if N1 52% vs. 36%; if N2 40% vs. 19%.
Toxicity: neutropenia 92%, febrile neutropenia 9%, toxic deaths 2%
Conclusion: Adjuvant vinorelbine/cisplatin extends survival

Douillard, IJORBP 2008.
pN1: benefit for PORT if no chemo arm (median OS 2.2 years vs. 4.2 years), detriment for PORT if chemo arm (7.8 years vs. 3.9 years)
pN2: benefit for PORT regardless of chemo arm; if no chemo (1.1 years vs. 1.9 years), if chemo (2.0 years vs. 3.9 years)
Conclusion: Positive effect of PORT in pN2 patients, negative effect in pN1 patients who were treated with chemotherapy

SEER analysis
7645 patients stage II or III NSCLC → lobectomy or pneumonectomy → PORT. Follow-up time of 3.5 years for patients still alive.

Lally, JCO 2006.
MVA: ↓ SURVIVAL: older age, T3-4 tumor stage, N2 node stage, male sex, fewer sampled lymph nodes, high +LN.
The use of PORT did not have a significant impact on survival.
Subset pN2 disease HR = 0.855, SS ↑ increase in survival.
Subset pN0 disease HR = 1.176; SS ↓ decrease in survival. pN1 disease HR = 1.097, SS ↓ decrease in survival.
CONCLUSION: In a population-based cohort, PORT use is associated with an increase in survival in patients with N2 nodal disease but not in patients with N1 and N0 nodal disease.

NCDB Robinson 2015. pN2 Analysis.
4483 patients. pN2 NSCLC tx from 2006-2010 (modern day techniques)
PORT improved survival median OS 45.2 vs 40.7 mo. 3 year PORT 59.3 vs 55.2. 5 year PORT 39.3 vs. 34.8.
Criticism wide variability in timing of PRT with respect ot chemo 40.5% received concurrent CRT, 42.8 received > 45 days after chemo.

NCDB Sequencing Study.
Background: Although several feasibility studies have demonstrated the safety of adjuvant concurrent chemoradiotherapy (CRT) for locally advanced or incompletely resected non–small-cell lung cancer (NSCLC), it remains uncertain whether this approach is superior to sequential chemotherapy followed by postoperative radiotherapy (C→PORT). We sought to determine the most effective treatment sequence.
RR. 2 cohorts of patients with nonmetastatic NSCLC who had received at least a lobectomy followed by multiagent chemotherapy and radiotherapy.
1. R0 resection and pN2 disease 2. R1-2 resection regardless of nodal status.

Francis, Lancet 2017
Median OS: COHORT 1 C→PORT 58.8 months vs. CRT 40.4 months (SS).
COHORT 2 C→PORT 42.6 months vs. CRT 38.5 months (NS).
After propensity score matching, C→PORT remained associated with improved OS compared with CRT in cohort one (hazard ratio, 1.35; P = .019), and there was no statistical difference in OS between the sequencing groups for cohort two (hazard ratio, 1.35; P = .19).
Conclusion Patients with NSCLC who undergo R0 resection and are found to have pN2 disease have improved outcomes when adjuvant chemotherapy is administered before, rather than concurrently with, radiotherapy. For patients with positive margins after surgery, there is not a clear association between treatment sequencing and survival.

Pre-op RT

Older trials in 1960 found no benefit for preoperative RT. No OS. Only maybe improved resectability.
But newer trials with strict criteria for resectability surgical staging of mediastinal nodes, and modern attention to RT planning led to renewed efforts.

VA Trial Randomized. 331 patients, with centrally located tumors amenable to endoscopic biopsy (peripheral lesions excluded).
Arm 1) Pre-op RT vs. Arm 2) Surgery alone. RT given 40-50 Gy to primary tumor + mediastinum. Surgery 4-6 week later (maximum 12 weeks).
Lobectomy 12%, majority pneumonectomy.

Shields, Cancer 1972.
Outcome: pCR 25%. 1-year OS pre-op RT 44% vs. surgery only 60% (SS); 4-year OS 12% vs. 21%. Survival decrement during first 6 months, then curves comparable. Survival also worse with higher pre-op RT dose
Toxicity: post-op mortality 12% both groups
Conclusion: Pre-op RT worse survival, manifested during first 6 months

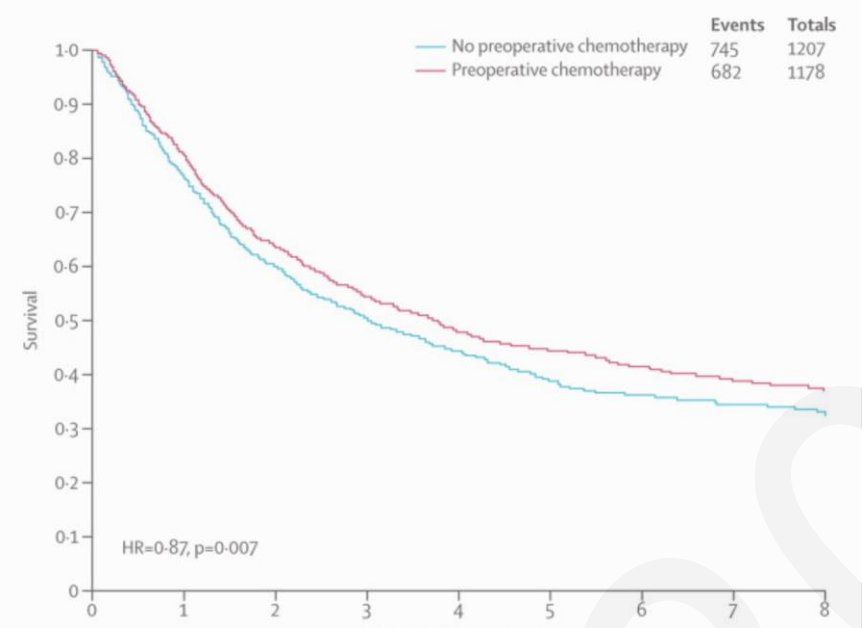
Pre-op C

Does induction chemotherapy benefit patients?

Metaanalysis

Background: Individual participant data meta-analyses of postoperative chemotherapy have shown improved survival for patients with non-small-cell lung cancer (NSCLC). We aimed to do a systematic review and individual participant data meta-analysis to establish the effect of preoperative chemotherapy for patients with resectable NSCLC.

←M→ 2385 patients in 15 randomized trials.



Lancet 2014 Results

Preoperative chemotherapy on survival (HR 0·87, 95% CI 0·78-0·96, p=0·007) = 13% ↓ in the RR of death.

This finding represents an absolute survival improvement of 5% at 5 years, from 40% to 45%.

There was no clear evidence of a difference in the effect on survival by chemotherapy regimen or scheduling, number of drugs, platinum agent used, or whether postoperative radiotherapy was given. There was no clear evidence that particular types of patient defined by age, sex, performance status, histology, or clinical stage benefited more or less from preoperative chemotherapy.

Recurrence-free survival (HR 0·85, 95% CI 0·76-0·94, p=0·002) and **time to distant recurrence** (0·69, 0·58-0·82, p<0·0001) results were both significantly in favour of preoperative chemotherapy although most patients included were stage IB-IIIA.

Results for **time to locoregional recurrence** (0·88, 0·73-1·07, p=0·20), although in favour of preoperative chemotherapy, were not statistically significant.

Interpretation: Findings, which are based on 92% of all patients who were randomised, and mainly stage IB-IIIA, show preoperative chemotherapy significantly improves overall survival, time to distant recurrence, and recurrence-free survival in resectable NSCLC. The findings suggest this is a valid treatment option for most of these patients. Toxic effects could not be assessed.

EORTC 08941 -- Induction platinum x3 cycles, then surgery vs. RT

←R→ 579 patients with unresectable IIIA-N2 NSCLC. "Unresectable" = N2 non-squamous; or N2 squamous exceeding Station 4R for right or Station 5/6 for left side. Platinum-based induction x3 cycles, then ←R→ | **1.** surgical resection | **2.** RT |.

Had to show at least "minor" response. ∴ Only 61% were randomized since induction response rate 61%.

RT: Start within 70 days of last chemo cycle. 3D planning + tissue correction.

Dose 60-62.5 Gy involved mediastinum and 40-46 uninvolved mediastinum. **RT arm compliance 55%**

Post-op RT given to 40% patients in the surgery arm only for +SM (if R1/R2, to 56 Gy).

Van Meerbeeck, J Natl Cancer Inst. 2007.

5-year outcome: OS resection 16% vs. RT 14% (NS); median OS 16 months vs. 17 months (NS)

pCR was only 5%.

Toxicity: After surgery 4% deaths. After RT Grade 3-4 pulmonary toxicity 7%, one death of RT pneumonitis (0.6%)

47% were pneumonectomies and only 50% had R0 resection.

Conclusion: Surgery did not improve OS or PFS. **Given low morbidity and mortality, RT should be preferred modality.**

INDUCTION CHEMO ALONE → SURGERY is just not enough. YOU REALLY NEED INDUCTION CRT if you want to do surgery (See Albain below).

Editorial PMID 17374824: high number of pneumonectomies, which have negative outcome after induction chemo; better local control with surgery. Surgery may be an option if patients experience "downstaging" and clear their mediastinal LNs. On the other hand, RT techniques also improving for better toxicity. Conclusion that chemotherapy-radiation is appropriate for IIIA patients with initial N2 disease.

M and M Surgery Arm, 2005. Van Schil P, Eur Respir J. 2005

167 patients in surgery arm: 50% R0; 47% pneumonectomies worse survival on subgroup analysis

Outcome: 50% R0, 40% pathologic downstaging to N0/N1

Toxicity: 30-day perioperative mortality 4%; reoperation 8%

Conclusion: morbidity and mortality acceptable

Gustave Roussy, 2000 (France). Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications." (Andre F, J Clin Oncol. 2000 Aug;18(16):2981-9.)

Retrospective. 702 patients with resected N2 disease, stratified into clinically positive and clinically negative but microscopically positive at surgery. Multi-institutional, 6 centers. Median F/U 4.3 years

5-year OS treated with surgery only:

Single level microscopic N2: 34% (site of LN+ had no prognostic significance)
Multiple levels microscopic N2: 11%
Single level clinical N2: 8%
Multiple levels clinical N2: 3%

5-year OS in clinical N2: surgery only 5% vs. preop chemo 18%

German GLCCG (1995-2003)

←R→ 524 patients with NSCLC Stage IIIA (33%) or resectable IIIB (67%). Primary endpoint PFS.

1. Induction C → CRT → surg 2. Induction C → surgery → PORT

ARM 1: Induction cisplatin 55 mg/m2 + etoposide 100 mg/m2 x3 cycles **→ CRT 45/30 in 1.5 Gy BID** with carboplatin 100 mg/m2 + vindesine 3mg.

ARM 2: Same induction → surgery → RT (54/30 if R0, 68.4/38). Surgery after 4-6 weeks.

Ruebe, ASTRO 2004. Phase III.

Results: 3-year OS 26.2% (Arm A) vs 24.6% (Arm B) (NS). 3-year PFS 17.8% vs 19.9% (NS). Difference was in toxicity, with worse Grade 3/4 esophagitis in Arm A (19% vs 3%), and worse Grade 3/4 pneumonitis in Arm B (6% vs 1%). No difference in treatment related toxicity.

Conclusion: both regimens are effective.

Thomas, Lancet Oncology 2008.

Outcome: Complete resection 37% vs. 32%.

If Complete Resection, mediastinal downstaging ARM1 46% vs. ARM2 29%, p=0.02, and pathological response 60% vs. 20%, p<0.0001.

Median PFS 10.0 mo vs. 9.5 (NS). 5-year PFS 16% vs. 14% (NS).

Both, 35% of patients undergoing surgery received a pneumonectomy. If pneumonectomy, treatment-related mortality 14% vs 6% (SS).

Conclusion: Preop Chemo-RT ↑ mediastinal downstaging, but doesn't ↑ survival**. After induction, pneumonectomy should be avoided.**

Pre-op CRT

European SAKK Trial
←R→ 232 p stage IIIA/N2 NSCLC | 3 c neoadjuvant cisplatin + docetaxel → RT 44 Gy → Surg | chemotherapy → surg |.
Cisplatin 100 mg/m(2) and docetaxel 85 mg/m(2), RT 44 Gy in 22 fractions over 3 weeks. 1^{O} event-free survival.

Pless, Lancet 2015.
Median EFS 12·8 vs. 11.6 months (NS). Median OS 37·1 months vs. 26·2 months.
Chemotherapy-related toxic effects were reported in most patients, but 91% of patients completed three cycles of chemotherapy. Radiotherapy-induced grade 3 dysphagia was seen in seven (7%) patients. Three patients died in the control group within 30 days after surgery.
INTERPRETATION: Radiotherapy did not add any benefit to induction chemotherapy followed by surgery. We suggest that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA/N2 non-small-cell lung cancer.
Criticisms: NOT designed to R/O noninferiority of OS. pCR this trial was 12-16%, whereas neoadjuvant CT is ~30%. 25 patients each arm did NOT receive assigned treatment. Finally, this is SEQUENTIAL C→ RT→ Surg.

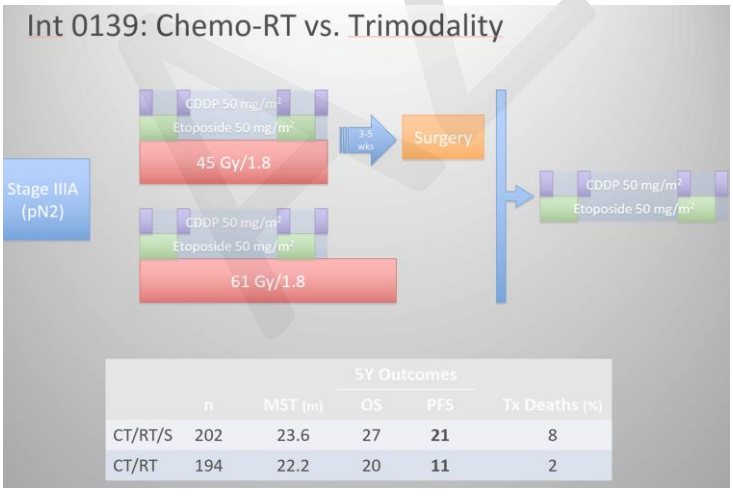
Intergroup N2 disease STUDY INT-0139 (RTOG 93-09, SWOG 93-36) (1994-2001) --
←R→ 396 patients with **stage IIIA (pN2)** lymph node positive NSCLC.
| 1. Induction CRT → CT restaging 2-4 weeks → **complete surgical resection** with LN evaluation **| 2. Definitive CRT |**
BOTH GET CONSOLIDATION C.

Induction CRT:	RT 45 Gy / 1.8	Cisplatin 50 mg/m2 x2 cycles, etoposide 50 mg/m2 x2 cycles.
Definitive CRT:	RT 61 Gy / 1.8	Same
Consolidation C:		Cisplatin/etoposide in both groups x2 cycles.

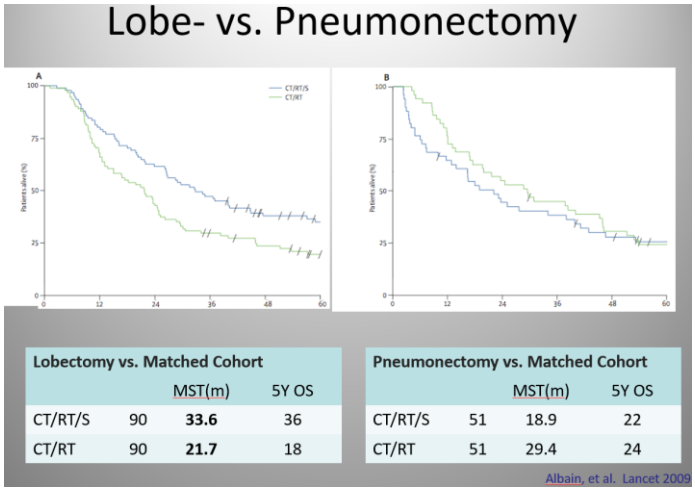
Primary endpoint OS.

Albain, JCO 2005.
Outcome: Median PFS: CRT+S 12.8 months vs. CRT 10.5 months (SS); 5-year PFS 22% vs. 11% (SS)
Median OS: 23.6 month vs. 22.2 months (NS); 5-year OS: 27% vs. 20% (p=0.1)
Subgroup analysis OS revealed better survival for patients who underwent a lobectomy (p = .002).
Trimodality therapy was not optimal when a pneumonectomy was required owing to the high mortality risk.
N0 status at surgery significantly predicted a ↑ 5-year survival rate.
Conclusion: significantly improved PFS but not OS with trimodality, UNLESS (subgroup) they get lobectomy vs. pneumonectomy.

Albain, Lancet 2009. Median F/U 1.8 years, for survivors 5.8 years.
Outcome: Median OS Induction 24 mo vs. definitive 22 mo (NS). 5-year OS 27% vs. 20% (NS).
Median PFS 13 months vs. 11 months (SS). 5-year PFS **CRT → surgery 22%** vs **CRT 11%**.
First relapse: primary tumor site 2% vs. 14%, regional LNs 7% vs. 3%, **brain 11% vs. 15%**
DM 37% vs. 42%. ∴ Seems to fail distantly, regardless of treatment and regardless of local control.
Subset analysis: Lobectomy vs matched CRT 2.8 years vs. 1.8 years (SS); pneumonectomy vs matched CRT 1.6 years vs. 2.4 years (NS)
This led to a 5-year OS DOUBLING of 18% → 36% if lobectomy alone.
Toxicity: Treatment-related death 8% vs. 2%. Grade 3-4 esophagitis 10% vs. 23% (SS), no difference in pneumonitis or nausea/vomiting
Conclusion: Chemo-RT with or without resection (preferably lobectomy) are all options for IIIA NSCLC
Pneumonectomy mortality rate was higher than expected at 26%.



	n	MST (m)	5Y Outcomes OS	PFS	Tx Deaths (%)
CT/RT/S	202	23.6	27	**21**	8
CT/RT	194	22.2	20	**11**	2



Lobectomy vs. Matched Cohort		MST(m)	5Y OS
CT/RT/S	90	**33.6**	36
CT/RT	90	**21.7**	18

Pneumonectomy vs. Matched Cohort		MST(m)	5Y OS
CT/RT/S	51	18.9	22
CT/RT	51	29.4	24

Albain, et al. Lancet 2009

RTOG 02-29 - Phase II. 2010 IJROBP Abstract: Stage IIIA(T1-3N2) or IIIB(N3) resectable at diagnosis.
Treated with induction chemo/RT, **carboplatin and taxol** weekly x 6 weeks and RT to 61.2 Gy. Surgery evaluation 4-6 wks after chemo/RT.
Consolidative carbo/taxol x 2 cycles. Recommended prophylactic cranial irradiation (on RTOG 02-14).
RT dose: 50.4 Gy (offcord by 45 Gy) + 10.8 Gy boost.

Result: 43 pts (75%) were evaluable; 36 pts underwent resection. 7 pts had residual mediastinal dz.
27/43 (63%) achieved mediastinal clearance: improved mediastinal sterilization (50-->70%, power of 80%, p=0.05)
Med f/u 20 months,** med OS: 26.6 mos; med PFS: 13.1 mos; 1-y OS: 77%; 1-y PFS: 52%
Toxicity: 14% (5/37) G3 post-op pulmonary complications; 1 post-op G5 toxicity (3%).
Conclusion: confirms the ability of neoadj CCRT to sterilize known mediastinal nodal disease.

SWOG 8805 - Phase II. 126 pts. Biopsy proven N2, N3, or T4. IIIA 60%, IIIB 40%. 85% of IIIA and 80% of IIIB were resected.
THINK OF THIS AS THE BUILDUP TO ALBAIN INT-0139.
Concurrent chemo/RT (2 cycles cisplatin + etoposide + 45 Gy RT), followed by surgery.

Albain, JCO 1995. Median f/u 2.4 yrs.
2-yr OS 37%, 3-yr 24-27%. Strongest predictor of survival was pCR in mediastinal LN (30 months vs 10 month MS; 5-yr OS 33% vs 11)%.
Conclusion: induction chemo/RT before surgery is feasible for N2 disease.
So.., for IIIA neoadjuvant CRT, but most people think for IIIB, is just neoadjuvant chemotherapy.
R sided tumors more morbidity for pneumonectomy.

Advanced: Inoperable NSCLC

- **NCCN guidelines**:
  - Workup: see above.
  - Recommended treatments: See above.

- Overview:
  - Patients were initially treated with radiation only, usually split course
  - **Dose-escalation in RTOG 73-01 (Perez)** established 60 Gy in 2 Gy/fx as the standard regimen
    - Median survival was ~10 months, with 3-year survival <10%
  - Hyperfractionated RT alone did not show any beneft
    - Continuous Hyperfractionated Accelerated RadioTherapy (CHART) showed a significant improvement in OS. However, logistics of delivering RT TID x12 days straight, combined with OS improvement with chemotherapy have limited its adoption
  - CALGB, RTOG, and UK studies in mid-1990's established induction chemo + RT superior for median OS, although absolute benefit was not large (2-4 months). There was a significantly higher proportion of long term survivors. There was no impact on local progression, but distal failure was significantly less
    - Hyperfractionated RT after chemo induction did not show any benefit over standard RT
    - Induction chemo alone, without RT, was comparable in median OS, but inferior in long term survivors compared to induction chemo + RT. **RT was considered a necessary component of treatment.**
  - At the same time, concurrent chemotherapy and RT were evaluated.
    - The only survival benefit of concurrent chemo-RT over RT alone was in an EORTC trial, which used split-course RT with a 3 week rest. The other 3 trials with standard RT fractions were negative. The chemo used was a single agent.
  - **Concurrent chemo (2 agents) with hyperfractionated RT resulted in OS benefit in 2 Yugoslavian trials**
  - Small overall chemo benefit was demonstrated in a meta-analysis setting in 1995, and confirmed to be 4% absolute benefit at 2 years in a subsequent meta-analysis.
    - Essentially any two agents are superior to any single agent; adding a third drug did not provide additional benefit
    - However, the timing of giving chemotherapy and RT was unclear. Both induction and concurrent chemo appear to provide survival benefit, induction chemo via improved distal control and concurrent chemo via improved local control.
  - Direct comparisons in several randomized trials established concurrent chemo-RT as the superior regimen, at the cost of increased in-field toxicity (especially esophagitis)
  - **There is no benefit to induction chemotherapy, followed by concurrent chemo-RT (CALGB B39801, LAMP)**.
    - The later RT starts, the worse the outcomes
  - **The current standard of care = concurrent chemo with 2 agents containing platinum, and thoracic RT to 60 Gy in QD fractions**.
    - **The advent of immunotherapy increased survival**. Thus, Durva has become standard of care.

Dosing of Chemo

See below study Elderly Okamoto 2020
Under Δ C

SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[1]

Preferred (squamous)
- Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[2]
- Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[3]

Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[4]
- Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5,6]
- Cisplatin 75–80 mg/m² day 1; vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1; etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[5]

Useful in Certain Circumstances

Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[7]
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[8]
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[9]

All regimens can be used for sequential chemotherapy/RT.

Previous Adjuvant Chemotherapy or Ineligible for Platinum-Based Chemotherapy
- Osimertinib 80 mg daily[10]
  - Osimertinib for patients with completely resected stage IIB-IIIA or high risk stage IB-IIA *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.

CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens

Preferred (nonsquamous)
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT[1,*,†,‡]
- Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT[2,3,*,†,‡] ± additional 4 cycles of pemetrexed 500 mg/m²[†,§]
- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[4,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Preferred (squamous)
- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[6,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Consolidation Therapy for Patients with Unresectable Stage III NSCLC, PS 0-1, and No Disease Progression After 2 or More Cycles of Definitive Chemoradiation

Durvalumab 10 mg/kg IV every 2 weeks for up to 12 months[r] (category 1)

[*] Regimens can be used as preoperative/adjuvant chemotherapy/RT.
[†] Regimens can be used as definitive concurrent chemotherapy/RT.
[‡] For eligible patients, durvalumab may be used after noted concurrent chemo/RT regimens.
[§] If using durvalumab, an additional 2 cycles of chemotherapy is not recommended, if patients have not received full-dose chemotherapy concurrently with RT.

RT alone / Hypofx

Florida Proton Phase I Hypofx CRT
18 patients treated (closed to slow accual) concurrent CRT stage II (28%), or III (72%). Half were N2.
Stepwise 5 + 2 dose intensification protocol all to 60 Gy RBE | 1. 2.5 GyRBE /fx x 24 | 2. 3.0 GyRBE / fx x 20 | 3. 3.53 GyRBE x 17 | 4. 4.0 GyRBE x 15 |.
GTV = gross tumor and nodes on 4D-CT + an additional 6 mm ITV margin on the lung tumor (not nodes) and a 5-10 mm PTV margin. Passive-scatter, uniform-scanning, and pencil-beam techniques were used.
1^{O} = grade ≥3 dose-limiting esophageal or pulmonary toxicity at 3 months.

Hoppe, IJROBP 2021
Two SAEs occurred among 7 patients treated at 3.53 GyRBE per fraction; however, per outside expert review, both were attributed to chemotherapy and unrelated to radiation therapy.
Conclusions: Hypofractionated proton therapy delivered at 2.5 to 3.53 GyRBE per fraction to a dose of 60 GyRBE with concurrent chemotherapy has an acceptable toxicity profile. Further exploration of this regimen is warranted on a phase 2 clinical trial.

Retrospective HypoFx for Stage III
42 patients with stage III disease 60 Gy in 15 fx. Most → induction chemotherapy. Eligible: < 7 cm post-chemo tumor burden. No esophagus abutment. No concurrent chemotherapy. RT = post-chemo primary and nodal disease. PTV = 5-10 mm. > 1/3 did NOT receive 60 Gy (toxicity).

Kong, IJROBP 2020. 46 months.
Median OS 47 months. 1-year OS 81% 2-year OS 69% 3-year OS 64% 5-year OS 32%.
The 1-, 2-, 3-, and 5-year progression-free survival rates were 58%, 35%, 25%, and 25%, respectively.
An isolated locoregional recurrence was seen in 12% of the patients (n = 5). The incidence of grade (G) 3 or higher treatment-related lung toxicity was 14% (n = 6), among which G3 toxicity was 9.5% (n = 4) and G5 toxicity was 4.8% (n = 2). Twelve percent of patients (n = 5) experienced G3 radiation esophagitis, and 2% (n = 1) had G4 esophageal toxicity.
Conclusions Patients with unresectable locally advanced non-small cell lung cancer treated with hypofractionated intensity modulated radiation therapy in doses up to 60 Gy at 4 Gy per fraction had promising survival, *although high-grade esophageal and lung toxicities were seen*. Our findings deserve further evaluation in prospective studies.

Phase III 60 Gy in 15 fractions
←R→ 103 patients NSCLC (stage II non-surgical candidates OR stage III NSCLC non CRT candidates due to PS ≥ 3)
| 1. conventional 60-66Gy/30-33fx | 2. hypofractionated 60Gy/15fx |. 1^{O} OS.
Chemotherapy was permissible sequentially either as induction or in the adjuvant setting.
53% SCC. 47% AC. 53/60 patients presented with stage III disease, 7/60 with stage II.

Iyengar, IJROBP 2016 Prelim Study Findings.
48/60 patients were evaluable due to adequate length of follow-up at this time. 56% of patients (27/48) were alive at last follow-up.
Median OS ~11.5 months (NS). Median PFS ~14 months (NS).
Grade 3 toxicities 10 vs. 6.
Conclusion
A curative approach with accelerated, hypofractionated radiation alone is equivalent in OS and PFS to conventional radiation in a population of poor PS patients, with less grade 3-5 toxicity, and a treatment course of half the time. Completion of this study will potentially change the paradigm of treatment of poor PS stage III NSCLC patients who cannot receive chemoradiation.

Iyengar, JAMA Oncol 2021 Final Eval
1-year OS 44.6% vs. 37.7% (NS). There were no Δ median OS, PFS, or time to LF, time to DM.
No Δ to toxic effects of grade 3 or greater between the 2 treatment groups.
Conclusions and Relevance This phase 3 randomized clinical trial found that hypofractionated IGRT (60 Gy in 15 fractions) was not superior to CFRT (60 Gy in 30 fractions) for patients with stage II/III NSCLC ineligible for concurrent chemoradiotherapy. Further studies are needed to verify equivalence between these radiotherapy regimens. Regardless, for well-selected patients with NSCLC (ie, peripheral primary tumors and limited mediastinal/hilar adenopathy), the convenience of hypofractionated radiotherapy regimens may offer an appropriate treatment option.

VA Lung Group (VALG) -- RT vs. placebo vs. chemotherapy
←R→ 3 arms. 800 patients. Localized but inoperable (mostly due to bulky disease). KPS 80-100 33%, KPS 50-70 55%.
1. RT **2.** placebo (lactose) **3.** chemo (not reported here). RT given: orthovolatage in 90% (200-260 kV), Cobalt-60 in 10%. Target dose 40-50 Gy, but 33% received <40 Gy (2/3 died, 1/3 medical complications)

Roswit, Radiology, 1968.
Outcome: Median OS: RT 4.6 months vs. placebo 3.7 months (NS); 1-year survival: RT 18% vs. placebo 14% (p=0.05).
Long-term survivors (top 25%): RT 10 months vs. 7.6 months (SS). Better survival if longer symptomatic prior to diagnosis, suggesting slower rate of growth
Conclusion: RT does not impact median OS, but improves long-term survival.

RTOG 73-01. 4 arm PRT

←R→ Dose escalation Stage III NSCLC.

Patients with T1, 2, 3-N0, 1, 2 tumors were randomized to four different regimens:

1. 4000 cGy split course (2000 cGy in five fractions, per 1 week, 2 weeks rest and additional 2000 cGy in five fractions, per 1 week)
2. 4000,
3. 5000
4. 6000 cGy continuous courses, five fractions per week.

Patients with T4, any N or N3, any T stage tumors were randomized to be treated

1. 3000 cGy tumor dose (TD), ten fractions in 2 weeks,
2. 4000 cGy split course (described above),
3. 4000 cGy continuous course

> **Perez, Cancer 1987.**
> 2-year OS was 10-18% with split course giving worst rates.
> **Conclusion: 60 Gy is standard dose**.

RTOG 02-13.

Phase I/II trial celecoxib concurrent with 60 Gy / 30 fx or 45 Gy / 15 fx stage IIB-IIIB lung cancer patients with "intermediate" prognosis (PS 2 or weight loss > 5%). Closed early after 13 patients. MS 10 months.

> **Gore, Clin Lung Cancer 2011.**
> Conclusion: Although underpowered, this one gives reference for management of intermediate prognosis patients.
> **Basically 45 Gy / 15 fractions was biologically equivalent regimen for maybe poor performers, which can be treated RT alone**.

CALGB 8433 trial.

←R→ 155 clinical or surgical stage III, histologically documented NSCLC; a CALGB performance status of 0-1; less than 5% loss of body weight in the 3 months preceding diagnosis; and radiographically visible disease.

| 1. C → RT | 2. RT alone | C: cisplatin (100 mg/m2 BSA IV days 1 and 29) and vinblastine (5 mg/m2 BSA IV weekly on days 1, 8, 15, 22, and 29). RT: 6000 cGy given in 30 fractions beginning on day 50 if C → RT.

> **Dillman, JNCI 1996.**
> Rate of tumor response, as determined radiographically, was 56% for the CT-RT group and 43% for the RT group (P = .092).
> Median OS 13.7 vs. 9.6 months (SS).
> **CONCLUSIONS:** Long-term follow-up confirms that patients with stage III NSCLC who receive 5 weeks of chemotherapy with cisplatin and vinblastine before radiation therapy have a 4.1-month increase in median survival. The use of sequential chemotherapy-radiotherapy increases the projected proportion of 5-year survivors by a factor of 2.8 compared with that of radiotherapy alone. However, inasmuch as 80%-85% of such patients still die within 5 years and because treatment failure occurs both in the irradiated field and at distant sites in patients receiving either sequential chemotherapy-radiotherapy or radiotherapy alone, the need for further improvements in both the local and systemic treatment of this disease persists.

Other trials: Kong, Int J Radiat Oncol Biol Phys 2020

Concurrent CRT Trials

Meta-analysis: **NSCLC Collaborative Group; 2010** "Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non-Small-Cell Lung Cancer." Meta-analysis. Individual patient data from 6 trials (CALGB 8831, WJLCG, RTOG 9410, GMMA Ankara, GLOT-GFPC NPC 95-01, EORTC 08972). 1205 patients. Median F/U 6 years.

Auperin, JCO 2010.
Outcome: Benefit of concomitant chemo-RT over sequential chemo → RT on OS (HR 0.84, SS).
ABSOLUTE OS BENEFIT 3-years of 5.7% (18% to 24%), **5-years 4.5% (11% to 15%)**. No difference in PFS (HR 0.9, p=0.07).
↓ in LR progression (HR 0.777, SS), with **5-year absolute ↓ of 6%** (35% to 29%).
No Δ distant progression (HR 1.04, NS), with 5-year rate of ~40%
Toxicity: Acute Grade 3-4 esophageal toxicity worse (RR 4.9, SS), increase from 4% to 18%; no significant difference in acute pulmonary toxicity
Conclusion: Concomitant chemo-RT compared with sequential chemo-RT improved overall survival, primarily through better locoregional control, **at cost of manageable increase in acute esophageal toxicity.**

RTOG 94-10 "Sequential vs Concurrent Chemoradiation for Stage III Non-Small Cell Lung Cancer: Randomized Phase III Trial RTOG 9410."
←R→ Inoperable / unresectable Stage II-IIIB, ineligible for RTOG 93-03. Elective nodal irradiation is required.
1. chemo (vinblastine + cisplatin) → RT begin on day 50. Vinblastine weekly x 5. Cispl. 100 mg/m2 q3w x 2. RT 45 Gy + 2 Gy x 9 boost (63 Gy total).
2. concomitant chemo/RT (same chemo & RT as in Arm 1). (Based on RTOG 90-15 but with qd RT)
3. concomitant chemo (oral etoposide and cisplatin) and hyperfractionated RT. Oral etoposide 50 mg BID given on RT days only for weeks 1-4. Cisplatin 50 mg/m2 on days 1,8,29,36. RT dose 69.6 Gy at 1.2 Gy BID. (Based on RTOG 91-06).
Published at a median f/u of 11 yrs (prior ASTRO Abstract in 2003).

Curran, J Natl Cancer Inst 2011.

Results:	Median OS:	SEQ 14.6 mo	vs. CON-QD 17.0 mo (SS vs. SEQ)	vs. CON-BID 15.6 mo.
	5-year OS:	SEQ 10%	vs. CON-QD 16% (SS vs. SEQ)	vs. CON-BID 13%

LC was NS (60-70% with arm 2 being the best).
Side effects: Arm 1 5% esophagus 40% Arm 2.
Conclusion: Concurrent chemo-RT with cisplatin confers a long-term survival benefit over sequential therapy.

RTOG 90-15 - PMID 7712445 - Phase I/II - BID RT with concurrent vinblastine + cisplatin. (Provided Arm 2 of RTOG 94-10)
RTOG 91-06 - PMID 8648357 - Phase II - BID RT with concurrent oral daily etoposide + IV cisplatin. (Provided Arm 3 of RTOG 94-10)

Induction Chemotherapy

Concurrent Chemo-RT +/- Induction Chemo: **There appears to be NO benefit to induction chemotherapy in 2 randomized trials.**

CALGB B39801 (1998-2002) -- Induction carboplatin/paclitaxel -> RT vs chemo-RT
←R→ 366 patients with unresectable Stage III NSCLC. Randomized to Arm 1) Concurrent carboplatin (AUC=2)/paclitaxel (50 mg/sq m) with RT 66 Gy. Arm 2) Induction with carboplatin(AUC=6)/paclitaxel (200 mg/sq m) x2 cycles, then concurrent chemo-RT as Arm 1

Vokes, JCO 2007. PMID 17404369.
Outcome: MS induction 12 months vs. no induction 14 months (NS); 2-year OS 29% vs. 31% (NS)
Toxicity: Induction chemo neutropenia (20% Grade 3-4), no difference between concurrent CRT arms
Conclusion: Addition of induction chemo added toxicity without survival benefit.
Comment: Low survival compared to other trials, possibly due to lower chemo dose due to using carboplatin and not cisplatin.

Criticism: Vokes only used 2D planning.

Locally Advanced Multimodality Protocol (LAMP), 2005 (1998-2001) - Randomized Phase II. Closed early due to nonaccrual. Opened before concurrent chemo-RT was established as standard, with Arm 1 sequential chemo-RT as control. Arm 2 was closed early at interim analysis. Eventually interest in Arm 1 slowed down, and trial was closed. Results compared to historical RTOG 88-08.
←R→ 276 pts. Stage IIIA or IIIB (medically inoperable N2, T4, or T3). KPS >= 70%, wt loss <= 10%.
Arm 1: C → RT.
2 cycles of paclitaxel (200 mg/m2) and carboplatin (AUC 6) every 3 weeks. RT on day 42 (3 weeks after last chemotherapy cycle), 45 Gy + 18 Gy = 63 Gy, to postchemo volume.
Arm 2: C → CRT
2 cycles of chemotherapy (as in Arm 1) followed by RT (as in Arm 1) given concurrently with weekly Taxol (45 mg/m2) + 2 cycles of carboplatin (AUC 2) q3weeks x 2 cycles
Arm 3: CRT → C
Concurrent chemo/RT (as in Arm 2) followed by two cycles of chemotherapy (as in Arms 1&2) 3-4 weeks after completion of concurrent therapy.

Belani, JCO 2005. Median f/u 39.6 months.
Median survivals 13 months vs 12.7 months vs **16.3 months**.
Overall survival at 1,2,and 3 years for Arm 1: 57%, 30%, 17;
Arm 2: 53%, 25%, 15%
Arm 3: 63%, 31%, 17%. NS for any of the arms compared to RTOG 88-08.
Conclusion: No statistically significant difference in survival for any of the arms (vs. RTOG 88-08). **Suggestion of improved outcome for Concurrent chemo/RT -> consolidative chemo**.

NOTE: CALGB 30105 (Dose escalated 74 Gy + Induction/concurrent carbo/taxol vs. carbo/gemcitabine). Socinski, JCO 2008.
←R→ 69 patients phase III. *Arm 2 closed prematurely due to toxicity.* Stage IIIA-B.
| 1. induction carbotaxol → concurrent carbotaxol RT 74 Gy | 2. Carboplatin + Gem → concurrent gem + RT 74 Gy |.
Primary endpoint OS at 1.5 years
Median OS median OS carbo/taxol 2.0 years vs. carbo/gem 1.0 years
Toxicity: High Grade 4-5 rate in carbo/gem arm
Conclusion: Carbo/taxol arm better and will be compared with standard dose TRT

Meta-analysis
Gustave-Roussy, 2004 "**Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen** in advanced NSCLC.
65 randomized trials performed 1980-2003 (13,601 patients)

Delbaldo, JAMA 2004.
Doublet vs. single-agent: better tumor response (OR 0.42), median OS (OR 0.3), 1-year OS (OR 0.80)
Triplet vs. doublet: better tumor response (OR 0.66), no impact on survival (OR 1.01, 1.00)
Conclusion: doublet better than single-agent; triplet no additional survival benefit

Japanese Elderly Study **If > 75 yo, go carboplatin pemetrexed**
←R→ 433 patients Phase III. NO targetable mutations | 1. Docetaxel monotherapy | 2. Carboplatin + pemetrexed → pemetrexed maintenance |.
1^{O} OS

Okamoto, JAMA 2020.
Median OS was 15.5 months vs. 18.7 months (HR 0.850, NS)
Pemetrexed BETTER Rates of leukopenia 68.7% → 28.0%, neutropenia 86% → 46.3%, G3-4 febrile neutropenia 17.8% → 4.2%.
Pemetrexed WORSE Rates thrombocytopenia 1.4% → 25.7%, anemia 1.9% → 29.4%.
Dose reductions were less frequent with carboplatin-pemetrexed.
Conclusion and Relevance Carboplatin-pemetrexed treatment followed by pemetrexed maintenance is a valid option for first-line treatment of elderly patients with advanced nonsquamous NSCLC.

Chinese Study -- **IF SCC, GO EP!**
←R→ 191 locally advanced Stage III NSCLC
SCC 65%, Adeno 20%, NOS 15%
1. CRT 60-66 Gy + etoposide 50 mg/m2 on days 1-5 and cisplatin 50 mg/m2 on days 1 and 8 every 4 weeks for two cycles (EP arm)
2. CRT 60-66 Gy + paclitaxel 45 mg/m2 and carboplatin (AUC 2) on day 1 weekly (carbotaxel arm).
The primary end point was overall survival (OS).

Liang, Ann Oncol 2017.
Absolute 3-year OS 15.0% favoring EP (p = 0.024). MS 23.3 mo vs. 20.7 (NS!!!)
Grade ≥2 radiation pneumonitis 18.9% vs. **33.3%** (P = 0.036) Grade ≥3 esophagitis 20.0% vs. 6.3%, P = 0.009).
Pulmonary think PC Esophagitis think **E**P
CONCLUSION: EP might be superior to weekly PC in terms of OS in the setting of concurrent chemoradiation for unresectable stage III NSCLC.

VA Health Data --- **If SCC, GO carbotaxel!**
RR 1842 NSCLC patients treated with CRT (EP and carbotaxel). 2001 – 2010.
Propensity matched **SCC 50%**, AC 20%, NOS 30%.

Santana-Davila, JCO 2015.
RESULTS: EP was used in 27% (n = 499). **NO DIFFERENCE IN SURVIVAL.**
Hospitalization EP 2.4 v carbotaxel 1.7; (P < .001) Outpatient visits (17.6 v 12.6 visits, respectively; P < .001)
Infectious complications (47.3% v 39.4%, P = .0022), Acute kidney disease/dehydration (30.5% v 21.2%, P < .001),
Mucositis/esophagitis (18.6% v 14.4%, respectively; P = .0246).
CONCLUSION: After accounting for prognostic variables, patients treated with EP versus CP had similar overall survival, but EP was associated with increased morbidity.

PROCLAIM
←R→ 555 stage IIIA/B unresectable **nonsquamous** NSCLC randomly
1. CRT 60-66 Gy + pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 IV q3 weeks x 3c → pemetrexed consolidation q3 weeks x 4c.
2. CRT 60-66 Gy + etoposide 50 mg/m2 and cisplatin 50 mg/m2 IV q 4 weeks x 2c → consolidation platinum-based doublet chemotherapy x 3c.
The primary objective was OS.

Senan JCO 2016. Enrollment was stopped early because of futility. Median OS 26.8 v 25.0 mo.
Pemetrexed + cisplatin SS ↓ drug-related G3-4 (64.0% v 76.8%; P = .001) AKA Neutropenia (24.4% v 44.5%; P < .001).
Conclusion: Pemetrexed-cisplatin combined with TRT followed by consolidation pemetrexed was not superior to standard chemoradiotherapy for stage III unresectable nonsquamous non–small-cell lung cancer.

Consolidation C

Hoosier Oncology Group **TERMINATION EARLY FUTILITY**
←R→ 203 stage IIIA or IIIB NSCLC, PS 0 to FEV 1 ≥ 1 L, and less than 5% weight loss. 34% female. 63 years; 39.4% stage IIIA, 60.6% stage IIIB.
All received concurrent CRT cisplatin and etoposide 50 mg/m^2 and chest XRT to 59.40 Gy.
If patient did NOT progress, then randomized | 1. docetaxel 75 mg/m^2 q 21d x 3c | 2. Obs |.

Hanna, JCO 2005
All comers MST 21.7 months. MST 21.2 months vs. 23.2 months (NS)..
Grade 3 to 5 toxicities during docetaxel included febrile neutropenia (10.9%) and pneumonitis (9.6%); 28.8% of patients were hospitalized during docetaxel (v 8.1% in observation arm), and 5.5% died as a result of docetaxel.
CONCLUSION: Consolidation docetaxel after PE/XRT results in ↑ toxicities but does **not further improve survival** compared with PE/XRT alone in patients with stage III inoperable NSCLC.

Jalal, Ann Oncol 2012
Median OS the overall study population was 21.5 months. 3-, 4-, and 5-year OS 30.7%, 18.0%, and 13.9%, respectively.
NS survival between D and O arms.
Older patients had similar MST (17.1 versus 22.8 months for younger patients, P = 0.15) but higher rates of grade 3/4 toxicity and hospitalization during induction.

Korean Adjuvant Chemo Trial KCSG-LU05-04
←R→ 437 all stage III NSCLC all received CRT → | 1. Obs | 2. consolidation chemo x 3c|.
CRT docetaxel (20 mg/m(2)) and cisplatin (20 mg/m(2)) was administered every week for 6 weeks with 66 Gy.
Adjuvant chemo = docetaxel and cisplatin DP (35 mg/m(2) each on days 1 and 8, every 3 weeks.

Ahn, JCO 2015.
WEAKNESS: In the consolidation arm, 143 patients (68%) received CC, of whom 88 (62%) completed three planned cycles.
Median PFS 8.1 vs. 9.1 months (NS). Median OS 20.6 and 21.8 (NS).
CONCLUSION: No difference. Definitive CRT should remain the standard of care.

PET- Boost Trial Closed to Slow Accrual

Background: We aimed to assess if radiation dose escalation to either the whole primary tumour, or to an 18F-FDG-PET defined subvolume within the primary tumour known to be at high risk of local relapse, could improve local control in patients with locally advanced non-small-cell lung cancer.
←R→ 150 inoperable, stage II-III NSCLC → dose-escalated RT to | 1. whole primary tumour | 2. or a PET-defined subvolume |.
RT = 66 Gy in 24 fractions (nodes) + SIB 72 Gy or ALARA via OAR constraints.
Median dose/fraction to the boosted volume was 3.30 Gy in the whole tumour group, and 3.50 Gy in the PET-subvolume group.
Inclusion: tumor size >4 cm, SUVMax >5.
1^{O} FFLF

Cooke, Radiother Oncol 2023
1-year FFLF rate 97% vs. 91%.
Acute grade ≥ 3 adverse events occurred in 23 (43 %) and 20 (38 %) patients, and late grade ≥ 3 in 12 (22 %) and 17 (32 %), respectively.
Grade 5 events occurred in 19 (18 %) patients in total, of which before disease progression in 4 (7 %) in the whole tumour group, and 5 (9 %) in the PET-subvolume group.
Conclusion Both strategies met the primary objective to improve local control with 1-year rates. However, both strategies led to unexpected high rates of grade 5 toxicity. Dose differentiation, improved patient selection and better sparing of central structures are proposed to improve dose-escalation strategies.

Hypofractionated Phase II
Prospective 75 patients newly diagnosed LA-NSCLC with unresectable stage III disease were recruited between June 2018 and June 2020.
RT = Phase 1: hypo-RT (40 Gy in 10 fractions) → Phase 2: hypo-boost (24-28 Gy in 6-7 fractions)
Chemo = concurrent weekly chemotherapy (docetaxel 25 mg/m2 and nedaplatin 25 mg/m2).
1^{O} PFS

Zhou, IJROBP 2023 28 months
ORR of the whole cohort was 94.7%.
Median PFS of 21.6 months.
1-year PFS 81.3%. 2-year PFS 43.3%. 1-year OS 94.7%. 2-year OS 72.4%.
52% of patients had grade ≥2 toxicity and required a treatment break after 10 fractions (phase 1).
The most frequent acute nonhematologic toxicity was radiation esophagitis. Grade (G) 2 and G3 acute radiation esophagitis were observed in 20 (26.7%) and 4 (5.3%) patients, respectively. Thirteen patients (13/75, 17.3%) had G2 pneumonitis and no G3-G5 acute pneumonitis occurred during follow-up.
Conclusions Hypo-RT followed by hypo-boost combined with concurrent weekly chemotherapy could yield satisfactory local control and survival outcomes with moderate radiation-induced toxicity in patients with LA-NSCLC. The new potent hypo-CCRT regimen significantly shortened treatment time and provided the potential opportunity for the combination of consolidative immunotherapy.

Accelerated KROG 09-03
←R→ 303 patients stage III unresectable NSCLC | 1. conventionally fractionated RT | 2. Hypofx RT |.
Conventional Fx: (arm 1; 124 patients) received a 2-Gy daily dose to a total cumulative dose of 44 Gy to the planning target volume (PTV) in 22 fractions and 60 Gy to the GTV in 30 fractions over 6 weeks.
Hypo Fx: (arm 2; 142 patients) received a 1.8-Gy daily dose to the PTV with a synchronous boost of 0.6 Gy to the GTV, for total cumulative doses of 45 Gy to the PTV and 60 Gy to the GTV in 25 fractions over 5 weeks.
All patients received concurrent weekly chemotherapy consisting of paclitaxel and cisplatin.

Kim, IJROBP 2022
ORR all patients 86.5% (arm 1, 84.6%; arm 2, 88.1%; P = .612).
Median OS 26 months (NS). Median PFS 11 months (arm 1, 10 months; arm 2, 13 months; P = .295).
2-year LC 62.4% vs. 54% (NS) 5-year LC 51% vs. 58.6% (NS).
There were no significant between-group differences in the cumulative incidence of grade ≥3 radiation pneumonitis (P = .134) or radiation esophagitis (P = .539). Rates of ≥ G3 pneumonitis were 7.6% vs 3.1%.
Conclusions This clinical trial did not confirm the superiority of accelerated 2.4-Gy hypofractionated RT compared with conventional 2-Gy fractionation in patients with unresectable stage III NSCLC undergoing concurrent chemoradiation therapy.

RTOG 06-17 - Phase III. 4 arm randomization. 60 Gy vs 74 Gy. Concurrent RT + Carbo/Taxol +/- Cetuximab.
Arms B and D (the two 74 Gy arms) were closed in 6/2011 after an interim analysis showed the high dose arms crossed a futility boundary. The trial will continue to accrue the 60 Gy arms A and C.
←R→ 544 initially was a 2x2 arm trial of either 60 vs 74 Gy and then ± cetuximab. All unresectable stage III non-small-cell lung cancer,=.
All CRT 45 mg/m 2 paclitaxel and carboplatin once a week (AUC 2) → 2 weeks after CRT, 2c consolidation chemotherapy separated by 3 weeks were given consisting of paclitaxel (200 mg/m 2) and carboplatin (AUC 6).

RT either 3DCRT or IMRT. The use of four-dimensional CT and image-guided radiation therapy were encouraged but not necessary.
For patients assigned to receive cetuximab, 400 mg/m 2 cetuximab was given on day 1 followed by weekly doses of 250 mg/m 2, and was continued through consolidation therapy. The primary endpoint was overall survival.

Bradley, Lancet 2015.
Use of cetuximab ↑ grade 3 or worse toxic effects (86% vs 70%); p<0·0001).
↑ Severe esophagitis 74 Gy [21%] vs. 60 Gy [7%], p<0·0001.
Interpretation: 74 Gy radiation given in 2 Gy fractions with concurrent chemotherapy was not better than 60 Gy plus concurrent chemotherapy for patients with stage III non-small-cell lung cancer, and might be potentially harmful. Addition of cetuximab to concurrent chemoradiation and consolidation treatment provided no benefit in overall survival for these patients.

Arms	MS (mo)	1-year OS	Median PFS	1-year PFS	1-year LF	1-year DM
60 Gy / 30 fx	28.7 mo.	80%	11.8 mo.	49.2%	16.3%	32.2%
74 Gy / 37 fx	20.3 mo.	69.8%	9.8 mo.	41.2%	24.8%	35.1%
p	**0.004**	**0.004**	NS	NS	NS	NS
Cetuximab	25 mo					
obs	24 mo					
p	NS					

PER PROTOCOL: The per protocol lung constraint in RTOG 0617 was for total (bilateral) lungs minus CTV. The recommended constraints were V20 ≤ 37% or alternatively a mean dose ≤ 20 Gy. Heart dose V40< 100% V45 < 2/3, V60 < 1/3. NCCN Mean heart dose < 20 Gy and V50 < 25%.

Bradley, Lancet 2019. Long term 5 year FU
Deaths (Grade 5). 3 deaths vs. 9 deaths (high dose).
Grade ≥3 dysphagia and esophagitis 3.2% and 5.0% vs. 12.1% and 17.4% (SS).
No Δ pulmonary toxicity, with grade ≥3 AEs in 20.6% and 19.3%.
5-year OS 32.1 vs. 18.3 %. Median OS 28.7 vs 20.3 months (P = .0072).
5-year PFS 23% vs. 13% (P = .055).
MVA factors ↑ OS: standard RT, tumor location, institution accrual volume, esophagitis/dysphagia, PTV, and heart V5.
IN MVA, heart V30 was ≈ heart V5. So basically any dose to heart was problematic.
Cetuximab conferred NO survival benefit at the expense of increased toxicity.
The prior signal of benefit in patients with higher H scores was no longer apparent.
The progression rate within 1 month of treatment completion in the SD arm was 4.6%. For comparison purposes, the resultant 2-year OS and PFS rates allowing for that dropout rate were 59.6% and 30.7%, respectively, in the SD arms.
CONCLUSION: A 60-Gy radiation dose with concurrent chemotherapy should remain the standard of care, with the OS rate being among the highest reported in the literature for stage III NSCLC. Cetuximab had no effect on OS. The 2-year OS rates in the control arm are similar to the PACIFIC trial.

Table 5. Multivariable Logistic Regression Analysis of CTCAE ≥ Grade 3 Pneumonitis

Covariate	Comparison	OR (95% CI)	*P*
RT technique	3D-CRT (RL) *v* IMRT	0.410 (0.171 to 0.986)	.046
AJCC stage group	IIIA (RL) *v* IIIB	2.276 (1.009 to 5.137)	.048
Lung V20, %	Continuous	1.071 (1.008 to 1.137)	.026
PTV, mL	Continuous (log-transformed)	1.701 (0.708 to 4.085)	.235

Chun JCO, 2017 Secondary analysis to compare IMRT with 3D-CRT.
3D-CRT 53% vs. IMRT 47%.
IMRT ↑ PTV SS, ↑ PTV/lungtotalvolume SS, ↑ stage IIIB (trending),

Two-year OS, progression-free survival, local failure, and distant metastasis-free survival were **NO Δ between IMRT and 3D-CRT**.
IMRT ↓ ≥ grade 3 pneumonitis (7.9% v 3.5%, P = .039) and ↓ risk in adjusted analyses (OR 0.41, SS).
IMRT ↓ heart doses (SS), and ↓ heart V40 (SS) = ↑ OS on adjusted analysis (SS).
Lung **V5** was **not** associated with any ≥ grade 3 toxicity.
Lung **V20** associated with ↑ ≥ grade 3 pneumonitis (SS).
Conclusion IMRT was associated with lower rates of severe pneumonitis and cardiac doses in NRG Oncology clinical trial RTOG 0617, which supports routine use of IMRT for locally advanced NSCLC.

Table A2. Multivariable Cox Model for Overall Survival

Covariate	Comparison	HR (95% CI)	*P*
Radiation therapy technique	3D-CRT (RL) *v* IMRT	1.05 (0.83 to 1.34)	.682
Age	Continuous	1.012 (0.999 to 1.026)	.08
Percent PTV covered by 100% of Rx dose	Continuous	0.996 (0.992 to 1.001)	.107
Heart V40	Continuous	1.012 (1.005 to 1.02)	< .001
Site accrual volume	Low (RL) *v* high volume	0.75 (0.59 to 0.96)	.021
PET staging	No (RL) *v* yes	0.78 (0.54 to 1.15)	.207

NOTE. Results are from a multivariable Cox model stratified by radiation therapy dose level (60 *v* 74 Gy). High volume, four or more patients accrued by institution; low volume, one to three patients accrued by institution.
Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; PET, positron emission tomography; PTV, planning treatment volume; RL, reference level; Rx, prescription; V40, volume receiving ≥ 40 Gy.

Kong, ASTRO 2020 Predictor of radioresistance?

321 patients with blood samples, with 275 having ERCC1 and ERCC2 SNPs genotyped. FU 68 months.
In n=163 60 Gy arms, Median OS 22 months (resistant genotype) vs. Median OS of 31 months (sensitive genotype) (HR 1.4, P = 0.076).
In n=112 74 Gy arms, Median OS 31 months (resistant genotype) vs. Median OS of 20 months (sensitive genotype) (HR 0.59, P = 0.025).
The interaction between radio-sensitivity and RT dose group was significant (p = 0.004), suggesting that the ERCC1/2 SNP signature's prognostic value significantly differed in 60Gy and 74Gy patients.
Conclusion
This study of RTOG0617 phase III trial patients validated ERCC1/2 SNP signature as a radiosensitivity biomarker of both tumor and normal tissue, which explained the fact that high dose radiation decreased survival in patients treated with high dose radiation when they carry a radiation sensitive genotype in DNA repair pathway. While further prospective validation study with larger sample size may be needed, this study confirms the possibility of personalized dose prescription according to testing of genotypic signature of DNA repair pathway.

ALSO, See HERE for another study using → RTOG 06-17 Evaluation for Heart LAD V15 Dose (Note: it was OS, SS!)

Split Course Study

←R→ 331 inoperable NSCLC
1. Split course RT → break → RT. 30 Gy in 10 fractions daily → 3 week break → 25 Gy in 10 fractions daily.
2. Split course CRT (same RT but) + 30 mg /m2 cisplatin, given on the first day of each treatment week;
3. Split course CRT (same RT but) + 6 mg / m2 cisplatin, given daily before radiotherapy.

Schaake-Koning NEJM 1992
RESULTS: 2-year and 3 year OS CRT (daily Cis) 26% and 16%. 2-year and 3-year CRT (weekly) 13% and 2%.
CONCLUSIONS: Cisplatin, given daily in combination with the radiotherapy described here to patients with nonmetastatic but inoperable non-small-cell lung cancer, **improved rates of survival and control of local disease at the price of substantial side effects.**

	RT	Weekly Cis	Daily Cis
CR	19	18	22
PR	43	41	45
No Δ	18	17	9
Disease progress	8	3	3

Continuous TID fractionation **CHART TRIAL**
←R→ 563 locally advanced NSCLC **1.** 1.5 Gy TID x 12 consecutive days **2.** 60 Gy in 30 fractions.

Saunders, Radiother Oncol 1999.
ALL COMERS RR death ↓ 22% ≈ 2-year survival from 20 to 29% (P = 0.008). RR Local progression ↓ 21% (P = 0.033).
Large SCC (19% ACs) subgroup RR death ↓ 30% ≈ 2-year survival from 20 to 33% (P = 0.0007) RR local progression ↓ 27% (P = 0.012).
Also, these SCC had RR local and or distant progression ↓ 25% (P = 0.025) and RR metastasis ↓ 24% (P = 0.043).

CONCLUSION: This analysis of mature data confirms that CHART is superior to conventional radiotherapy in achieving local tumour control and survival in locally advanced NSCLC. This demonstrates the importance of cellular repopulation as a cause of failure in the radiotherapy of NSCLC. The reduction in the risk of metastasis confirms that improved local tumour control, even in lung cancer, can reduce the incidence of metastasis. This trial shows that control of local tumour can lead to an improvement in long term survival.

Elective Nodal Irradiation

MSKCC IFRT Study
RR 524, definitive IFRT. Only LN+ by biopsy or ≥ 1.5 cm short axis by CT included in CTV. Elective nodal failure (ENF) defined as recurrence in initially LN- in absence of local failure. Median F/U 3.4 years

Rosenzweig, JCO 2007.
Outcome: ENF in 6%; 2-year elective nodal control 92%, local control 51%; median time to nodal failure 6 months
Nodal dose-response (from incidental nodal irradiation): **86% failures in regions receiving dose <45 Gy vs. 14% failures if receiving >45 Gy (SS). In nodal regions receiving <45 Gy, failure rate 1.4% vs. if >45 Gy failure rate 0.6% (SS)**
Conclusion: IFRT didn't cause significant failure in LN regions not included in CTV

Editorial (PMID 17984182): Discrepancy between surgical data and RT data about LN failures. Discussion about incidental nodal irradiation and its dose-effect on nodal failure. **Elective nodal failure occur in < 10% of those who receive IFRT.**

MSKCC 3DCRT Study
RR 171 pts tx'd w/ 3D-CRT at MSKCC b/w 1991-98. Only +nodes by biopsy or >/= 1.5 cm in short axis on CT were included in CTV.
Q: What is the failure rate WITHOUT ENI?

Rosenzweig, IJROBP 2001. **Only 11 patients (6.4%) with elective nodal failure were identified.**
Tumor control at 2 yrs 38%, elective nodal control 91%.
Conclusion: Local control much more problematic than elective nodal control; omission of elective nodal irradiation did not significantly worsen nodal failures outside of CTV.]

Shandong, 2006. Elective Nodal vs IFRT, in inoperable Stage III NSCLC.
←R→ 200, inoperable Stage III NSCLC, treated with induction chemo x2 cycles followed by concurrent chemo-RT, followed by 2-3 cycles.
RT randomized to **1.** ENI vs. **2.** IFRT. Dose IFRT to 68-74 Gy and ENI to 60-64 Gy.
IFRT defined as pre-CHT tumor volume and any mediastinal nodes bx+ or >1cm short-axis on CT. Chemo cisplatin-based doublet.

Yuan S, American Journal of Clinical Oncology, 2007.
Toxicity: Pneumonitis ENI 29% vs. IFRT 17% (SS)
5-year LC: 36% vs. 51%, (SS).

	Response Rate	1-year OS	2-year OS	5-year OS	Pneumonitis
ENI	**79%**	60.4%	**25.6%**	18.3%	**29%**
IFRT	**90%**	69.9%	**39.4%**	25.1%	**17%**
	SS	--	**SS**	--	**SS**

Conclusion: IFI arm achieved better **overall response** and **local control** than ENI arm, and it allowed a dose of 68 to 74 Gy to be safely administered to patients with inoperable stage III NSCLC. Outcome improvement can be expected by conformal IFI combined with chemotherapy for stage III NSCLC.

Immunotherapy

Per NCCN 2022, immunotherapy only appears on NSCLC-18, which is after all the definitive treatment. Recommendation for immunotherapy, therefore, is only after complete definitive tx including durvalumab → progression of disease OR upfront stage IVB. Upfront Immunotherapy to treatment-naïve patients is an area of active research and upfront/definitive usage is being investigated. Many new trials show First Line Efficacy.

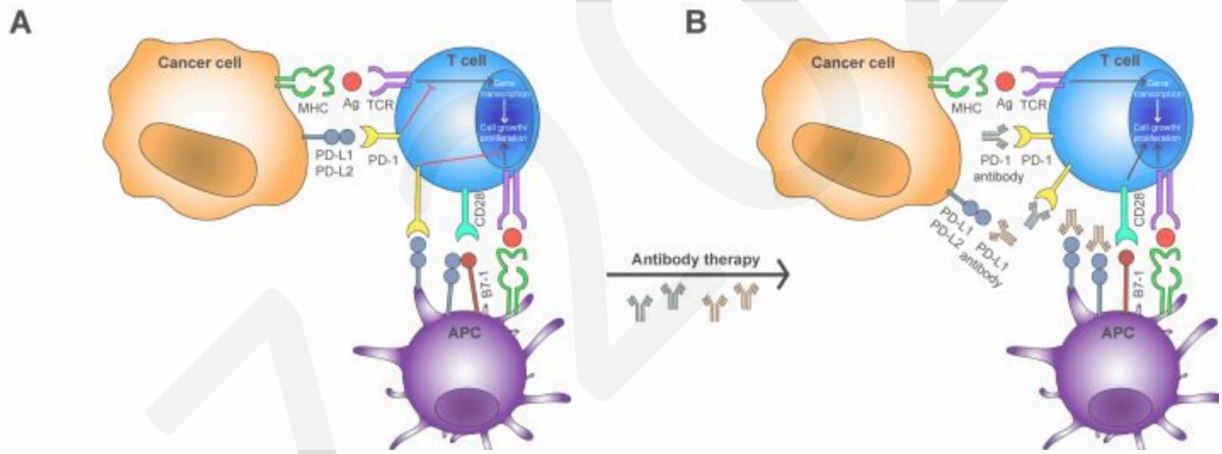
Not all immunotherapy trials with concurrence chemoradiation shows a significant benefit however. Ipilimumab, a CTLA4 inhibitor, has shown in a phase I trial to have concerning grade 5 pulmonary toxicity (26%!) n= 5/19… with 16 patients (84%) had grade ≥3 (G3+) possible treatment-related toxicity.[13]

The use of immune checkpoint inhibitors increased from < 5% in 2015 to > 45% in 2019. 2-year OS ↑ (young patients ≤ 55 yo) 36% in 2011 to 50% in 2018. 2-year OS (≥ 75 yo) ↑ from 31 to 36%.[14]

PD-L1 / PD-1

Background

PD-1 and PD-L1 inhibitors are important immune checkpoint inhibitors (ICIs) for the treatment of cancer after the discovery of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). A study using antibodies in a mouse model published by Dong et al in 2002 showed that local immunosuppression could be eliminated by blocking the binding of PD-1 and PD-L1. The discovery laid the foundation for later immunotherapy for cancer based on T cells. In the same year, Carter et al proposed the concept of treating cancer by blocking PD-1 and PD-L1. Subsequently, pharmaceutical companies began trying to develop PD-1/PD-L1 inhibitors, and the first clinical trial to evaluate nivolumab was launched in 2006.[15]



"Mechanism of anti-tumor immune surveillance and PD-1/PD-L1 inhibitors. (A) Shows that PD-L1 is highly expressed in tumor cells and tumor-related APCs, while PD-1 is highly expressed in tumor-infiltrating lymphocytes. The combination of PD-L1 and PD-1 can inhibit the activation, proliferation and anti-tumor function of CD8+ T cells and realize tumor immune escape. (B) Shows that after antibody treatment, anti-PD-1 will bind to PD-1, preventing PD-1 from binding to PD-L1 or PD-L2, and anti-PD-L1 will bind to PD-L1, blocking the binding of PD-L1 to PD-1 and B7-1, releasing the tumor-specific killing ability of T cells."

[13] https://www.redjournal.org/article/S0360-3016(23)00046-9/fulltext
[14] https://jamanetwork.com/journals/jamaoncology/article-abstract/2800947
[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7490077/#:~:text=(A)%20Shows%20that%20PD%2D,and%20realize%20tumor%20immune%20escape.

Common Drugs[16]

PD-1 Drugs

Pembrolizumab (formerly MK-3475 or lambrolizumab, Keytruda) was developed by Merck and first approved by the Food and Drug Administration in 2014 for the treatment of melanoma. It was later approved for metastatic non-small cell lung cancer and head and neck squamous cell carcinoma. In 2017, it became the first immunotherapy drug approved for use based on the genetic mutations of the tumor rather than the site of the tumor. It was shown, that patients with higher non-synonymous mutation burden in their tumors respond better to the treatment. Both their objective response rate and progression-free survival was shown to be higher than in patients with low non-synonymous mutation burden.

Nivolumab (Opdivo) was developed by Bristol-Myers Squibb and first approved by the FDA in 2014 for the treatment of melanoma. It was later approved for squamous cell lung cancer, renal cell carcinoma, and Hodgkin's lymphoma.

Cemiplimab (Libtayo) was developed by Regeneron Pharmaceuticals and first approved by the FDA in 2018 for the treatment of cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

Dostarlimab (Jemperli) – was developed by GlaxoSmithKline and was first approved for the treatment of mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer by the FDA in April of 2021.[13] On August 17, 2021, the FDA granted accelerated approval for the treatment of mismatch repair deficient (dMMR) recurrent or advanced solid tumors.[14]

Retifanlimab (Zynyz) was developed by Incyte and first granted accelerated approval by the FDA in March 2023 for the treatment of Merkel cell carcinoma (MCC).

PD-L1 Drugs

Atezolizumab (Tecentriq) is a fully humanised IgG1 (immunoglobulin 1) antibody developed by Roche Genentech. In 2016, the FDA approved atezolizumab for urothelial carcinoma and non-small cell lung cancer.

Avelumab (Bavencio) is a fully human IgG1 antibody developed by Merck Serono and Pfizer. Avelumab is FDA approved for the treatment of metastatic merkel-cell carcinoma. It failed phase III clinical trials for gastric cancer.

Durvalumab (Imfinzi) is a fully human IgG1 antibody developed by AstraZeneca. Durvalumab is FDA approved for the treatment of urothelial carcinoma and unresectable non-small cell lung cancer after chemoradiation.

Notes: **Perhaps PD-1/PD-L1 interaction** is a better biomarker (than PD-L1 expression) to assess immunotherapy response rates.

Study: Predicting Tumor Response: **PD-1/PD-L1 interaction** vs. PD-L1 expression[17]
RR of 188 immune checkpoint inhibitor-treated patients' paraffin-embedded tumor samples NSCLC.
Quantified the intercellular PD-1/PD-L1 interaction using a high-throughput automated quantitative imaging platform (quantitative functional proteomics [QF-Pro]). **Results:** Showed no correlation between the extent of PD-1/PD-L1 interaction and PD-L1 expression. Importantly, PD-L1 expression scores used clinically to stratify patients correlated poorly with overall survival; by contrast, patients showing a high PD-1/PD-L1 interaction had significantly better responses to anti–PD-1/PD-L1 treatments, as evidenced by increased overall survival. This relationship was particularly strong in the setting of first-line treatments. **CONCLUSION:** The functional readout of PD-1/PD-L1 interaction as a predictive biomarker for the stratification of patients with non–small-cell lung carcinoma, combined with PD-L1 expression, should significantly improve the response rates to immunotherapy. This would both capture patients excluded from checkpoint immunotherapy (high PD-1/PD-L1 interaction but low PD-L1 expression, 24% of patients) and additionally avoid treating patients who despite their high PD-L1 expression do not respond and suffer from side effects.

[16] https://en.wikipedia.org/wiki/PD-1_and_PD-L1_inhibitors#:~:text=PD%2D1%20inhibitors%20and%20PD,for%20several%20types%20of%20cancer.
[17] https://ascopubs.org/doi/full/10.1200/JCO.22.01748

Durvalumab

Common Understanding in METASTATIC NSCLC: PD-L1 > 50% → monotherapy Pembro. PD-L1 < 50% platinum-doublet + pembro.

One interesting note about the PACIFIC trial (N Engl J Med. 2017 Nov 16;377(20):1919-1929.PMID:28885881) is that many patients received neoadjuvant chemotherapy, mostly because its more common outside the US to start chemotherapy while radiation planning in ongoing.

PACIFIC Trial: Antonia, NEJM 2017.

BACKGROUND: Most w/ loc advanced, unresectable, NSCLC have disease progression despite definitive CRT (ie. C → concurrent CRT). This study compared the anti-programmed death ligand 1 antibody durvalumab as **consolidation therapy** with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy.

METHODS: 713 patients who had received two or more cycles (defined according to local practice) of platinum-based chemotherapy (containing etoposide, vinblastine, vinorelbine, a taxane [paclitaxel or docetaxel], or pemetrexed) **concurrently with definitive radiation therapy** (54 to 66 Gy), in which the mean dose to the lung was less than 20 Gy, the V20 (the volume of lung parenchyma that received 20 Gy or more) was less than 35%, or both. Additional inclusion criteria: no disease progression, age ≥ 18 years, WHO of 0 or 1, an estimated life expectancy of ≥ 12 weeks. EXCLUDE If previous PD-1 or PD-L1 exposure.

RANDOMIZE 2:1: | **1. durvalumab** (at a dose of 10 mg per kilogram of body weight IV) | **2. placebo** every 2 weeks for up to 12 months |. The study drug was administered 1 to 42 days after the patients had received chemoradiotherapy. 1^{O} PFS and OS.

RESULTS: Med PFS 16.8 mos vs. 5.6 mo. with placebo. The 12-month PFS 55.9% vs. 35.3%. 18-month PFS 44.2% vs. 27.0%. Response rate 28.4% vs. 16.0%; P<0.001, median duration of response was longer (72.8% vs. 46.8% of the patients had an ongoing response at 18 months). The median time to death or distant metastasis 23.2 months vs. 14.6 months; P<0.001.

Side effects: Grade 3 or 4 29.9% vs. 26.1% placebo. Most common = pneumonia (4.4% and 3.8%, respectively). A total of 15.4% of patients in the durvalumab group and 9.8% of those in the placebo group discontinued the study drug because of adverse events.

CONCLUSIONS: PFS and everything favors durvalumab. NOTE: OVERALL survival IMMATURE at time of this publication.

NCCN recommends for IIIB/IIIC.

Weakness: a good number of patients have induction therapy.

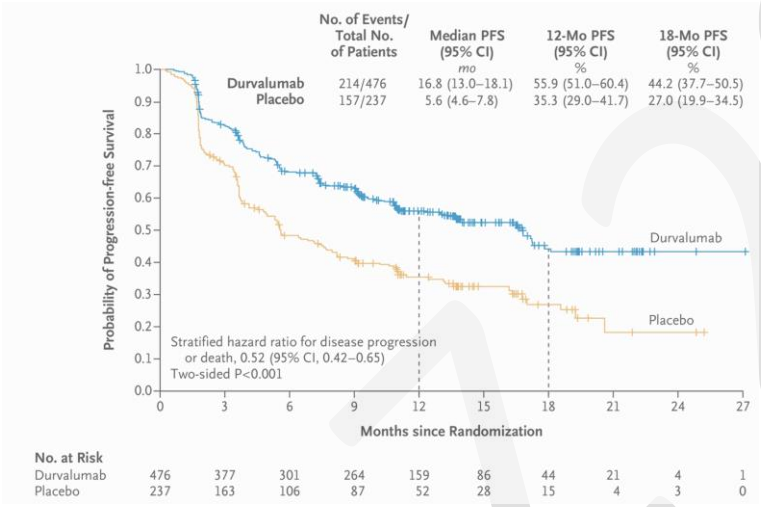


Table 2. Antitumor Activity in the Intention-to-Treat Population.*

Variable	Durvalumab (N=443)†	Placebo (N=213)†	Treatment Effect‡	P Value
Objective response				
No. of patients with response	126	34		
% of patients (95% CI)	28.4 (24.3–32.9)	16.0 (11.3–21.6)	1.78 (1.27–2.51)	<0.001
Best overall response — no. (%)§				
Complete response	6 (1.4)	1 (0.5)		
Partial response	120 (27.1)	33 (15.5)		
Stable disease	233 (52.6)	119 (55.9)		
Progressive disease	73 (16.5)	59 (27.7)		
Could not be evaluated	10 (2.3)	1 (0.5)		
Duration of response — mo				
Median	NR	13.8	0.43	
95% CI		6.0–NR	0.22–0.84	
Ongoing response at data cutoff point — %¶				
At 12 mo	72.8	56.1		
At 18 mo	72.8	46.8		

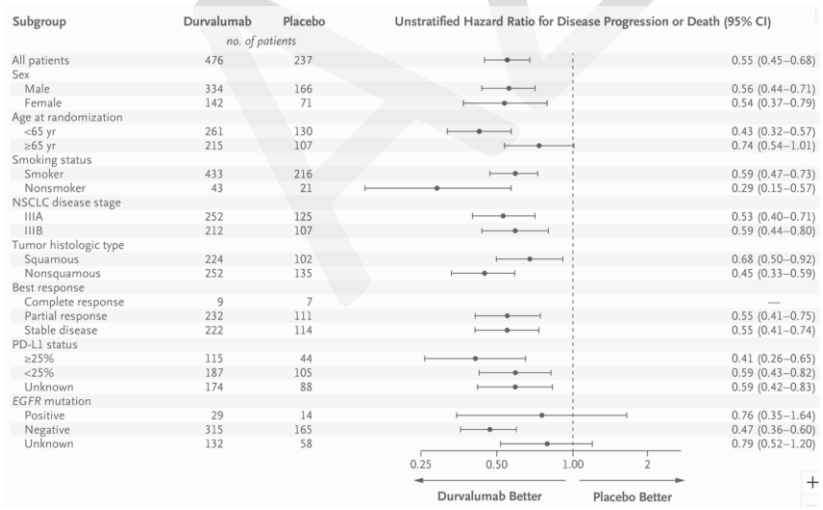


Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

PACIFIC TRIAL 5-year UPDATE

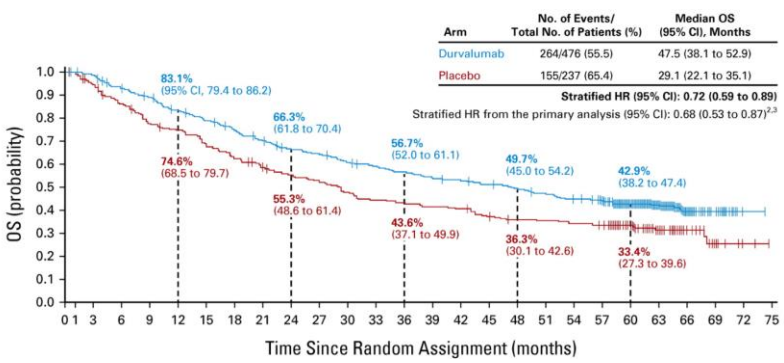
Spigel, JCO 2022

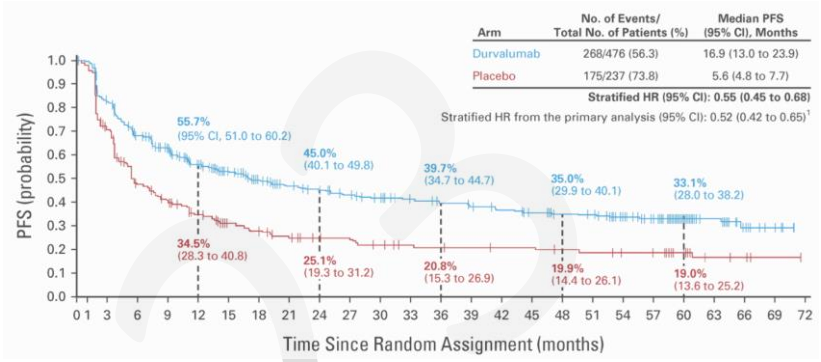
Median OS 47.5 vs. 29.1 months) Median PFS 16.9 vs 5.6 months

5-year OS 42.9% vs. 33.4% 5-year PFS 33.1% vs. 19.0%.

ITT MVA Prognosis of SS ↑ Survival = Durvalumab use, age <65, non-squamous, PS 0, Asian race, female.

CONCLUSION These updated analyses demonstrate robust and sustained OS and durable PFS benefit with durvalumab after chemoradiotherapy. An estimated 42.9% of patients randomly assigned to durvalumab remain alive at 5 years and 33.1% of patients randomly assigned to durvalumab remain alive and free of disease progression, establishing a new benchmark for standard of care in this setting.





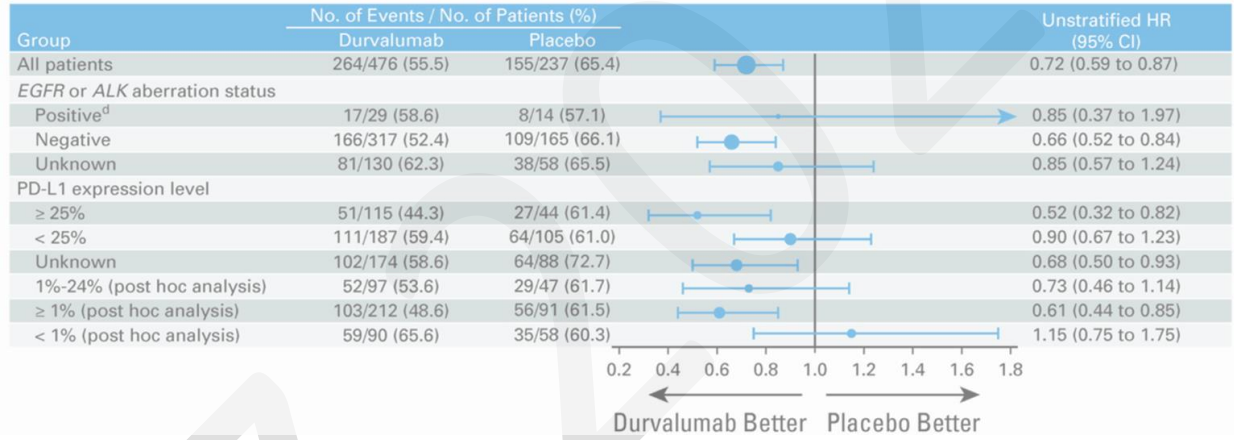


TABLE 3. Multivariable Cox Regression Analysis of Prognostic Baseline Factors for Overall Survival in the Intent-to-Treat Population

	Comparator		Reference		
Baseline Variable	**Group**	**No. of Events/Total No. of Patients (%)**	**Group**	**No. of Events/Total No. of Patients (%)**	**HR (95% CI)**
Treatment arm	Durvalumab	264/476 (55.5)	Placebo	155/237 (65.4)	0.71 (0.58 to 0.87)[a]
Age, years	≥ 65	210/322 (65.2)	< 65	209/391 (53.5)	1.30 (1.06 to 1.59)[a]
Disease stage[b]	IIIB	182/319 (57.1)	IIIA	227/377 (60.2)	1.03 (0.84 to 1.26)
Best response to prior treatment[c]	CR/PR	195/365 (53.4)	SD	216/338 (63.9)	0.88 (0.72 to 1.08)
Tumor histologic type	Squamous	205/326 (62.9)	Nonsquamous	214/387 (55.3)	1.28 (1.04 to 1.58)[a]
WHO PS	1[d]	233/365 (63.8)	0	186/348 (53.4)	1.23 (1.01 to 1.50)[a]
Prior platinum CT agent[e]	Cisplatin	215/395 (54.4)	Carboplatin	190/301 (63.1)	0.84 (0.69 to 1.03)
Race	Asian	95/192 (49.5)	White	310/494 (62.8)	0.63 (0.49 to 0.81)[a]
	Black or African American	7/14 (50.0)			0.81 (0.38 to 1.73)
	Other[f]	7/13 (53.8)			0.91 (0.41 to 1.99)
Sex	Male	304/500 (60.8)	Female	115/213 (54.0)	1.27 (1.01 to 1.61)[a]
Smoking status	Smoker	384/649 (59.2)	Nonsmoker	35/64 (54.7)	0.83 (0.56 to 1.22)
Time from CRT to random assignment, days	≥ 14	312/531 (58.8)	< 14	107/182 (58.8)	0.97 (0.77 to 1.22)
EGFR or *ALK* aberration status	Positive[g]	25/43 (58.1)	Negative	275/482 (57.1)	1.06 (0.69 to 1.64)
	Unknown	119/188 (63.3)			0.95 (0.73 to 1.23)
PD-L1 expression level	TC ≥ 25%	78/159 (49.1)	TC < 25%	175/292 (59.9)	0.82 (0.62 to 1.07)
	Unknown	166/262 (63.4)			1.19 (0.92 to 1.54)

Pneumonitis with Durvalumab Study
RR 783 patients LA-NSCLC definitive cCRT either | 1. before ICI consolidation 2011-2017; N = 448 | 2. afterward 2017- 2021; N = 335.
1^{O} grade ≥2 pneumonitis (G2P).

Yegya-Raman, IJROBP 2023
G2P 31.4% vs 20.1% (P < .001)
NS interaction between ICI era treatment and either V20Gy or mean lung dose.
Cut-point analysis revealed a lung V20 threshold of 28% in the ICI era (1-year G2P rate 46.0% above vs 19.8% below; P < .001).
Among patients receiving ICI consolidation, lung V5 was not associated with G2P.
G3P was not higher in the ICI era (1-year cumulative incidence 7.5% vs 6.0%; P = .39; IPTW-adjusted multivariable subdistribution hazard ratio, 1.12; 95% confidence interval, 0.63-2.01; P = .70).
Conclusions In patients with LA-NSCLC treated with cCRT, the adoption of ICI consolidation was associated with an increase in G2P but not G3P. With ICI consolidation, stricter lung dose constraints may be warranted.

VA Health PD-L1 Expression Levels (Prognostic and Predictive)
RR N=312 patients stage III NSCLC 2017-2021 treated with adj durvalumab = PD-L1 expression subgroups (<1%, 1%-49%, and 50%-100%.)
N=994 patients stage III NSCLC 2015-2016 treated without adj durvalumab.
PD-L1 expression was <1%, 1% to 49%, and 50% to 100% in 109 (34.9%), 96 (30.7%), and 107 (34.3%) patients, respectively

Bryant, IJROBP 2022
↑ PD-L1 expression associated with ↑ PFS (aHR, 0.84 per 25% absolute increase in expression; P = .003)
↑ PD-L1 expression associated with ↑ OS (aHR, 0.86 per 25% absolute increase in expression; P = .036).
Compared with the no-durvalumab group, PFS was longer for PD-L1 50% to 100% (aHR, 0.44; 95% CI, 0.32-0.60; P < .001)
PD-L1 1% to 49% (aHR, 0.64; 95% CI, 0.47-0.86; P = .003)
but not PD-L1 <1% (aHR, 0.84; 95% CI, 0.64-1.10; P = .19).
Similar results were found for OS, with no significant difference between the no-durvalumab group and PD-L1 <1% (aHR, 0.81; 95% CI, 0.58-1.13; P = .22).
Conclusions Increasing tumor PD-L1 expression is prognostic for PFS and OS among patients with stage III NSCLC treated with adjuvant durvalumab, and patients with PD-L1 expression <1% may have limited benefit from adjuvant durvalumab.

Attempts to Improve on Durvalumab

COAST TRIAL More immuno?
Background: Durvalumab significantly improves overall survival for patients with unresectable stage III non–small-cell lung cancer and no progression after concurrent chemoradiotherapy (cCRT). Building upon that standard of care, COAST is a phase II study of durvalumab alone or combined with the anti-CD73 monoclonal antibody oleclumab or anti-NKG2A monoclonal antibody monalizumab as consolidation therapy in this setting.
←R→ 189 unresectable stage III NSCLC → no progression after cCRT ratio 1:1:1, ≤ 42 days post-cCRT
| 1. durvalumab | 2. Durva + oleclumab | 3. Durva + monalizumab | … for up to 12 months, stratified by histology.
1^{O} investigator-assessed confirmed objective response rate (ORR; RECIST v1.1).

Herbst, JCO 2022 Interim analysis 11.5 months
Confirmed ORR 17.9% vs. 30.0% vs. 35.5% (SS).
12-month PFS 33.9% vs. 62.6% vs. 72.7% (SS).
≥ G3 adverse 39.4% vs. 40.7% vs. 27.9%
CONCLUSION Both combinations increased ORR and prolonged PFS versus durvalumab alone. Safety was similar across arms with no new or significant safety signals identified with either combination. These data support their further evaluation in a phase III trial.

Japanese DOLPHIN TRIAL Concurrent Immuno without Chemo?
Background: Administration of durvalumab after concurrent chemoradiotherapy is the standard treatment of unresectable, locally advanced non–small cell lung cancer (NSCLC); however, 20% to 30% of patients do not receive durvalumab because of adverse events (AEs) during concurrent chemoradiotherapy. In addition, radiotherapy and immunotherapy have a synergistic effect.
Prospective Phase II 35 patients → RT (60 Gy) concurrent + maintenance durvalumab immunotherapy, 10 mg/kg every 2 weeks, for up to 1 year.
RT was completed in 97.1% of patients.

Tachihara, JAMA Oncol 2023 22.8 months
12-month PFS rate 72.1% Median PFS 25.6 months.
ORR 90.9% Treatment completion rate 57.6%.
Among 34 patients evaluated in the safety analysis set, AEs of grade 3 or 4 occurred in 18 patients (52.9%), and of grade 5 in 2 patients (5.9%).
Pneumonitis or radiation pneumonitis of any grade occurred in 23 patients (67.6%), and of grades 3 or 4 in 4 patients (11.8%).
Conclusions and Relevance Findings from this phase 2 nonrandomized controlled trial indicate that durvalumab immunotherapy combined with curative radiotherapy for patients with PD-L1–positive, unresectable, locally advanced NSCLC is a promising treatment with tolerable AEs and is appropriate as a study treatment for phase 3 clinical trials.

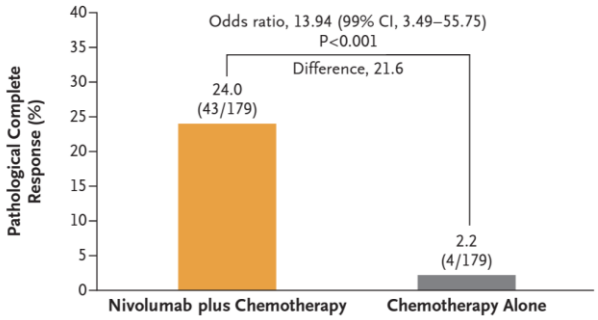
Other Studies

Checkmate-816 **PRE-OP Immunotherapy** **IB (≥ 4 cm)–IIIA**

←R→ IB (≥ 4 cm)–IIIA (per AJCC 7th ed) resectable NSCLC 2:1 | 1. Nivo + Chemo Doublet | 2. C alone |. 64% Stage IIIA. Minimally invasive 30 vs. 22%. Lobectomy 77% vs. 61%. Pneumonectomy 17% vs. 25%. R0 achieved 17% vs. 25%. No known EGFR/ALK alterations.

Definitive surgery was to be performed within 6 weeks of treatment.

Of the patients who underwent randomization, 83.2% of those in the nivolumab-plus-chemotherapy group and 75.4% of those in the chemotherapy-alone group underwent surgery.



Forde, NEJM 2022

Median EFS 31.6 vs. 20.8 months (HR 0.63; P=0.005).

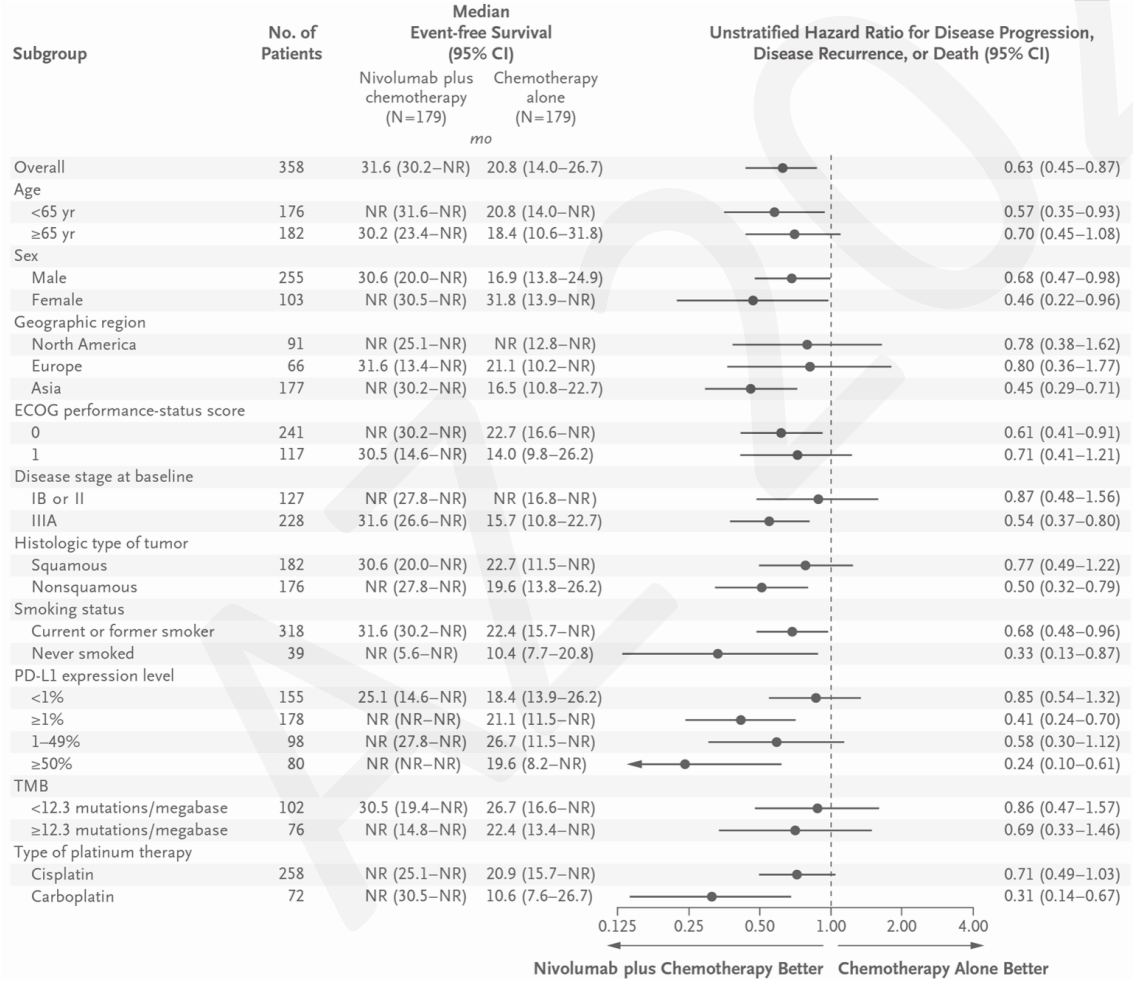
pCR 24.0% vs. 2.2% (OR 13.94; P<0.001).

At the first prespecified interim analysis, the hazard ratio for death was 0.57 (99.67% CI, 0.30 to 1.07) and did not meet the criterion for significance.

Grade 3 or 4 treatment-related adverse events occurred in 33.5% of the patients in the nivolumab-plus-chemotherapy group and in 36.9% of those in the chemotherapy-alone group.

CONCLUSIONS

In patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response than chemotherapy alone. The addition of nivolumab to neoadjuvant chemotherapy did not increase the incidence of adverse events or impede the feasibility of surgery.



Spicer, JCO 2021

pCR 24% vs. 2.2% (SS).

In patients who had surgery, major pathologic response rate 12.7% vs. 46.8%.

The radiographic objective response 37% vs. 54%.

Subset of 87 patients with available samples, circulating tumor DNA (ctDNA) was more likely to clear when nivolumab was given: 56% vs 34%.

Any-grade and grade 3–4 surgery-related AEs were reported in 41% vs 47% and 11% vs 15% of the NIVO + chemo vs chemo arms, respectively. Grade 5 surgery-related AEs were reported in 2 vs 0 pts in the NIVO + chemo vs chemo arms; 0 vs 3 pts died due to treatment-related AEs, respectively.

Conclusions: In CheckMate 816, neoadjuvant NIVO + chemo did not impede the feasibility and timing of surgery, nor the extent or completeness of resection vs chemo alone; treatment was tolerable and did not increase surgical complications. NIVO + chemo led to increased depth of pathological response. The surgical outcome data from CheckMate 816 along with significant improvement in pCR support NIVO + chemo as a potential neoadjuvant option for patients with stage IB to IIIA resectable NSCLC.

NADIM II **Sister Trial for Checkmate-816** **stage IIIA or IIIB NSCLC**

BACKGROUND Approximately 20% of patients with non–small-cell lung cancer (NSCLC) receive a diagnosis of stage III disease. There is no current consensus regarding the most appropriate treatment for these patients.

←R→ 86 Phase II 2:1 Ratio resectable stage IIIA or IIIB NSCLC → | 1. neoadjuvant nivolumab plus platinum-based chemotherapy | 2. chemo alone |.

Neoadjuvant paclitaxel (200 mg/m2 once a day) and carboplatin (area under curve 6) plus nivolumab (360 mg) once on day 1 of each 21-day cycle, for three cycles, followed by adjuvant nivolumab monotherapy for 1 year (240 mg once every 2 weeks for 4 months, followed by 480 mg once every 4 weeks for 8 months).

Patients in the experimental group who had R0 resections received adjuvant treatment with nivolumab for 6 months.

Surgery was performed in 93% of the patients in the experimental group and in 69% in the control group (relative risk, 1.35; 95% CI, 1.05 to 1.74).

1^{O} pCR.

Provencio, NEJM 2023

pCR 37% vs. 7% (RR 5.34; P=0.02).

2-year PFS 67.2% vs. 40.9% (HR 0.47; SS). 2-year OS 85.0% vs. 63.6% (HR 0.43; SS).

Grade 3 or 4 adverse events occurred in 11 patients in the experimental group (19%; some patients had events of both grades) and 3 patients in the control group (10%).

CONCLUSIONS In patients with resectable stage IIIA or IIIB NSCLC, perioperative treatment with nivolumab plus chemotherapy resulted in a higher percentage of patients with a pathological complete response and longer survival than chemotherapy alone.

NOTE: vs. Checkmate-816, this trial used maintenance nivo → 6 months after surgery. It also included N2 disease (66%).

NOTE 2: could NAI be better for patients who proceed to radiation as well?

Keynote-671 Merck's Attempt to Replicate Checkmate-816's success with its own drug: Pembro

←R→ 797 NSCLC resectable stage II, IIIA, or IIIB (N2 stage) | 1. NAI pembrolizumab (200 mg) | 2. placebo | once every 3 weeks. Each arm + cisplatin-based chemotherapy for 4 cycles → surgery → adjuvant pembrolizumab (200 mg) or placebo once every 3 weeks for up to 13 cycles.

Wakelee, NEJM 2023 **25.2 months 1st interim analysis**

2-year EFS 62.4% vs. 40.6% (HR 0.58; P<0.001).

2-year OS 80.9% vs. in 77.6% (P=0.02, which did not meet the significance criterion).

Major PR 30.2% vs. 11.0% (SS) pCR 18.1% vs. 4.0% (SS).

Across all treatment phases, 44.9% of the participants in the pembrolizumab group and 37.3% of those in the placebo group had treatment-related adverse events of grade 3 or higher, including 1.0% and 0.8%, respectively, who had grade 5 events.

CONCLUSIONS

Among patients with resectable, early-stage NSCLC, neoadjuvant pembrolizumab plus chemotherapy followed by resection and adjuvant pembrolizumab significantly improved event-free survival, major pathological response, and pathological complete response as compared with neoadjuvant chemotherapy alone followed by surgery. Overall survival did not differ significantly between the groups in this analysis.

Retrospective Smoking Stratification Can Smoking be a Proxy for Tumor Mutation Burden (TMB?)

315 patients with NSCLC ≥ 50% PD-L1 status. Smokers: 36 (11%) never, 42 (13%) light, and 237 (75%) heavy.

All treated with ICI.

Gainor, Ann Oncol 2020.

ObR observed in 27%, 40%, and 40% of never, light, and heavy smokers, respectively (p = 0.18, between never vs. heavy).

Median PFS and median DoR were numerically shorter in never and light smokers compared with heavy smokers.

(PFS 3.0 versus 4.0 versus 5.4 months; median DOR 6.9 versus 10.8 versus 17.8 months). All NS.

Conclusions PD-(L)1 inhibitors are associated with antitumor activity in NSCLC with PD-L1 TPS ≥50% regardless of smoking status. Nevertheless, there is a signal of potentially decreased durability among never and light smokers that should be further evaluated. Distinct immunobiologic features may affect initial response versus durability of antitumor immunity to programmed cell death 1 (PD-1) blockade.

NOTE: Consider data from KETNOTE-042, which also showed no OS with pembrolizumab among never smokers w/ PD-L1 ≥ 50%.

Retrospective **PD-L1 % and response to pembro**

187 patient s/p 1st line pembro monotherapy for NSCLC with PD-L1 expression ≥ 50% without Δ EGFR and ALK.

Aguilar, Ann Oncol 2019

Those with PDL1 expression of ≥ 90% had almost double the objective response rate (32.7% → 60%) of those with 50-89% expression.

Also, these patients had ↑ OS (not reached vs. 15.9 months, SS)

Conclusion Among patients with NSCLC and PD-L1 expression of ≥50% treated with first-line pembrolizumab, clinical outcomes are significantly improved in NSCLCs with a PD-L1 expression of ≥90%. These findings have implications for treatment selection as well as for clinical trial interpretation and design.

Phase I Concurrent CRT + Pembrolizumab

Multicenter 21 **patients advanced, unresectable Stage III NSCLC → Pembro concurrent with CRT (weekly carboplatin paclitaxel + 60 Gy RT).**

Dose cohorts
1. Full dose pembrolizumab (200 mg intravenously every 3 weeks) 2 to 6 weeks after chemoradiotherapy
2. Red. dose pembrolizumab (100 mg intravenously every 3 weeks) starting day 29 of chemoradiotherapy
3. Full dose pembrolizumab starting day 29 of chemoradiotherapy
4. Red. dose pembrolizumab starting day 1 of chemoradiotherapy
5. Full dose pembrolizumab starting day 1 of chemoradiotherapy.

Jabbour, JAMA 2020.

No dose-limiting toxic effects in any cohort were observed.
One case of grade 5 pneumonitis occurred in the safety expansion cohort with the cohort 5 regimen.
Immune-related adverse events of at least grade 3 occurred in 4 patients (18%).
Median PFS (≥ 1 dose pembro) 18.7 months (n=21). 6-month PFS 81%. 12-month PFS 69.7%.
Median PFS (≥ 2 dose pembro) 21.0 months (n=19).
Conclusions and Relevance These findings suggest that combined treatment with PD-1 inhibitors and chemoradiotherapy for stage III NSCLC is tolerable, with promising PFS of 69.7% at 12 months, and requires further study.

KEYNOTE 010 **PREVIOUSLY TREATED NSCLC**

Background: Despite recent advances in the treatment of advanced non-small-cell lung cancer, there remains a need for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.
←R→ Phase II/III. 1034 previously treated NSCLC with PD-L1 expression **on at least 1% of tumour cells.**
1. pembrolizumab 2 mg/kg **2. pembrolizumab 10 mg/kg** **3. docetaxel 75 mg/m 2 every 3 weeks**. 1^{O} OS in PD-L1 ≥ 50%.

Herbst, Lancet 2015.

Median OS 10·4 months, 12·7 months, 8·5 months. OS Pembro 2mg vs. docetaxel (SS).
OS Pembro 10mg vs. docetaxel (SS). Median PFS 3·9 months. 4·0 months, 4·0 months. NS
If ≥ 50% of tumour cells PD-L1 OS pembrolizumab 2 mg/kg 14.9 mo vs. docetaxel 8.2 mo (SS).
OS pembrolizumab 10 mg/kg 17.3 mo vs. docetaxel 8.2 mo (SS).
PFS pembrolizumab 2 mg/kg 5.0 mo. vs. docetaxel 4.1 mo (SS).
PFS pembrolizumab 10 mg/kg 5.2 mo. vs. docetaxel 4.1 mo (SS).
Grade 3–5 treatment-related adverse events pembrolizumab 13% vs. docetaxel 35%.

Interpretation Pembrolizumab prolongs overall survival and has a favourable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. These data establish pembrolizumab as a new treatment option for this population and validate the use of PD-L1 selection.

KEYNOTE-024 **Untreated advanced NSCLC**

←R→ 305 untreated advanced NSCLC with **PD-L1 expression on at least 50%** and no EGFR mutation or ALK translocation.
| 1. pembrolizumab (200 mg every 3 weeks) | 2. investigator's choice of platinum-based chemotherapy |.
Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression.

Reck, NEJM 2016.

RESULTS
Median PFS 10.3 vs. 6.0 months (SS). 6-month OS 80.2% vs. 72.4% SS).
Response rate 44.8% vs. 27.8% (SS). Median duration of response NOT REACHED vs. 6.3 months (SS).
Treatment-related adverse events of any grade ↓ 73.4% vs. 90.0% (SS).
G 3, 4, or 5 treatment-related adverse events ↓ 26.6% vs. 53.3% (SS).
CONCLUSIONS In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy. (Funded by Merck; KEYNOTE-024 ClinicalTrials.gov number, NCT02142738.)

KEYNOTE-042 **TREATMENT NAÏVE Locally advanced or metastatic NSCLC**

Background: First-line pembrolizumab monotherapy improves overall and progression-free survival in patients with untreated metastatic non-small-cell lung cancer (without EGFR or ALK Δ) with a programmed death ligand 1 (PD-L1) tumour proportion score (TPS) of 50% or greater. We investigated overall survival after treatment with pembrolizumab monotherapy in patients with a PD-L1 TPS of 1% or greater.
←R→ Phase III 1274 patients
1. pembrolizumab 200 mg every 3 weeks for up to 35 cycles **2. the investigator's choice of platinum-based C for four to six cycles.**
1^{O} OS in TPS of 50% or greater, 20% or greater, and 1% or greater.

Mok, Lancet 2019.

TPS ≥ 50% (47%), TPS ≥ 20 (64%). As of Feb 26, 2018, median follow-up was 12·8 months.
OS benefit all three TPS populations.
Median OS by TPS population were 20·0 months vs. 12·2 months TPS (≥ 50%), 17·7 vs. 13·0 (≥ 20%), and 16·7 vs. 12·1 (≥ 1%).
Treatment-related adverse events Grade ≥ 3 pembro 18% vs. chemo 41%.
Death was same (2%) and (2%).
Interpretation The benefit-to-risk profile suggests that pembrolizumab monotherapy can be extended as first-line therapy to patients with locally advanced or metastatic non-small-cell lung cancer without sensitising EGFR or ALK alterations and with low PD-L1 TPS.

KEYNOTE-189 LANDMARK PEMBRO **STUDY.**

BACKGROUND: First-line therapy advanced NSCLC that lacks targetable mutations is platinum-based chemotherapy. If PD-L1 ≥ 50%, pembrolizumab has replaced cytotoxic chemotherapy as the first-line treatment of choice. The addition of pembrolizumab to chemotherapy resulted in significantly higher rates of response and longer progression-free survival than chemotherapy alone in a phase 2 trial.

METHODS: ←R→ 2:1 ratio 616 patients with metastatic non-squamous NSCLC **(wild type = no EGFR or ALK Δ)** who had received no previous treatment for metastatic disease:

Pemetrexed and a platinum-based drug + either| **1.** 200 mg of pembrolizumab | **2.** placebo | every 3 weeks for 4 cycles
→ followed by | **1.** pembrolizumab | **2.** placebo | for up to a total of 35 cycles
→ pemetrexed maintenance therapy.

Crossover to pembrolizumab monotherapy permitted among patients in the placebo group if disease progression. **1^{O}** OS and PFS.

Gandhi, NEJM 2018.

RESULTS: FU of 10.5 months, OS at 12 months = **69.2% pembrolizumab-combination group** vs. **49.4%** in the placebo-combination group (HR for death, 0.49; P<0.001). Improvement in overall survival was seen across all PD-L1 categories that were evaluated.
Median PFS 8.8 months vs. 4.9 months (HR 0.52; P<0.001). Adverse events ≥ grade 3 67.2% vs. 65.8%.
CONCLUSIONS. In patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by Merck; KEYNOTE-189 ClinicalTrials.gov number, NCT02578680.)

Gadgeel, JCO 2020 23.1 month FU
Median OS was 22.0 months vs. 10.7 months (HR 0.56; SS).
Median PFS 9.0 vs. 4.9 HR, 0.48; SS).
Median time from randomization to objective tumor progression/death on next-line treatment 17.0 vs. 9.0 months (HR, 0.49; SS)
OS and PFS benefits with pembrolizumab were observed regardless of PD-L1 expression or presence of liver/brain metastases. Incidence G3-5 AE similar in the pembrolizumab-combination (71.9%) and placebo-combination (66.8%) groups.
CONCLUSION First-line pembrolizumab plus pemetrexed-platinum continued to demonstrate substantially improved OS and PFS in metastatic nonsquamous NSCLC, regardless of PD-L1 expression or liver/brain metastases, with manageable safety and tolerability.

IMPower 150: Addition of atezolizumab (PD-L1) in first-line setting 1,202 patients with stage 4 or recurrent metastatic nonsquamous NSCLC.

3 cohorts. Cohort A atezolizumab (Tecentriq, Genentech) + chemotherapy (n =402).
Cohort B atezolizumab + chemotherapy + bevacizumab (Avastin, Genentech) (n = 400). EXP ARM
Cohort C received chemotherapy + bevacizumab (n = 400). CONTROL ARM
The median age for all cohorts was 63 years and each cohort were 60% male.
Patients were divided into either ITT wild-type (87%) or EGFR or ALK-positive (13%).
Investigator-assessed PFS and OS served as the primary endpoints; secondary endpoints included overall response rate and safety

RESULTS: Researchers reported a median OS of 19.2 months (95% CI; 17-23.8) in patients from the experimental arm compared with patients in the control group which had a median OS of 14.7 months (95% CI; 13.3-16.9) (HR = 0.78; 95% CI, 0.64-0.96).

The addition of atezolizumab to chemotherapy and bevacizumab resulted in an OS of 13.2 months compared with 9.1 **months in patients with liver metastases** who received bevacizumab plus chemotherapy (HR = 0.54; 95% CI, 0.33-0.88).
Serious adverse events were reported in 39% of patients in cohort A, 44% of patients in cohort B and 34% of patients in cohort C.

IMpower010 Adjuvant Atezolizumab.

←R→ Phase III 1280 patients completed resected (R0) Stage IB (≥ 4 cm tumors) to Stage IIIA NSCLC.
All had platinum-based chemotherapy → | 1. adjuvant atezolizumab (1200 mg every 21 days; for 16 cycles or 1 year) | 2. best supportive care |.
1^{O} DFS (**Group 1.** stage II-IIIA disease with ≥ 1% PD-L1, **2.** stage II-IIIA any PD-L1, **3.** all patients). Most (88%) had stage II-IIIA disease.

Felip, Lancet 2021. FU 32·2 months.
2-year DFS (**Group 1**) 75% vs. 61% (SS). 3-year DFS (**Group 1**) 60% vs 48% (SS).
2-year DFS (**Group 2**) 70% vs. 62% (SS). 3-year DFS (**Group 1**) 56% vs 50% (SS).
DFS (**Group 3**) not significant.
Benefit MOST apparent if PD-L1 ≥ 50%.
OS not yet mature.
Atezolizumab-related G3-4 AE occurred in 53 (11%) of 495 patients and grade 5 events in four patients (1%).
Interpretation IMpower010 showed a disease-free survival benefit with atezolizumab versus best supportive care after adjuvant chemotherapy in patients with resected stage II–IIIA NSCLC, with pronounced benefit in the subgroup whose tumours expressed PD-L1 on 1% or more of tumour cells, and no new safety signals. Atezolizumab after adjuvant chemotherapy offers a promising treatment option for patients with resected early-stage NSCLC.

Post-op

PEARLS / KEYNOTE-091

Pembrolizumab is a standard-of-care for advanced non-small-cell lung cancer (NSCLC). We assessed pembrolizumab as adjuvant therapy for completely resected stage IB–IIIA NSCLC.

←R→ 1955 completely resected, stage IB (tumours of ≥4 cm in diameter), II, or IIIA NSCLC any histology or PD-L1 expression level.

Adjuvant chemotherapy was to be considered for stage IB disease and was strongly recommended for stage II and IIIA disease.

| 1. pembrolizumab 200 mg | 2. Placebo |. Both administered intravenously every 3 weeks for up to 18 cycles.

1^{O} DFS in overall population and also PD-L1 tumour proportion score (TPS) of ≥ 50%.

O'Brien, Lancet Oncol 2022 **35.6 months**

Median DFS Overall Population 53·6 months vs. 42·0 (HR 0·76, p=0·0014).

PD-L1 TPS ≥ 50% Not Reached in both.

Grade ≥3 side effects 34% vs. 26%

G5 n=4 (1%) vs. 0.

One due to both cardiogenic shock and myocarditis, one due to both septic shock and myocarditis, one due to pneumonia, and one due to sudden death.

Interpretation Pembrolizumab significantly improved disease-free survival compared with placebo and was not associated with new safety signals in completely resected, PD-L1-unselected, stage IB–IIIA NSCLC. Pembrolizumab is potentially a new treatment option for stage IB–IIIA NSCLC after complete resection and, when recommended, adjuvant chemotherapy, regardless of PD-L1 expression.

Phase II Atezolizumab+C

Prospective 30 patients with resectable stage IB–IIIA NSCLC + Hx of smoking.

23 (77%) had stage IIIA disease. 29 (97%) patients were taken into the operating theatre, and 26 (87%) **underwent successful R0 resection**.

All → NAC IV atezolizumab (1200 mg) + carboplatin (AUC 5) on day 1, + nab-paclitaxel (100 mg/m 2) on days 1, 8, and 15… of each 21-day cycle.

Patients without disease progression after two cycles proceeded to receive two further cycles, which were then followed by surgical resection.

1^{O} major pathological response, defined as the presence of 10% or less residual viable tumour at the time of surgery.

Shu, Lancet 2020.

17/30 (57%; 95% CI 37–75) of 30 patients had a major pathological response.

Grade 3–4 adverse events were neutropenia (15 [50%] of 30 patients), ↑ ALT 2/30, ↑ AST 2/30, thrombocytopenia 2/30.

Serious treatment-related adverse events included one (3%) patient with grade 3 febrile neutropenia, one (3%) patient with grade 4 hyperglycaemia, and one (3%) patient with grade 2 bronchopulmonary haemorrhage. There were no treatment-related deaths.

Interpretation Atezolizumab plus carboplatin and nab-paclitaxel could be a potential neoadjuvant regimen for resectable non-small-cell lung cancer, with a high proportion of patients achieving a major pathological response, and manageable treatment-related toxic effects, which did not compromise surgical resection.

Gefetinib trials.

Chinese Adjuvant Trial. Zhong, Lancet 2018.

483 completely resected (R0), stg II–IIIA (N1–N2), EGFR Δ (exon 19 del or exon 21 Leu858Arg) NSCLC | 1. Gefitinib | 2. Cisplatin + Vinorelbine |. Gefitinib (250 mg daily) for 24 mo or IV vinorelbine (25 mg/m2 on days 1 and 8) + IV cisplatin (75 mg/m2 on day 1) q3wk for four cycles.

Median DFS gefitinib 28·7 months vs. 18·0 months (HR 0·60, p=0·0054).

Interpretation Adjuvant gefitinib led to significantly longer disease-free survival compared with that for vinorelbine plus cisplatin in patients with completely resected stage II–IIIA (N1–N2) EGFR-mutant NSCLC. Based on the superior disease-free survival, reduced toxicity, and improved quality of life, adjuvant gefitinib could be a potential treatment option compared with adjuvant chemotherapy in these patients. However, the duration of benefit with gefitinib after 24 months might be limited and overall survival data are not yet mature.

Japanese IMPACT Trial. Tada, JCO 2021.

234 completely resected (R0) pathologic stage II-III NSCLC w/ EGFR Δ (exon 19 del or L858R) | 1. Gefitinib | 2. Cisplatin + Vinorelbine |. Gefetinib (250 mg once daily) for 24 months. Cisplatin (80 mg/m2 on day 1) plus vinorelbine.

Median DFS 35.9 months vs. 25.1 months. However, 4 year DFS was NS. OS NS.

CONCLUSION Although adjuvant gefitinib appeared to prevent early relapse, it did not prolong DFS or OS. However, similar DFS and OS may justify adjuvant gefitinib in the selected patient subsets, especially those deemed ineligible for platinum-doublet adjuvant therapy; however, this was not a noninferiority trial.

SBRT + Immuno

Phase II SBRT + I Trial

Background: SABR is the standard treatment for medically inoperable early-stage NSCLC, but regional or distant relapses, or both, are common. Immunotherapy reduces recurrence and improves survival in people with stage III NSCLC after chemoradiotherapy, but its utility in stage I and II cases is unclear. We therefore conducted a randomised phase 2 trial of SABR alone compared with SABR with immunotherapy (I-SABR) for people with early-stage NSCLC.

←R→ 156 Stage IA-IIB ≤ 7 cm (N0M0 all). | 1. SABR-I | 2. SABR alone |.

I = 4c nivolumab (480 mg, once every 4 weeks, with the first dose on the same day as, or within 36 h after, the first SABR fraction).

SABR = 50 Gy in 4 fractions (87%), 70 Gy in 10 fractions "no-fly zone" (13%).

1^{O} 4-year event-free survival (local, regional, or distant recurrence; second primary lung cancer; or death).

Chang, Lancet 2023 **33 month follow-up**

4-year EFS 77% vs. 53% (HR 0·38; p=0·0056) → ITT population, HR 0·42; SS.

There were no grade 3 or higher adverse events associated with SABR. In the I-SABR group, ten participants (15%) had grade 3 immunologial adverse events related to nivolumab; none had grade 3 pneumonitis or grade 4 or higher toxicity.

LR 13 → 0%, RR 11 → 6%, DM 16 → 3%.

Interpretation Compared with SABR alone, I-SABR significantly improved event-free survival at 4 years in people with early-stage treatment-naive or lung parenchymal recurrent node-negative NSCLC, with tolerable toxicity. I-SABR could be a treatment option in these participants, but further confirmation from a number of currently accruing phase 3 trials is required.

SBRT + Durvalumab Study

←R→ Phase II single center 60 enrolled early-stage I-IIIA NSCLC | 1. Durva → SBRT | 2. Durva Alone |. SBRT = 8 Gy × 3 consecutive daily fractions.

Altorki, Lancet 2021.

Major PR 53.3% vs. 6·7% (SS). In the 16 patients in the dual therapy group with a major pathological response, eight (50%) had pCR.

Grade 3–4 adverse events 6 (20%) vs. five (17%).

Frequent grade 3–4 events were hyponatraemia (three [10%] patients in the durvalumab monotherapy group) and hyperlipasaemia (three [10%] patients in the durvalumab plus radiotherapy group). Two patients in each group had serious adverse events (pulmonary embolism [n=1] and stroke [n=1] in the durvalumab monotherapy group, and pancreatitis [n=1] and fatigue [n=1] in the durvalumab plus radiotherapy group). No treatment-related deaths or deaths within 30 days of surgery were reported.

Interpretation Neoadjuvant durvalumab combined with stereotactic body radiotherapy is well tolerated, safe, and associated with a high major pathological response rate. This neoadjuvant strategy should be validated in a larger trial.

Comment: Benefit SBRT + Durvalumab was also shown in a similar 18 patient phase 1/2 trial.[18] All → Stage I-IIA. All durvalumab x 1 cycles → SBRT 5 days later → additional 4 cycles of durvalumab q4 weeks. SBRT = 54 Gy in 3 fractions (n=16), 50 Gy in 4 fractions (n=1), 65 Gy in 10 fractions (n=1). 2-year LC 94%, 2 years OS 89%.

[18] https://www.redjournal.org/article/S0360-3016(23)00325-5/fulltext

Chinese **SINDAS Trial** Upfront Ablative RT + TKI

Background: Adding radiotherapy (RT) to systemic therapy improves progression-free survival (PFS) and overall survival (OS) in oligometastatic non-small cell lung cancer (NSCLC). Whether these findings translate to epidermal growth factor receptor (EGFR)–mutated NSCLC remains unknown. The SINDAS trial (NCT02893332) evaluated first-line tyrosine kinase inhibitor (TKI) therapy for EGFR-mutated synchronous oligometastatic NSCLC and randomized to upfront RT vs no RT.

←R→ 133 biopsy-proven EGFR Δ AC + synchronous (newly diagnosed, treatment naïve) oligometastatic (≤5 metastases; ≤2 lesions in any one organ) NSCLC without brain metastases. All patients first-generation TKI (gefitinib, erlotinib, or icotinib)→ | 1. no RT | 2. RT |.

T-stage = 1 (10%), 2 (25%), 3 (30%), 4 (30%), unknown (< 5%).

N-stage = 0 (12%), 1 (30%), 2 (40%), 3 (15%), unknown (< 5%).

RT = SBRT (25-40 Gy in 5 fractions depending on tumor size and location) **to all metastases** and **the primary tumor/involved regional lymphatics**.

1^{O} ITT PFS.

Variable[a]	Progression-free survival		Overall survival	
	HR (95% CI)	*P*[b]	HR (95% CI)	*P*[b]
Zubrod performance status (0 vs 1-2)	0.50 (0.22 to 0.75)	.02	0.01 (0.01 to 0.44)	.02
Clinical T classification (T3-4 vs.T1-2)	1.10 (0.99 to 1.22)	.09	2.06 (1.08 to 5.54)	.02
Clinical N classification (N2-3 vs N0-1)	—	—	1.56 (1.19 to 3.69)	.06
Number of metastases (3-5 vs 1-2)	1.96 (1.30 to 4.70)	.004	1.93 (1.21 to 3.07)	.004
EGFR mutation (exon 19 deletion vs exon 21 mutation)	0.94 (0.61 to 1.43)	.09	0.09 (0.02 to 0.38)	.001
Randomization arm (TKI only vs TKI + RT)	1.39 (1.07 to 1.95)	.005	2.11 (1.31 to 5.97)	.004

Wang, JNCI 2022 23.6 months follow-up

Median PFS 12.5 months vs 20.2 months (P < .001)

Median OS 17.4 months vs 25.5 months (P < .001)

Local control improved with RT around 55.4% → 91.2% (SS).

Treatment yielded no grade 5 events and a 6% rate of symptomatic grade 3-4 pneumonitis in the TKI with RT arm. Based on the efficacy results of this prespecified interim analysis, the ethics committee recommended premature cessation of this trial.

Conclusions As compared with a first-line TKI alone, addition of upfront local therapy using RT statistically significantly improved PFS and OS for EGFR-mutated NSCLC.

Chinese Phase II Upfront Ablative RT + TKI

←R→ 74 patients NSCLC with an EGFR-sensitive mutation (19DEL or 21L858R) w/ stage IV.

First-line EGFR-TKIs (gefitinib, erlotinib, and icotinib) → achieved stable disease or partial response → enrolled after three months.

| 1. EGFR-TKI alone | 2. EGFR-TKIs +SBRT combo |.

In the combination-group, different tumor sites were irradiated at doses ranging from 30–50 Gy in five fractions.

Considering the short duration of SBRT, the TKIs were continued during the radiotherapy.

1^{O} PFS **Closed at 62/72 patients = slow accrual**

Peng, Radiother Oncol 29.4 months

Median PFS 9.0 vs 17.6 months (HR = 0.52, P = 0.016).

Median OS 23.2 vs 33.6 months (HR = 0.53, P = 0.026).

There was no grade 3 or greater toxicity observed in either group, the grade 2 adverse events were 50% in the EGFR-TKIs + SBRT group while the percentage was 45.2% in the EGFR-TKIs group.

Conclusions The addition of SBRT significantly delayed the onset of acquired resistance to EGFR-TKIs and prolonged the PFS and OS of patients. Radiotherapy of the primary lesion alone might be superior to metastatic sites. Further confirmatory studies are needed to confirm our findings.

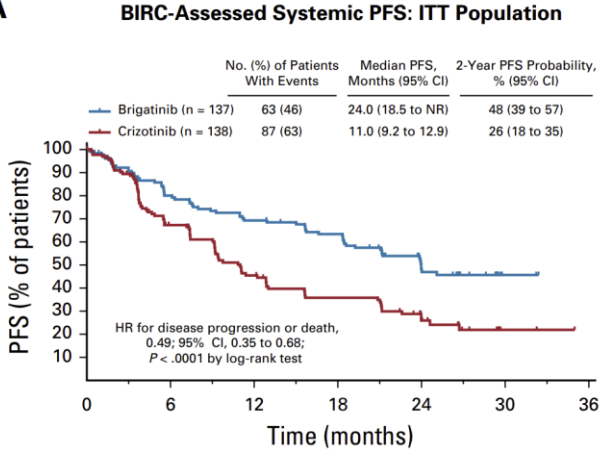
NOTE: Excellent Metaanalysis (Wu, et. al.)[19] found that local consolidative therapy (LCT) may improve the PFS and OS of mNSCLC without increasing the risk of high-grade AEs.

[19] https://www.redjournal.org/article/S0360-3016(22)00169-9/fulltext

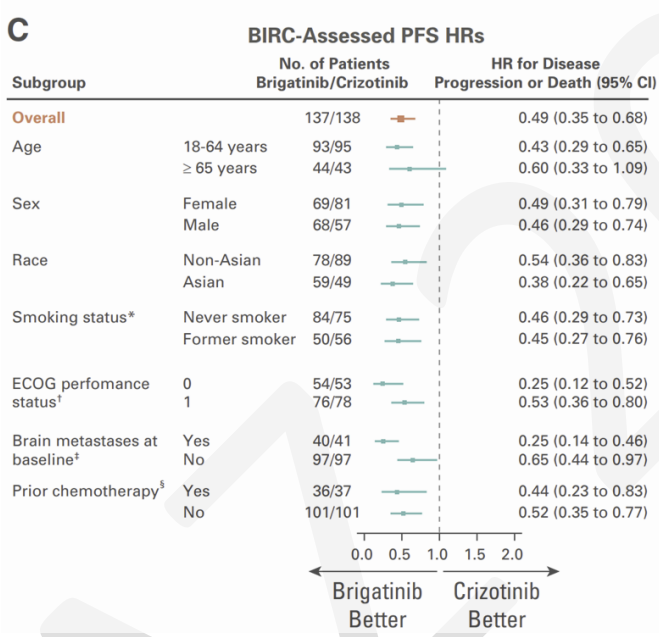
ALK (5%)

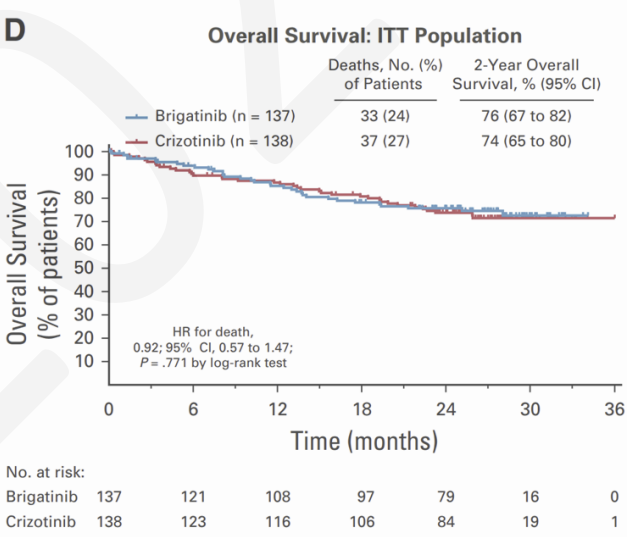
ALTA-1L Brigantinib vs. crizotinib (1st line therapy) for Δ ALK (anaplastic lymphoma kindase) NSCLC
←R→ Phase III 275 patients | 1. Brigatinib | 2. Crizotinib |.
1O PFS 25 months follow-up.

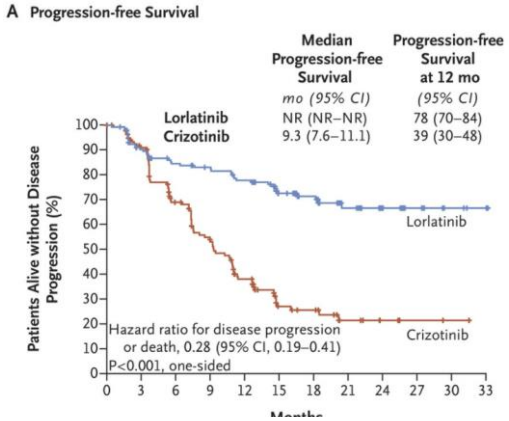
A

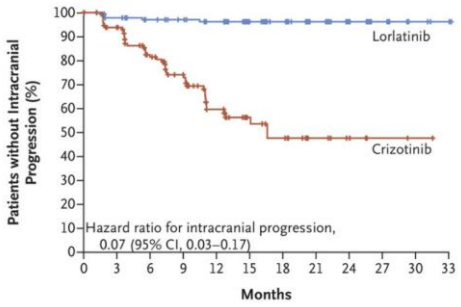


Camidge, JCO 2020.
Median PFS 24 months vs. 11 months (HR 0.49, SS) .
No new safety concerns emerged.
Brigatinib delayed median time to worsening of global health status/QoL scores compared with crizotinib (HR, 0.7, p = .049).
Brigatinib daily area under the plasma concentration–time curve was not a predictor of PFS (HR, 1.005 [95% CI, 0.98 to 1.031]; P = .69).
CONCLUSION Brigatinib represents a once-daily ALK inhibitor with superior efficacy, tolerability, and QoL over crizotinib, making it a promising first-line treatment of ALK-positive NSCLC.









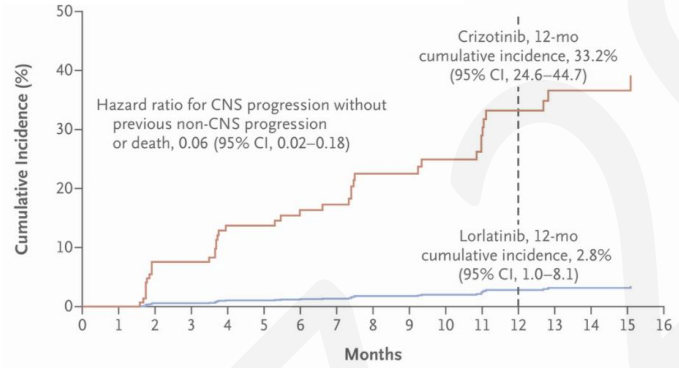
CROWN Lorlatinib vs. crizotinib (1st line therapy) for Δ ALK (anaplastic lymphoma kindase) NSCLC
←R→ 296 patients | 1. Lorlatinib | 2. Crizotinib |.
1O PFS

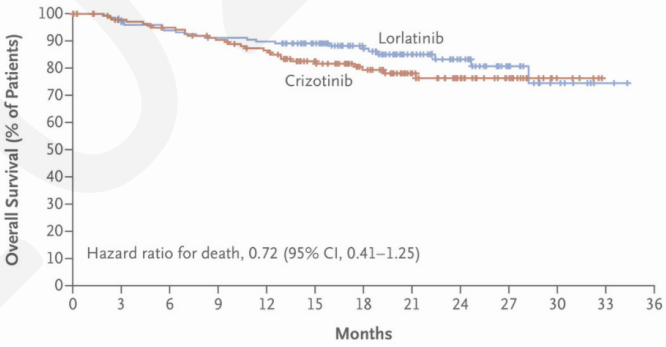
Shaw, NEJM 2020. INTERIM
1-year DFS 78% vs. 39% (HR 0.28; P<0.001).
Objective response 76% vs. 58%. Intracrainal response brain mets 82% vs. 23%.

Complete intracranial response 71% for lorlatinib.

Most common adverse events with lorlatinib were hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects. Lorlatinib was associated with more grade 3 or 4 adverse events (mainly altered lipid levels) than crizotinib (in 72% vs. 56%). Discontinuation of treatment because of adverse events occurred in 7% and 9% of the patients, respectively.

CONCLUSIONS In an interim analysis of results among patients with previously untreated advanced ALK-positive NSCLC, those who received lorlatinib had significantly longer progression-free survival and a higher frequency of intracranial response than those who received crizotinib. The incidence of grade 3 or 4 adverse events was higher with lorlatinib than with crizotinib because of the frequent occurrence of altered lipid levels.



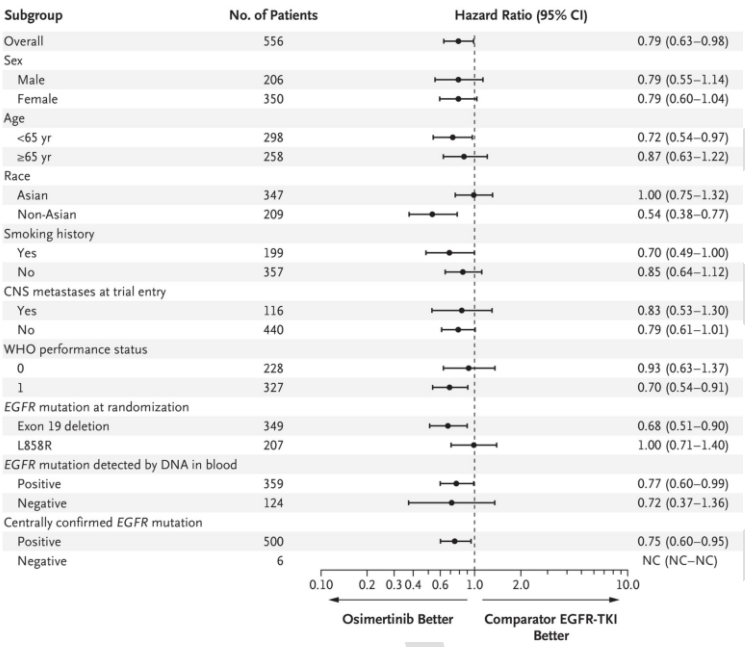


Excellent Review: Adjuvant Treatments for Surgically Resected Non–Small Cell Lung Cancer Harboring EGFR Mutations[20]

Osimertinib

FLAURA Trial EGFR-TKI Osimertinib vs. older gefitinib or erlotinib as FIRST LINE
←R→ 556 patients previously untreated advanced (or metastatic) NSCLC with an EGFR mutation (exon 19 deletion or L858R allele)
| 1. osimertinib (80 mg once daily) | 2. one of two other EGFR-TKIs (gefitinib 250 mg once daily or erlotinib 150 mg once daily |.
PFS 1^{O}. Overall survival was a **secondary** end point.

Soria, NEJM 2018.
PFS drastically improved 18.9 vs. 10.2 mo (HR 0.46, SS).
Median duration of response 17.2 vs. 8.5.
Adverse events of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% vs. 45%).



Ramalingam, NEJM 2020
Median OS 38.6 months vs. 31.8 months (HR 0.8; P=0.046).
3-years STILL using a trial regimen 28% vs. 9% (SS). Median exposure was 20.7 months and 11.5 months, respectively.
Adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group.

CONCLUSIONS Among patients with previously untreated advanced NSCLC with an EGFR mutation, those who received osimertinib had longer overall survival than those who received a comparator EGFR-TKI. The safety profile for osimertinib was similar to that of the comparator EGFR-TKIs, despite a longer duration of exposure in the osimertinib group.

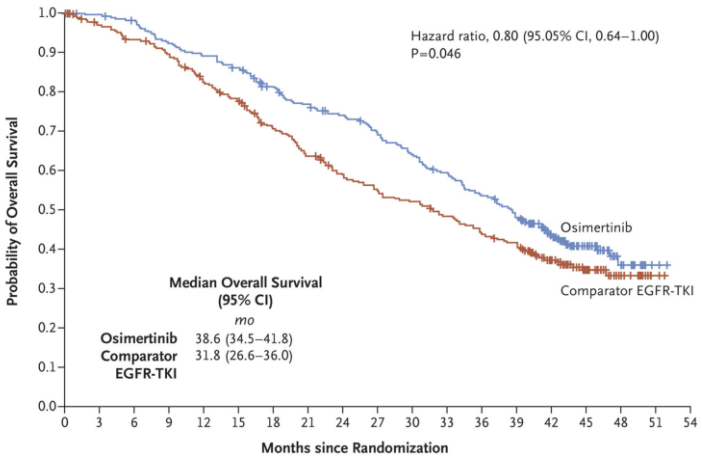
NOTE: Importantly, patients in arm [2] with a T790M-mutation after progression were eligible to crossover to osimertinib, and 31% did so, likely diminishing the gap in overall survival. Plus the rates of toxicity between arms was virtually identical. Perhaps most celebrated should be the long wait time for survival events across the board. **TBL**: 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.

Reungwetwattana, JCO 2018 **CNS PENETRATION PAPER**
Inclusion: Asymptomatic or **stable** CNS metastases were included. If symptomatic CNS mets, neurologic status required stable ≥ 2 weeks after completion of definitive therapy and corticosteroids. A preplanned subgroup analysis with **1^{O} CNS PFS.** 200 patients had available brain scans at baseline, 128 (osimertinib, n = 61; standard EGFR-TKIs, n = 67) had measurable and/or nonmeasurable CNS lesions, including 41 patients (osimertinib, n = 22; standard EGFR-TKIs, n = 19) with ≥ 1 measurable CNS lesion.

NOTE: An important detail is the definition of "measurable" disease, which had to be at least 1 cm or 2x the thickness of MRI slices. So we end up with 128 patients with brain lesions but only 41 with "measurable" disease. Nearly 75% of patients had 1-3 brain metastases, and roughly 25% had received prior brain radiation.
Results: Median CNS PFS **not reached vs. 13.9 months** (HR 0.48, P = .014)
CNS ObR rates in only measurable CNS 91% vs. 68% (OR 4.6, P = .066).
CNS ObR rates in OVERALL all patients 66% vs. 43% (OR 2.5, P = .011).

Probability of experiencing a CNS progression event was consistently lower with osimertinib versus standard EGFR-TKIs.

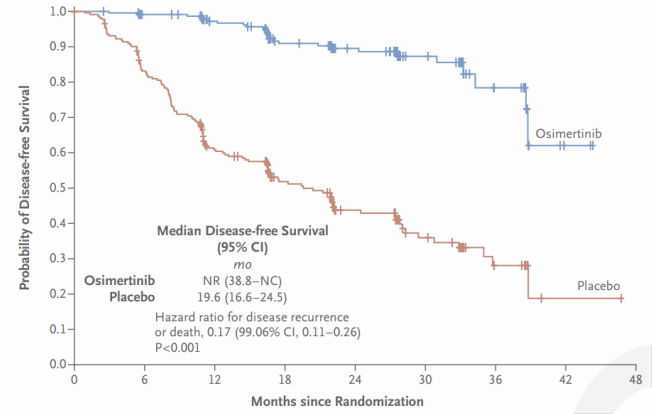
Conclusion Osimertinib has CNS efficacy in patients with untreated EGFR-mutated non-small-cell lung cancer. These results suggest a reduced risk of CNS progression with osimertinib versus standard EGFR-TKIs.

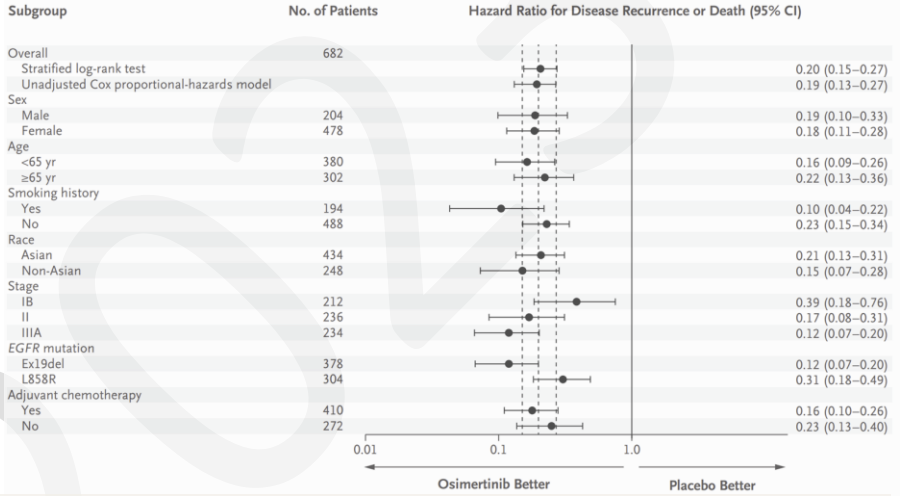


[20] https://jamanetwork.com/journals/jamaoncology/article-abstract/2804891

ADAURA (**Maintenance** Osimertinib 3rd gen, CNS active, EGFR-TKI) >>> EGFR-TKI (gefitinib/erlotinib).
←R→ 682 patients 30% (early stage I-IIIA), surgery as 1O tx s/p complete tumor resection → adj C (if needed) → | 1. Osimertinib | 2. Placebo |.
Adj C is standard of care in patients with resected stage II-III (some IB), but these have high recurrences.
Osimertinib 80 mg once daily orally or PBO to receive treatment for up to 3 years.
Stage IB 31/31%, stage II/IIIA 69/69%, female 68/72%, ex19del 55/56%, L858R 45/44%.
No Radiation was allowed.

Wu, NEJM 2020 / Herbst, ASCO 2020
2-year DFS (II–IIIA pts), 90% vs. 44% (HR 0.16, SS).
2-year DFS (overall population), 89% vs. 53% (SS).
2% of patients on osimertinib had CNS events compared to 11% with placebo (an 82% RR ↓ in the risk of CNS disease or death).
OS was immature (4% maturity) with 29/682 deaths (osimertinib n=9, PBO n=20) at DCO.
The safety profile was consistent with the known safety profile of osimertinib.
Conclusions: Adjuvant osimertinib is the 1st targeted agent in a global trial to show a statistically significant and clinically meaningful improvement in DFS in pts with stage IB/II/IIIA EGFRm NSCLC after complete tumor resection and adjuvant chemotherapy, when indicated. Adjuvant osimertinib provides an effective new treatment strategy for these pts. **ALSO ↓ CNS RECURRENCE**.





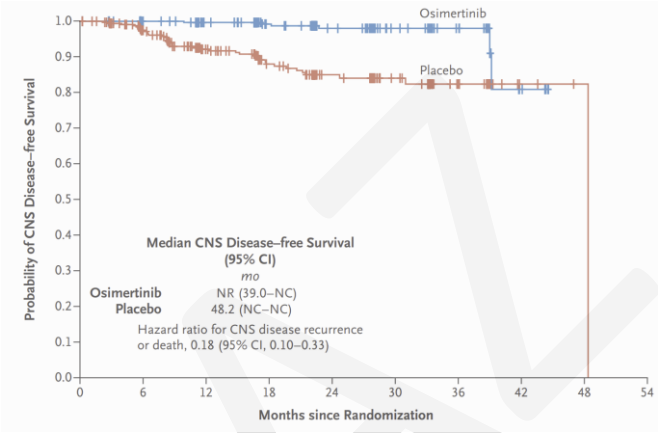


Table 2. Adverse Events.*

Adverse Event	Osimertinib (N=337)				Placebo (N=343)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
	number of patients (percent)							
Diarrhea	156 (46)	116 (34)	32 (9)	8 (2)	68 (20)	54 (16)	13 (4)	1 (<1)
Paronychia	85 (25)	31 (9)	50 (15)	3 (1)	5 (1)	3 (1)	2 (1)	0
Dry skin	79 (23)	75 (22)	3 (1)	1 (<1)	22 (6)	18 (5)	4 (1)	0
Pruritus	65 (19)	49 (15)	16 (5)	0	30 (9)	28 (8)	2 (1)	0
Cough	62 (18)	43 (13)	19 (6)	0	57 (17)	42 (12)	15 (4)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)	14 (4)	10 (3)	4 (1)	0
Nasopharyngitis	47 (14)	30 (9)	17 (5)	0	35 (10)	25 (7)	10 (3)	0
Upper respiratory tract infection	45 (13)	24 (7)	19 (6)	2 (1)	35 (10)	19 (6)	16 (5)	0
Decreased appetite	44 (13)	29 (9)	13 (4)	2 (1)	13 (4)	9 (3)	4 (1)	0
Mouth ulceration	39 (12)	32 (9)	7 (2)	0	8 (2)	6 (2)	2 (1)	0
Dermatitis acneiform	37 (11)	29 (9)	8 (2)	0	16 (5)	12 (3)	4 (1)	0

Tsuboi, NEJM 2023
5-year OS 85% vs. 73% (HR 0.49; P<0.001).
Overall population (stage IB to IIIA disease), 5-year OS 88% vs. 78% (SS).
One new serious adverse event, pneumonia related to coronavirus disease 2019, was reported after the previously published data-cutoff date (the event was not considered by the investigator to be related to the trial regimen, and the patient fully recovered). Adjuvant osimertinib had a safety profile consistent with that in the primary analysis.
CONCLUSIONS Adjuvant osimertinib provided a significant overall survival benefit among patients with completely resected, EGFR-mutated, stage IB to IIIA NSCLC. (Funded by AstraZeneca; ADAURA ClinicalTrials.gov number

AURA and AURA 2 POOLED EGFR-TKI Osimertinib

Two Phase 2 trial. IN total 411 patients received osimertinib (second line 129 patients vs. third line or later = 282).

Ahn, Cancer 2019.

Median treatment exposure was 16.4 months. **The objective response rate was 66%, median response duration was 12.3 months.**

Median PFS 9.9 months. Median OS 26.8 months. 1, 2, 3 year OS were 80%, 55%, and 37%, respectively.

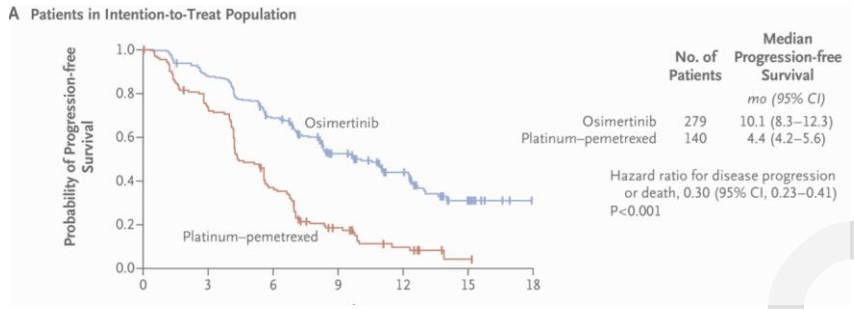
Grade ≥3 possibly causally related (investigator assessed) adverse events were reported in 65 patients (16%), and the most common were rash (grouped terms; 42%; grade ≥3, 1%) and diarrhea (39%; <1%).

CONCLUSIONS: This pooled analysis represents the most mature clinical trial data for osimertinib in patients with pretreated, T790M-positive, advanced non-small cell lung cancer, further establishing osimertinib as a standard of care for this patient population.

AURA 3 Osimertinib vs. Platinum

←R→ Phase III 419 patients T790M-positive advanced NSCLC s/p disease progression after first-line EGFR-TKI therapy, in a 2:1 ratio to receive either | 1. oral osimertinib (80 mg once daily) | 2. IV intravenous pemetrexed (500 mg / m^2) + either carboplatin (AUC5) or cisplatin (75 mg / m^2) | every 3 weeks for up to six cycles; maintenance pemetrexed was allowed.

1^O investigator-assessed progression-free survival.



Mok, NEJM 2017

Median PFS 10.1 months vs. 4.4 months (HR 0.30; P<0.001).

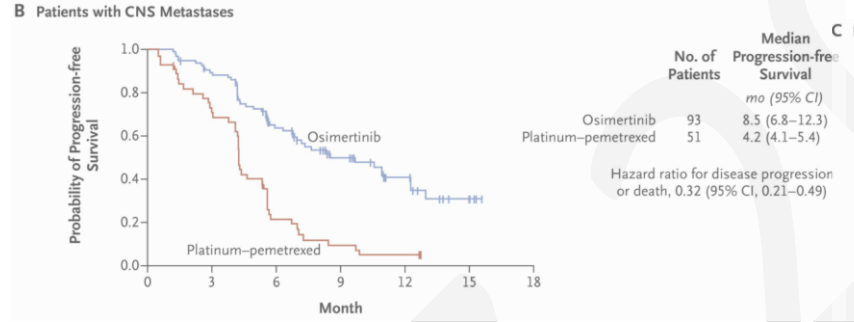
Objective response rate was 71% vs. 31% (OR 5.39; P<0.001).

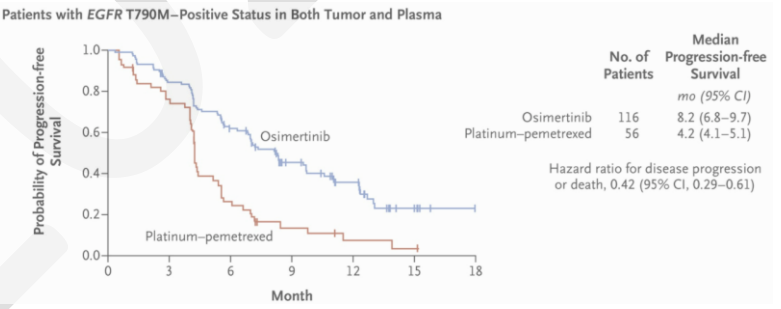
Among 144 patients with metastases to CNS, median PFS 8.5 months vs. 4.2 months (HR 0.32; SS).

The % of patients with adverse events of ≥ G3 grade 3 lower with osimertinib (23%) than with platinum therapy plus pemetrexed (47%).

CONCLUSIONS

Osimertinib had significantly greater efficacy than platinum therapy plus pemetrexed in patients with T790M-positive advanced non–small-cell lung cancer (including those with CNS metastases) in whom disease had progressed during first-line EGFR-TKI therapy.





BLOOM Phase 1 Leptomeningeal Study

Phase 1 41 patients with leptomeningeal disease from ΔEGFR advanced NSCLC with progression on previous EGFR-TKI therapy.

If cytologically confirmed LM → received osimertinib 160 mg once daily.

Yang, JCO 2020.

LM ORR and DoR by neuroradiologic BICR were 62% (95% CI, 45% to 78%) and 15.2 months (95% CI, 7.5 to 17.5 months), respectively.

Overall, ORR by investigator was 41% (95% CI, 26% to 58%)

and **median DoR was 8.3 months** (95% CI, 5.6 to 16.5 months).

Median investigator-assessed PFS was 8.6 months (95% CI, 5.4 to 13.7 months) with 78% maturity.

Median OS was 11.0 months (95% CI, 8.0 to 18.0 months) with 68% maturity.

CSF tumor cell clearance was confirmed in 11 (28%; 95% CI, 15% to 44%) of 40 patients.

Neurologic function was improved in 12 (57%) of 21 patients with an abnormal assessment at baseline.

The adverse event and PK profiles were consistent with previous reports for osimertinib.

CONCLUSION Osimertinib showed meaningful therapeutic efficacy in the CNS and a manageable safety profile at 160 mg once daily in patients with EGFRm NSCLC and LM.

TABLE 2. Response to Treatment

Measure	Response, No. (%)				
	LM by BICR[a]	LM by Investigator[a]	CNS by Investigator[b]	Non-CNS by Investigator[c]	Overall[d] by Investigator[e]
No. of patients	37	41	12	38	41
Best objective response					
Complete response[f]	12 (32)	1 (2)	0 (0)	0 (0)	0 (0)
Partial response[f]	11 (30)	10 (24)	7 (58)	17 (45)	17 (42)
Stable disease ≥ 6 weeks	12 (32)	25 (61)	3 (25)	14 (37)	17 (42)
Progression	1 (3)	3 (7)	1 (8)	6 (16)	6 (15)
Not evaluable	1 (3)	2 (5)	1 (8)	1 (3)	1 (2)
ORR,[f,g] % (95% CI)	62 (45 to 78)	27 (14 to 43)	58 (28 to 85)	45 (29 to 62)	41 (26 to 58)
DCR at 12 weeks, No. (%; 95% CI)	35 (95; 82 to 99)	32 (78; 62 to 89)	10 (83; 52 to 98)	27 (71; 54 to 85)	30 (73; 57 to 86)
Median DoR,[h] months (95% CI)	15.2 (7.5 to 17.5)	18.9 (7.6 to NC)	11.0 (3.8 to NC)	8.3 (5.6 to NC)	8.3 (5.6 to 16.5)

Chinese Side Effects *Concurrent RT + Osimertinib*.
Historically, when the first-gen TKI erlotinib was combined with thoracic radiotherapy (TRT), 37.5% of patients developed ≥G2 radiation pneumonitis.

> **Jia, Radiother Oncol 2020.**
> Retrospective 11 patients. ECOG 0-1 inclusion criteria. V5 all patients < 50%. V20 all patients < 24%. RT generally 60 Gy in 30 fx.
> RP seen in all 11 patients. Nearly 2/3s had G2 RP and nearly 1/2 had G3 RP. 1 patent had fatal RP (and had only 30 Gy in 15 fractions!!!),
> **Conclusions**: In summary, for the first time, our study reports an especially high rate of grade 2 or worse RP in patient treated with combination TRT and Osimertinib, even though total lung V5, V20 and MLD seem unlikely to have induced the RP. This serves as a warning that physicians must practice caution when adding TRT to an Osimertinib regimen. Meanwhile, TRT is an optimal treatment in patients suffering from local and slow progressing tumors and should not be entirely omitted. Future studies need to investigate the safe time interval between Osimertinib and TRT administration.

Chinese **SINDAS Trial** Upfront Ablative RT + TKI
Background: Adding radiotherapy (RT) to systemic therapy improves progression-free survival (PFS) and overall survival (OS) in oligometastatic non-small cell lung cancer (NSCLC). Whether these findings translate to epidermal growth factor receptor (EGFR)–mutated NSCLC remains unknown. The SINDAS trial (NCT02893332) evaluated first-line tyrosine kinase inhibitor (TKI) therapy for EGFR-mutated synchronous oligometastatic NSCLC and randomized to upfront RT vs no RT.
←R→ 133 biopsy-proven EGFR Δ AC + synchronous (newly diagnosed, treatment naïve) oligometastatic (≤5 metastases; ≤2 lesions in any one organ) NSCLC without brain metastases. All patients first-generation TKI (gefitinib, erlotinib, or icotinib)→ | 1. no RT | 2. RT |.
T-stage = 1 (10%), 2 (25%), 3 (30%), 4 (30%), unknown (< 5%).
N-stage = 0 (12%), 1 (30%), 2 (40%), 3 (15%), unknown (< 5%).
RT = SBRT (25-40 Gy in 5 fractions depending on tumor size and location) **to all metastases** and **the primary tumor/involved regional lymphatics**.
1^{O} ITT PFS.

Variable[a]	Progression-free survival		Overall survival	
	HR (95% CI)	*P*[b]	HR (95% CI)	*P*[b]
Zubrod performance status (0 vs 1-2)	0.50 (0.22 to 0.75)	.02	0.01 (0.01 to 0.44)	.02
Clinical T classification (T3-4 vs.T1-2)	1.10 (0.99 to 1.22)	.09	2.06 (1.08 to 5.54)	.02
Clinical N classification (N2-3 vs N0-1)	—	—	1.56 (1.19 to 3.69)	.06
Number of metastases (3-5 vs 1-2)	1.96 (1.30 to 4.70)	.004	1.93 (1.21 to 3.07)	.004
EGFR mutation (exon 19 deletion vs exon 21 mutation)	0.94 (0.61 to 1.43)	.09	0.09 (0.02 to 0.38)	.001
Randomization arm (TKI only vs TKI + RT)	1.39 (1.07 to 1.95)	.005	2.11 (1.31 to 5.97)	.004

Wang, JNCI 2022 23.6 months follow-up
Median PFS 12.5 months vs 20.2 months (P < .001)
Median OS 17.4 months vs 25.5 months (P < .001)
Local control improved with RT around 55.4% → 91.2% (SS).

Treatment yielded no grade 5 events and a 6% rate of symptomatic grade 3-4 pneumonitis in the TKI with RT arm. Based on the efficacy results of this prespecified interim analysis, the ethics committee recommended premature cessation of this trial.

Conclusions As compared with a first-line TKI alone, addition of upfront local therapy using RT statistically significantly improved PFS and OS for EGFR-mutated NSCLC.

Chinese Phase II Upfront Ablative RT + TKI
←R→ 74 patients NSCLC with an EGFR-sensitive mutation (19DEL or 21L858R) w/ stage IV.
First-line EGFR-TKIs (gefitinib, erlotinib, and icotinib) → achieved stable disease or partial response → enrolled after three months.
| 1. EGFR-TKI alone | 2. EGFR-TKIs +SBRT combo |.
In the combination-group, different tumor sites were irradiated at doses ranging from 30–50 Gy in five fractions.
Considering the short duration of SBRT, the TKIs were continued during the radiotherapy.
1^{O} PFS **Closed at 62/72 patients = slow accrual**

> **Peng, Radiother Oncol** 29.4 months
> Median PFS 9.0 vs 17.6 months (HR = 0.52, P = 0.016).
> Median OS 23.2 vs 33.6 months (HR = 0.53, P = 0.026).
> There was no grade 3 or greater toxicity observed in either group, the grade 2 adverse events were 50% in the EGFR-TKIs + SBRT group while the percentage was 45.2% in the EGFR-TKIs group.
> **Conclusions** The addition of SBRT significantly delayed the onset of acquired resistance to EGFR-TKIs and prolonged the PFS and OS of patients. Radiotherapy of the primary lesion alone might be superior to metastatic sites. Further confirmatory studies are needed to confirm our findings.

NOTE: Excellent Metaanalysis (Wu, et. al.)[21] found that local consolidative therapy (LCT) may improve the PFS and OS of mNSCLC without increasing the risk of high-grade AEs.

[21] https://www.redjournal.org/article/S0360-3016(22)00169-9/fulltext

Other Studies

KEYNOTE-789 **Metastatic**

Background: EGFR TKIs are standard 1L therapy for metastatic NSCLC with sensitizing EGFR mutations; however, most pts ultimately experience PD.
←R→ 492 patients | 1. pembro + chemo (n = 245) | 2. pbo + chemo (n = 247) |.
TKI-resistant, EGFR-mutant, metastatic NSCLC. (Documented DEL19 or L858R EGFR mutation), → progression after EGFR TKI treatment were enrolled.
Dose: 35 cycles of pembro 200 mg Q3W or placebo (pbo) Q3W plus 4 cycles of pem and carboplatin or cisplatin Q3W followed by maintenance pem.
1^{O} Dual Endpoints PFS and OS.

Yang, ASCO 2023 Abstract **2nd Interim Analysis**

Median PFS 5.6 vs. 5.5 months (NS).
Median OS 15.9 vs. 14.months (NS). 1-year OS 61.6% vs 59.4% 2-year OS 30.6% vs 26.4%.
HR for OS was similar in PD-L1 TPS ≥50% (HR, 0.84) and TPS <50% groups (HR, 0.85).
ORR (95% CI) in ITT was 29.0% (23.4%–35.1%) with pembro + chemo vs 27.1% (21.7%–33.1%) with pbo + chemo.
Median DOR was 6.3 (2.3 to 40.8+) mo vs 5.6 (1.8+ to 40.6+) mo.
Grade ≥3 treatment-related AEs occurred in 43.7% of pts in pembro + chemo arm and 38.6% in pbo + chemo arm
Grade 5 AEs occurred in 0.4% vs 0.8%.
Grade ≥3 immune-mediated AEs and infusion reactions occurred in 4.5% of pts in the pembro + chemo arm and 2.0% in the pbo + chemo arm; 0.4% vs 0% had grade 5 events.
Conclusions: In the KEYNOTE-789 study, addition of pembro to chemo in pts with TKI-resistant, EGFR-mutant, metastatic nonsquamous NSCLC did not significantly prolong PFS and OS in comparison to pbo + chemo. AEs were manageable in both arms, and no new safety signals were identified.

Chinese SBRT EGFR-TKI Phase II **Metastatic**

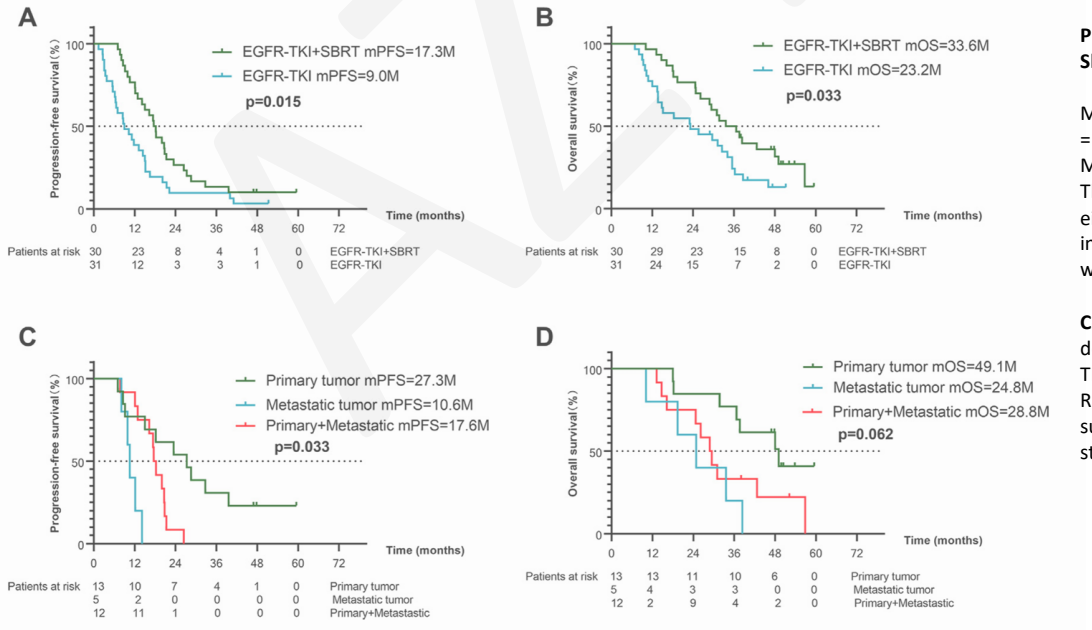
Background: EGFR-TKIs have a significant therapeutic effect in the treatment of advanced NSCLC with EGFR Δ. However, the acquired resistance greatly limits the survival benefit of EGFR-TKIs for EGFR-mutant NSCLC patients. We aimed to assess the efficacy and safety of stereotactic body radiotherapy (SBRT) plus EGFR-TKIs in these patients.

←R→ 62 patients NSCLC + EGFR-sensitive mutation (19DEL or 21L858R) and diagnosed at stage IV.
Enrolled: First-line EGFR-TKIs including gefitinib, erlotinib, and icotinib → achieved stable disease or partial response enrolled after three months.
| 1. SBRT plus EGFR-TKIs | 2. EGFR-TKIs treatment alone |.

RT = Different tumor sites were irradiated at doses ranging from 30–50 Gy in five fractions.
Considering the short duration of SBRT, the TKIs were continued during the radiotherapy.
1^{O} PFS.

Table 2
Baseline characteristics of Radiotherapy.

Characteristic	EGFR-TKI + SBRT group (n = 30)
Radiotherapy site volume, median (range)	
GTV (cm3)	36.1(5.6–162.0)
PTV (cm3)	48.7(12.3–204.5)
Radiotherapy site classification, n (%)	
Primary	13(43.33)
Metastasis	5(16.67)
Primary + Metastasis	12(40.00)
Radiation Site	**Dose (Gy/fractions) , n (%)**
Lung	40 Gy/5F, 10(33.33)
	50 Gy/5F, 14(46.67)
mediastinum	30 Gy/5F, 7(23.33)
Adrenal gland	30 Gy/5F, 2(6.67)
liver	40 Gy/5F, 3(10.00)
Bone	30 Gy/5F, 5(16.67)
Brain	30 Gy/5F, 7(23.33)



Peng, Radiother Oncol 2023
Slow accrual → closed at 62 of 72 patients.
29.4 months followup
Median PFS 17.6 months vs. 9 months (HR = 0.52, P = 0.016).
Median OS 33.6 months vs. 23.2(HR 0.53 P = 0.026).
There was no grade 3 or greater toxicity observed in either group, the grade 2 adverse events were 50% in the EGFR-TKIs + SBRT group while the percentage was 45.2% in the EGFR-TKIs group.

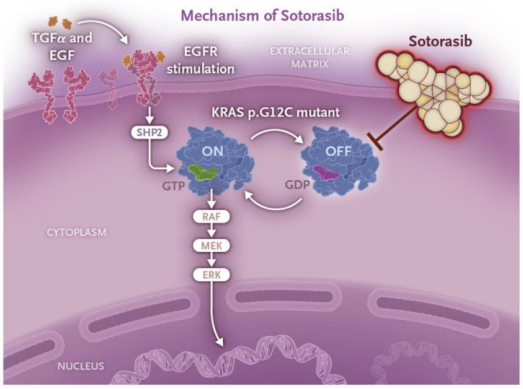
Conclusions The addition of SBRT significantly delayed the onset of acquired resistance to EGFR-TKIs and prolonged the PFS and OS of patients. Radiotherapy of the primary lesion alone might be superior to metastatic sites. Further confirmatory studies are needed to confirm our findings.

ARCHER 1050 Asian 2nd gen EGFR Dacomitinib EGFR Δ study.
←R→ 452 patients **with newly diagnosed** NSCLC with activating EGFR mutations. | 1. Dacomitinib | 2. Gefitinib |.
IIIB-IV NSCLC to daily dacomitinib 45 mg or gefitinib 250 mg
The final OS analysis was conducted with a data cutoff date of February 17, 2017; at that time 220 deaths (48.7%) were observed.

Mok, JCO 2018.
Median OS was 34.1 months vs. 26.8 months (HR OS was 0.760, P = .044).
30-month OS 56.2% vs. 46.3% (SS).
Median PFS 14.7 mo vs. 9.2 mo (SS).
NO SUBGROUP HAD A SS benefit individually.
Conclusion In patients with advanced NSCLC and EGFR activating mutations, dacomitinib is the first second-generation epidermal growth factor receptor tyrosine kinase inhibitor (TKI) to show significant improvement in OS in a phase III randomized study compared with a standard-of-care TKI. Dacomitinib should be considered one of the standard treatment options for these patients.
Bottom Line: Dacomitinib improves overall survival compared with gefitinib among (mostly) Asian patients with EGFR-aberrant NSCLC, but verdict is still out on how it stacks up next to its progeny osimertinib. | Mok, J Clin Oncol 2018

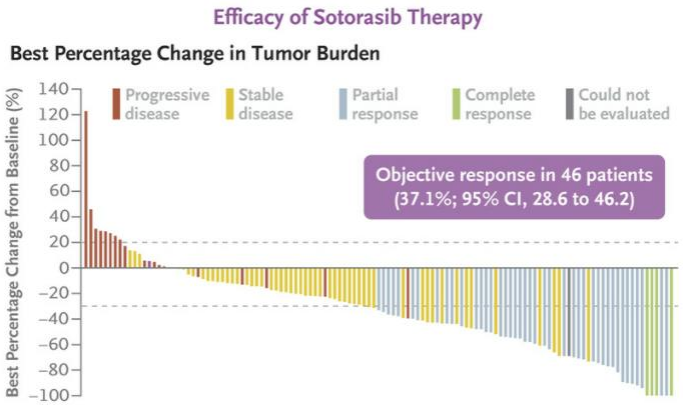
Note: Approximately 50% of patients from the dacomitinib arm and 62% from the gefitinib arm received additional treatment, and most of these patients received chemotherapy. Secondly, many patients received a 3rd gen Osimertinib. A third potentially contributing factor is that, although the presence of CNS metastases was an exclusion criterion for the study, the brain was the primary site of disease progression for more patients in the gefitinib arm (n = 11) than in the dacomitinib arm (n = 1)

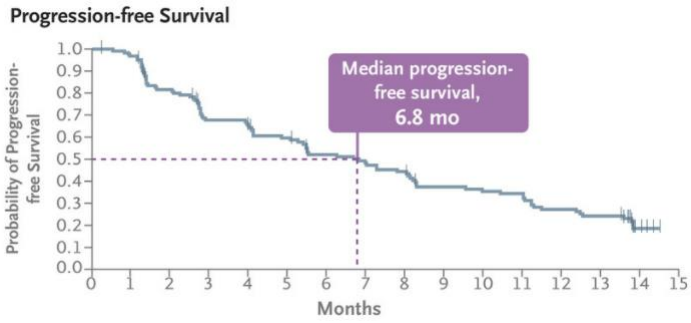
KRAS (25%)



CodeBreaK100 **Phase II Sotorasib**
Phase II 126 patients (81% s/p both platinum based chemo and PD-1 or PD-L1).
All KRAS Δ p.G12C advanced NSCLC.
1^{O} objective response.

Skoulidis, NEJM 2021.
Objective Response 46 patients (37.1%). CR in 4 (3.2%). PR in 42 (33.9%).
Median duration of response was 11.1 months. Disease control occurred in 100 patients (80.6%).
Median PFS was 6.8 months. Median OS 12.5 months.
Treatment-related adverse events occurred in 88 of 126 patients (69.8%), including G3 in 25 patients (19.8%) and G4 in 1 (0.8%).
Responses were observed in subgroups defined according to PD-L1 expression, tumor mutational burden, and co-occurring mutations in STK11, KEAP1, or TP53.
CONCLUSIONS In this phase 2 trial, sotorasib therapy led to a durable clinical benefit without new safety signals in patients with previously treated KRAS p.G12C–mutated NSCLC.





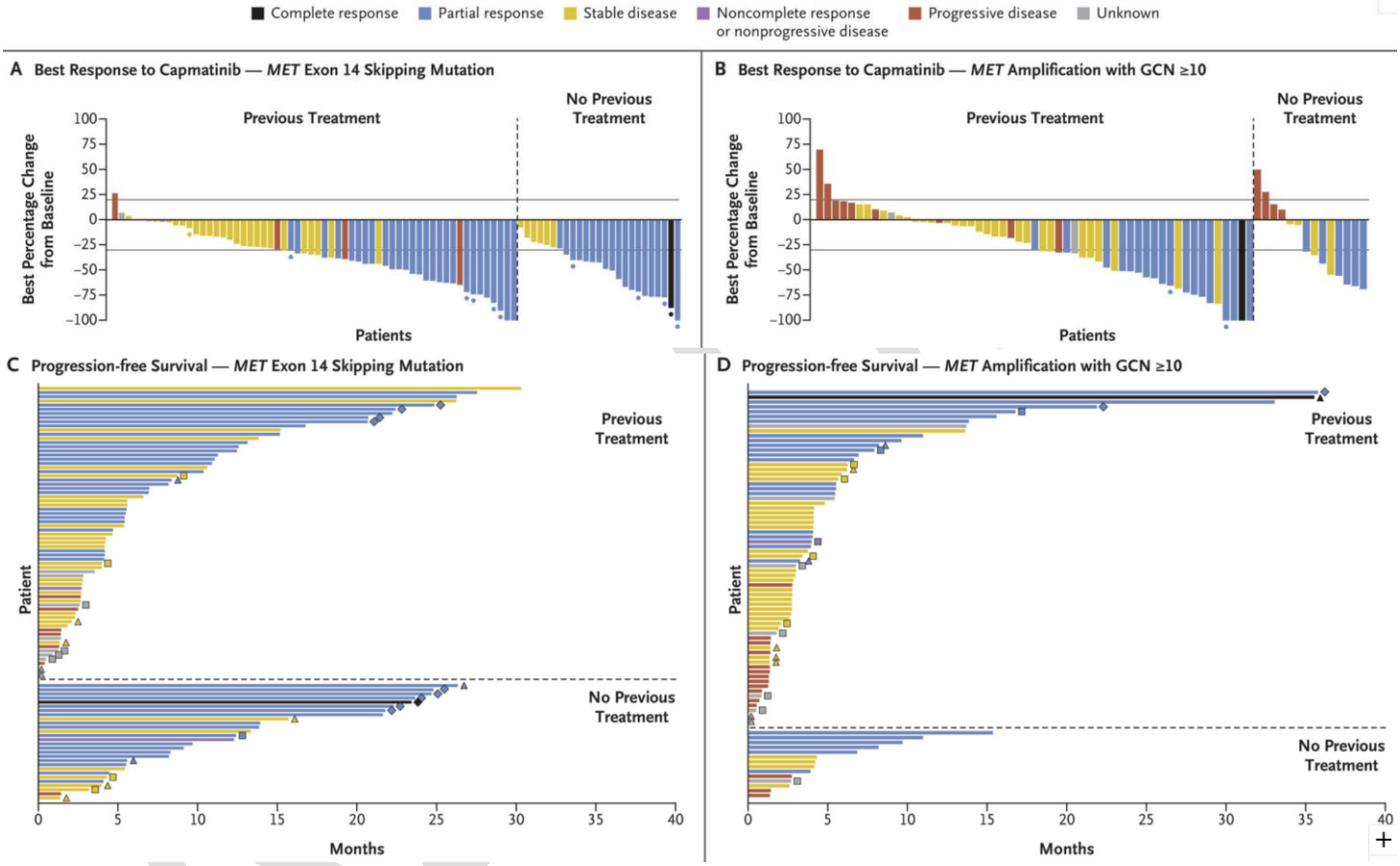
MET (1%)

GEOMETRY Mono-1 **Capmatinib** Δ MET exon 14 skipping mutation inhibitors.
Like RET, MET driver mutations are generally exclusive of other driver mutations. (poor prognosis)
Phase 2, n = 365 all NSCLC with Δ MET Driver mutations. All → received capmatinib (400-mg tablet) twice daily.
1^{O} OS (complete or partial response).

Wolf, NEJM 2020

S/P 1-2 lines of therapy (n=69)	Overall response 41%	Median duration of response 9.7 months.
S/P No Prior TX (n=28)	Overall response 68%	Median duration of response 12.6 months.
Met amp gene copy < 10	Overall response 7-12%	
Met amp gene copy ≥ 10	Overall response 29% (previous tx) and 40% (no prior tx).	

Adverse events = peripheral edema (in 51%) and nausea (in 45%); these events were mostly of grade 1 or 2.
CONCLUSIONS Capmatinib showed substantial antitumor activity in patients with advanced NSCLC with a MET exon 14 skipping mutation, particularly in those not treated previously. The efficacy in MET-amplified advanced NSCLC was higher in tumors with a high gene copy number than in those with a low gene copy number. Low-grade peripheral edema and nausea were the main toxic effects.

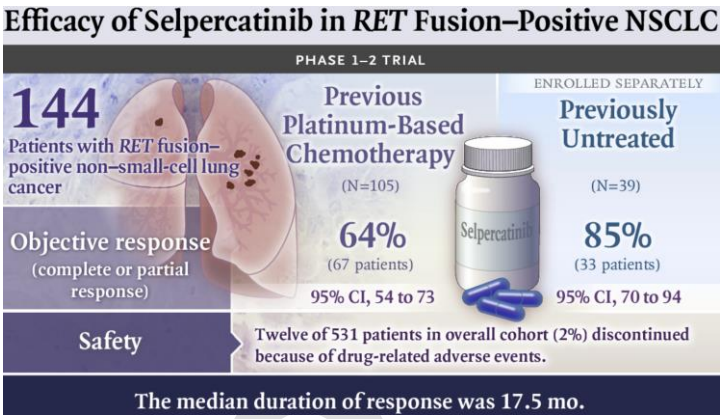


Other Studies:

Sequist, Lancet 2020. Phase 1B. ΔEGFR and ΔMET-driven acquired resistance population s/p progressed on EGFR TKIs.
PO osimertinib and savolitinib (MET-inhibitor) daily. Dosages depended on the arms aka "Parts B or D" the patients were placed into (complex trial).
Objective partial responses were observed in 66 (48%) patients in "part B" and 23 (64%) in "part D."
CONCLUSIONS: The combination of osimertinib and savolitinib has acceptable risk–benefit profile and encouraging antitumour activity in patients with MET-amplified, EGFR mutation-positive, advanced NSCLC, who had disease progression on a previous EGFR TKI. This combination might be a potential treatment option for patients with MET-driven resistance to EGFR TKIs.

Paik, NEJM 2020. Phase 2 VISION trial. 99 patients followed with MET exon 14 skipping mutation → PO daily tepotinib (500 mg).
9-month follow-up. Median duration of response of 11.1 months. Response rate ~50%. Adverse events ≥G3 → 28% of the patients (peripheral edema 7%).
Adverse events led to permanent discontinuation of tepotinib in 11% of the patients. CONCLUSIONS
CONCLUSIONS: Among patients with advanced NSCLC with a confirmed MET exon 14 skipping mutation, the use of tepotinib was associated with a partial response in approximately half the patients.

RET (1%)



LIBRETTO-001 RET-fusionΔ is mutually exclusive to other mutations.
RET-fusionΔ ↑↑ risk brain mets.
Phase I-II 144 patients → (n=105) previous platinum chemotherapy
→ (n = 39) treatment naïve
→ **Selpercatinib Trial**.
1º ObR (CR or PR).

Drilon, NEJM 2020.
Among previous chemo, ObR 64%.
Median duration response 17.5 months.
Among treatment naïve, ObR = 85%.
Among CNS mets (n=11), ObR intracrantial = 91%.
≥G3 hypertension (in 14% of the patients), ↑ ALT (in 12%), ↑ AST (in 10%), hyponatremia (in 6%), and lymphopenia (in 6%).
A total of 12 of 531 patients (2%) discontinued selpercatinib because of a drug-related adverse event.
CONCLUSIONS Selpercatinib had durable efficacy, including intracranial activity, with mainly low-grade toxic effects in patients with RET fusion–positive NSCLC who had previously received platinum-based chemotherapy and those who were previously untreated. (Funded by Loxo Oncology and others; LIBRETTO-001 ClinicalTrials.gov number, NCT03157128. opens in new tab.)

Response	Previous Platinum Chemotherapy		Previously Untreated	
	Independent Review (N=105)	Investigator Assessment (N=105)	Independent Review (N=39)	Investigator Assessment (N=39)
Objective response — % (95% CI)	64 (54–73)	70 (60–78)	85 (70–94)	90 (76–97)
Best response — no. (%)				
Complete response	2 (2)	2 (2)	0	1 (3)
Partial response	65 (62)	71 (68)	33 (85)	34 (87)†
Stable disease	30 (29)	25 (24)	4 (10)	2 (5)
Progressive disease	4 (4)	2 (2)	1 (3)	1 (3)
Could not be evaluated	4 (4)	5 (5)	1 (3)	1 (3)
Duration of response				
Patients with a response — no.	67	73	33	33‡
Patients with censored data — no./total no. (%)	44/67 (66)	45/73 (62)	26/33 (79)	26/33 (79)
Median duration of response — mo (95% CI)	17.5 (12.0–NE)	20.3 (15.6–24.0)	NE (12.0–NE)	NE (12.0–NE)
Median follow-up — mo	12.1	14.8	7.4	7.4
Progression-free survival				
Patients with censored data — no. (%)	61 (58)	58 (55)	30 (77)	30 (77)
Median progression-free survival — mo (95% CI)	16.5 (13.7–NE)	18.4 (16.4–24.8)	NE (13.8–NE)	NE (13.8–NE)
Median follow-up — mo	13.9	16.4	9.2	9.2
1-yr progression-free survival — % (95% CI)	66 (55–74)	68 (58–76)	75 (56–87)	75 (55–87)

SCCs

KEYNOTE-407 Metastatic rationale for Chemo + Pembro

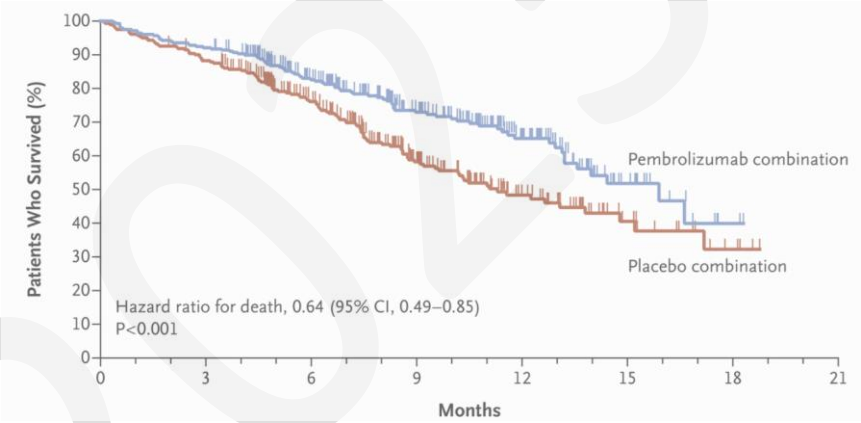
←R→ 559 metastatic TX naïve SCC NSCLC. | 1. Chemo + Pembro | 2. Chemo + Saline |.
Chemo = Carboplatin + either paclitaxel or Abraxane for 1st 4 cycles.
Pembro 200 mg up to 35 cycles.
1O OS and PFS.

Paz-Ares, NEJM 2018 Median FU 7.8 mo.
Median OS 15.9 months vs. 11.3 months (HR 0.64; P<0.001).
OS benefit was consistent regardless of the level of PD-L1 expression.
Median PFS 6.4 months vs. 4.8 months (HR 0.56; P<0.001).
AE ≥ G3 69.8% vs. 68.2%. Discontinuation of TX 13.3% vs. 6.4%.

CONCLUSIONS In patients with previously untreated metastatic, squamous NSCLC, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer overall survival and progression-free survival than chemotherapy alone.

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

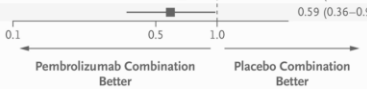
Characteristic	Pembrolizumab Combination (N=278)	Placebo Combination (N=281)
Age		
Median (range) — yr	65 (29–87)	65 (36–88)
<65 yr — no. (%)	127 (45.7)	127 (45.2)
Male sex — no. (%)	220 (79.1)	235 (83.6)
Region of enrollment — no. (%)		
East Asia	54 (19.4)	52 (18.5)
Rest of the world	224 (80.6)	229 (81.5)
ECOG performance-status score — no. (%)†		
0	73 (26.3)	90 (32.0)
1	205 (73.7)	191 (68.0)
Smoking status — no. (%)		
Current or former	256 (92.1)	262 (93.2)
Never	22 (7.9)	19 (6.8)
Histologic features — no. (%)		
Squamous	272 (97.8)	274 (97.5)
Adenosquamous‡	6 (2.2)	7 (2.5)
Brain metastases — no. (%)	20 (7.2)	24 (8.5)
PD-L1 tumor proportion score — no. (%)§		
<1%	95 (34.2)	99 (35.2)
≥1%	176 (63.3)	177 (63.0)
1–49%	103 (37.1)	104 (37.0)
≥50%	73 (26.3)	73 (26.0)
Could not be evaluated¶	7 (2.5)	5 (1.8)
Previous therapy for nonmetastatic disease — no. (%)		
Thoracic radiotherapy	17 (6.1)	22 (7.8)
Neoadjuvant or adjuvant therapy	5 (1.8)	8 (2.8)



Event	Pembrolizumab Combination (N=278)		Placebo Combination (N=280)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	273 (98.2)	194 (69.8)	274 (97.9)	191 (68.2)
Event leading to discontinuation of all treatment components†	37 (13.3)	34 (12.2)	18 (6.4)	18 (6.4)
Event leading to discontinuation of any treatment component‡	65 (23.4)	54 (19.4)	33 (11.8)	29 (10.4)
Discontinuation of pembrolizumab or placebo	48 (17.3)	44 (15.8)	22 (7.9)	21 (7.5)
Discontinuation of carboplatin	31 (11.2)	28 (10.1)	21 (7.5)	19 (6.8)
Discontinuation of paclitaxel or nab-paclitaxel	44 (15.8)	33 (11.9)	28 (10.0)	24 (8.6)
Event leading to death§	23 (8.3)	23 (8.3)	18 (6.4)	18 (6.4)
Event leading to death that was attributed to a trial regimen by an investigator¶	10 (3.6)	10 (3.6)	6 (2.1)	6 (2.1)
Event occurring in ≥15% of patients in either group‖				
Anemia	148 (53.2)	43 (15.5)	145 (51.8)	57 (20.4)
Alopecia	128 (46.0)	1 (0.4)	102 (36.4)	3 (1.1)
Neutropenia	105 (37.8)	63 (22.7)	92 (32.9)	69 (24.6)
Nausea	99 (35.6)	3 (1.1)	90 (32.1)	4 (1.4)
Thrombocytopenia	85 (30.6)	19 (6.8)	65 (23.2)	18 (6.4)
Diarrhea	83 (29.9)	11 (4.0)	65 (23.2)	6 (2.1)
Decreased appetite	68 (24.5)	6 (2.2)	82 (29.3)	5 (1.8)
Constipation	64 (23.0)	2 (0.7)	61 (21.8)	3 (1.1)
Fatigue	63 (22.7)	9 (3.2)	72 (25.7)	11 (3.9)
Asthenia	60 (21.6)	6 (2.2)	59 (21.1)	10 (3.6)
Arthralgia	57 (20.5)	4 (1.4)	40 (14.3)	2 (0.7)
Peripheral neuropathy	57 (20.5)	3 (1.1)	45 (16.1)	2 (0.7)
Vomiting	45 (16.2)	1 (0.4)	33 (11.8)	6 (2.1)
Cough	37 (13.3)	2 (0.7)	47 (16.8)	3 (1.1)
Dyspnea	36 (12.9)	4 (1.4)	45 (16.1)	3 (1.1)

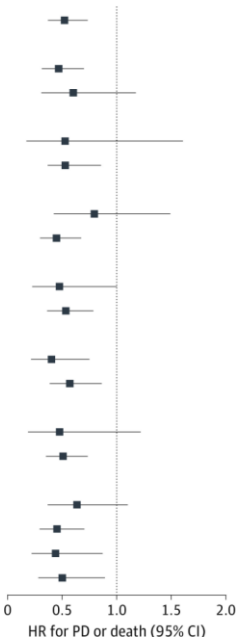
B Subgroup Analysis of Overall Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	205/559	0.64 (0.49–0.85)
Age		
<65 yr	88/254	0.52 (0.34–0.80)
≥65 yr	117/305	0.74 (0.51–1.07)
Sex		
Male	167/455	0.69 (0.51–0.94)
Female	38/104	0.42 (0.22–0.81)
ECOG performance-status score		
0	48/163	0.54 (0.29–0.98)
1	157/396	0.66 (0.48–0.90)
Region of enrollment		
East Asia	34/106	0.44 (0.22–0.89)
Rest of the world	171/453	0.69 (0.51–0.93)
PD-L1 tumor proportion score		
<1%	73/194	0.61 (0.38–0.98)
≥1%	129/353	0.65 (0.45–0.92)
1–49%	76/207	0.57 (0.36–0.90)
≥50%	53/146	0.64 (0.37–1.10)
Taxane-based drug		
Paclitaxel	140/336	0.67 (0.48–0.93)
Nab-paclitaxel	65/223	0.59 (0.36–0.98)



C Tislelizumab plus PC vs PC

Study	Events/ patients, No.	HR for PD or death (95% CI)
Overall	136/241	0.52 (0.37-0.73)
Age, y		
<65	101/166	0.47 (0.31-0.70)
≥65	35/75	0.60 (0.31-1.18)
Sex		
Female	13/23	0.53 (0.17-1.61)
Male	123/218	0.53 (0.37-0.76)
ECOG performance status		
0	39/63	0.80 (0.42-1.49)
1	97/178	0.45 (0.30-0.67)
Smoking status		
Never	29/47	0.48 (0.23-1.00)
Current or former	107/194	0.53 (0.36-0.79)
Disease stage		
IIIB	45/82	0.40 (0.22-0.75)
IV	91/159	0.57 (0.38-0.86)
Liver metastasis		
Yes	18/29	0.48 (0.19-1.22)
No	118/212	0.51 (0.35-0.73)
PD-L1 expression in TC		
<1%	52/97	0.64 (0.37-1.10)
≥1%	84/144	0.45 (0.29-0.70)
1%-49%	36/61	0.44 (0.22-0.87)
≥50%	48/63	0.50 (0.28-0.89)

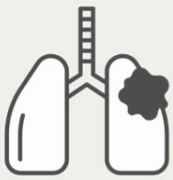


Chinese **RATIONALE-307** Tisleizumab + Chemo Study
←R→ 355 patients TX naïve IIIB/IV SCC NSCLC. All treatments in a 21-day cycle. Men 92%. Median Age 62.
| 1. Tislelizumab + Paclitaxel + Carboplatin |
| 2. Tislelizumab + nab-paclitaxel + carboplatin |
| 3. Paclitaxel + Carboplatin |.
Tislelizumab 200 mg. Paclitaxel 175 mg/m^2. Caroplatin AUC 5.
1^O PFS.

Wang, JAMA Oncol 2021. Median FU 8.6 months.
Median PFS 7.6 months vs. 7.6 months vs. 5.5 months (AvC, BvC, SS).
ORR and ↑ DoR
Arm A (72.5%, 8.2 months) vs. Arm B (74.8%; 8.6 months) vs Arm C (49.6%; 4.2 months).
No association was observed between PD-L1 expression and IRC-assessed PFS or ORR.
Discontinuation of any TX n=15 (12.5%; arm A), n=35 (29.7%; arm B), and n=18 (15.4%; arm C).
In each arm, the most common grade of 3 or greater AE was decreased neutrophil levels, which aligned with known chemotherapy toxic effects.
Six treatment-related AEs leading to death occurred; however, no deaths were solely attributed to tislelizumab.
Conclusions and Relevance In this phase 3 randomized clinical trial, adding tislelizumab to chemotherapy was associated with significantly prolonged IRC-assessed PFS, higher IRC-assessed ORRs, and a manageable safety/tolerability profile in patients with advanced sq-NSCLC, regardless of PD-L1 expression.

POPULATION

330 Men, 30 Women



Adults with treatment-naive locally advanced or metastatic squamous non–small-cell lung cancer (sq-NSCLC)

Mean (range) age: 62 (34-74) y

INTERVENTION

355 Patients randomized and analyzed

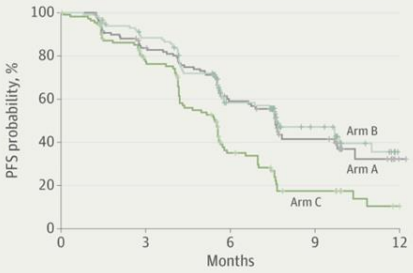
120 Arm A: tislelizumab+paclitaxel and carboplatin
IV tislelizumab, 200 mg, paclitaxel, 175 mg/m^2, and carboplatin (target area under the concentration [AUC] of 5 mg/mL•min) on day 1 every 3 wk

118 Arm B: tislelizumab+nab-paclitaxel and carboplatin
IV tislelizumab, 200 mg (day 1), nab-paclitaxel, 100 mg/m^2 (days 1, 7, and 15), and carboplatin (day 1) every 3 wk

117 Arm C: chemotherapy alone
IV paclitaxel 175 mg/m^2 (day 1) and carboplatin (target AUC 5 mg/mL•min, day 1) every 3 wk

FINDINGS

PFS was significantly prolonged with the addition of tislelizumab to paclitaxel+carboplatin (Arm A) or nab-paclitaxel+carboplatin (Arm B) compared with chemotherapy alone (Arm C)



Median (95% CI) PFS, mo:
Arm A: 7.6 (95% CI, 6.0-9.8)
Arm B: 7.6 (95% CI, 5.8-11.0)
Arm C: 5.5 (95% CI, 4.2-5.7)
Arm A vs C: hazard ratio (HR), 0.52 (95% CI, 0.37-0.74); *P*<.001
Arm B vs C: HR, 0.48 (95% CI, 0.34-0.68); *P*<.001

SETTINGS / LOCATIONS

46 Hospitals in China

PRIMARY OUTCOME

Progression-free survival (PFS), as assessed by an independent review committee and defined as the time from randomization to the first objectively documented disease progression or death from any cause

Oligo/Metastatic

Excellent Review **Articles:**

Jasper, JCO 2022	https://ascopubs.org/doi/abs/10.1200/JCO.21.01719
Giuliani IJROBP 2020	https://www.redjournal.org/article/S0360-3016(19)34008-8/fulltext
Gomez, JCO 2019	https://ascopubs.org/doi/10.1200/JCO.19.00201
Palma, Lancet 2019	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32487-5/fulltext
Iyengar, JAMA 2918	https://jamanetwork.com/journals/jamaoncology/fullarticle/2654785

TTF LUNAR Trial

←R→ 276 patients ≥ 22 years or older **metastatic** NSCLC progressing on or after platinum-based therapy, + ECOG PS ≤ 2.
Previous platinum-based therapy was required, but no restriction was placed on the number or type of previous lines of systemic therapy.
| 1. TTF + investigator's choice of ICI [nivolumab, pembrolizumab, or atezolizumab] or docetaxel) | 2. No TTF + Systemic |.
156 (57%) had non-squamous non-small-cell lung cancer.
87 (32%) had received a previous immune checkpoint inhibitor.
TTFields therapy (150 kHz) delivered continuously to the thoracic region + recommend average of at least 18 h/day device usage.
1^{O} OS.

Leal, Lancet 2023 **10.6 months**

Median OS 13·2 months vs. 9·9 months (HR 0·74, p=0·035).
In the safety population (n=267), serious adverse events of any cause were reported in 70 (53%) of 133 patients receiving TTFields therapy plus standard therapy and 51 (38%) of 134 patients receiving standard therapy alone. The most frequent grade 3–4 adverse events were leukopenia (37 [14%] of 267), pneumonia (28 [10%]), and anaemia (21 [8%]).
TTFields therapy-related adverse events were reported in 95 (71%) of 133 patients; these were mostly (81 [85%]) grade 1–2 skin and subcutaneous tissue disorders. There were three deaths related to standard therapy (two due to infections and one due to pulmonary haemorrhage) and no deaths related to TTFields therapy.
Interpretation TTFields therapy added to standard therapy significantly improved overall survival compared with standard therapy alone in metastatic non-small-cell lung cancer after progression on platinum-based therapy without exacerbating systemic toxicities. These data suggest that TTFields therapy is efficacious in metastatic non-small-cell lung cancer and should be considered as a treatment option to manage the disease in this setting.

Excellent response and commentary to the trial: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00394-7/fulltext

Oligo Tumor Control and SBRT

RR 1033 patients with 1700 oligomets (OMs).
25.2% NSCLC, 22.7% colorectal, 12.8% prostate, and 8.1% breast histology.
Solitary OM (57%) vs. 4-5 mets (8.6%).
Patients who failed locally in any SBRT-directed OM within 6 mo were at 3.6-fold higher risk of death and 2.7-fold higher risk of WSP compared to those who remained locally-controlled ($p < 0.001$). Similar associations existed for each duration of LC investigated through 3 yrs post-SBRT.

Cao, Radiother Oncol 2023

There was no significant difference in risk of widespread progression (WSP) or death between patients who failed in a subset of SBRT-treated lesions vs. patients who failed in all lesions. Minimum dose (Dmin) to the GTV/ITV was most predictive of LC when compared to prescription dose, PTV Dmin, and PTV Dmax.
Sensitivity analysis for achieving 1-yr LC > 95% found thresholds of 41.2 Gy and 55.2 Gy in 5 fractions for smaller (< 27.7 cc) and larger radioresistant lesions, respectively.
Tota LR 1-year 10%, 2-year 20%, 3 year 24%.
Conclusion
This large multinational cohort suggests that the duration of LC following OM-directed SBRT strongly correlates with WSP and OS.

TROG SAFRON II.

←R→ Phase II 90 patients with 1-3 non-central lung mets ≤ 5 cm | 1. 28 Gy x 1 | 12 Gy x 4 | SBRT fractionations.
1^{O} G ≥3 AE. 66 mean age, and 64% were male.

Siva, JAMA 2021.
≥ G3 AE 2 (5%) vs. 1 (3%) NS.
No significant differences were found between the multifraction arm and single-fraction arm for freedom from local failure (hazard ratio [HR], 0.5; 95% CI, 0.2-1.3; P = .13), overall survival (HR, 1.5; 95% CI, 0.6-3.7; P = .44), or disease-free survival (HR, 1.0; 95% CI, 0.6-1.6; P > .99). There were no significant differences observed in patient-reported outcomes.
Conclusions and Relevance In this randomized clinical trial, neither arm demonstrated evidence of superior safety, efficacy, or symptom burden; however, single-fraction SABR is more efficient to deliver. Therefore, single-fraction SABR, as assessed by the most acceptable outcome profile from all end points, could be chosen to escalate to future studies.

Chinese SINDAS
←R→ 133 with lung AC, EGFRΔ, Stage IV, ≤ 5 oligomets, ≤ 2 ECOG, no brain disease, no systemic therapy | 1. 1st line TKI alone | 2. TKI + all site SBRTs |.
1O PFS. 19.6-month follow-up.

Wang, ASCO 2020.
Median PFS 12.5 months vs. 20.2 months (HR 0.62, SS). Median OS 17.4 months vs. 25.5 months (HR 0.68, SS).
Grade 3/4 adverse events included pneumonitis (7.3% vs. 2.9%; P> .05) and esophagitis (4.4%vs. 3.0% P> .05).
Conclusions: Upfront stereotactic radiotherapy to sites at diagnosis along with first line TKI improved both progression-free survival and overall survival significantly compared with TKI alone. This finding suggests aggressive local therapy to sites at diagnosis should be explored further in large cohort phase III trials as a standard treatment option in this clinical scenario.

MD Anderson Oligometastatic Trial
Phase 2 ←R→ stage IV NSCLC, ≤ 3 mets after first-line systemic therapy, ECOG ≤ 2, **no disease progression before randomisation**.
First-line therapy was ≥ 4c x platinum-doublet **or** ≥ 3 months of EGFR or ALK inhibitors.
| local consolidative therapy RT±C or Surg for all lesions ± subsequent maintenance treatment | to maintenance/obs treatment alone |.
Randomisation was not masked and was balanced dynamically on five factors: number of metastases, response to initial therapy, CNS metastases, intrathoracic nodal status, and EGFR and ALK status.
1O PFS

Gomez, Lancet 2016.
The study was terminated early after randomisation of 49 patients.
Median follow-up time for all randomised patients of 12·39 months.
Median PFS 11·9 months vs. 3·9 months (SS).
Adverse events were similar between groups, with no grade 4 adverse events or deaths due to treatment.

Gomez, JCO 2019.
Updated median follow-up time of 38.8 months.
Median PFS 14.2 months vs. 4.4 months (SS.) **Median OS 41.2 months vs. 17.0 months (SS).**
Survival after progression 37.6 months vs. 9.4 months (SS).
Of the 20 patients who experienced progression in the MT/O arm, nine received LCT to all lesions after progression, and the median OS was 17 months (95% CI, 7.8 months to not reached).
CONCLUSION In patients with oligometastatic NSCLC that did not progress after front-line systemic therapy, LCT prolonged PFS and OS relative to MT/O.

Checkmate 017

BACKGROUND: SCC NSCLC with disease progression during or after first-line C. Efficacy and safety of nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody, as compared with docetaxel in this patient population.

←R→ 272 patients **1. Nivolumab** vs. **2 docetaxel**. Nivo 3 mg / kg q 2 weeks. Doce 75 mg / m^2 q 3 weeks. The primary end point was overall survival.

Brahmer, NEJM 2015

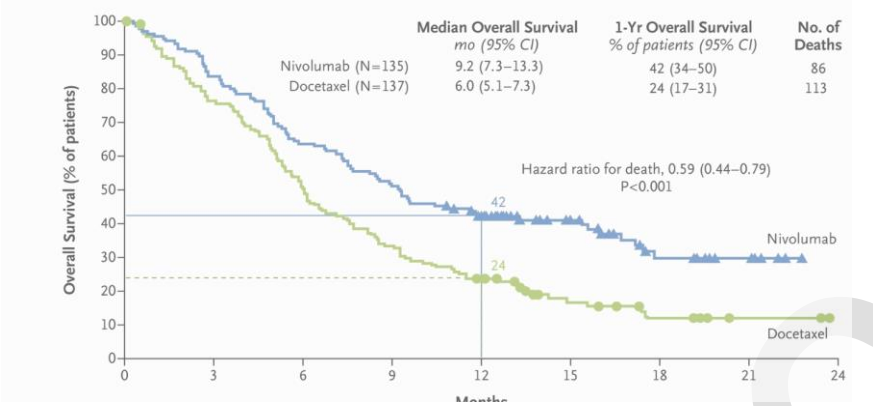
Median OS 9.2 months vs. 6.0 months. The risk of death was 41% ↓ with nivolumab (SS).

1-year OS 42% vs. 24%. The response rate was 20% vs. 9% (P=0.008).

Median PFS 3.5 months vs. 2.8 months. The expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit.

Grade 3 or 4, Nivo 7% vs. Doce 55%.

CONCLUSIONS Among patients with advanced, previously treated squamous-cell NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level.



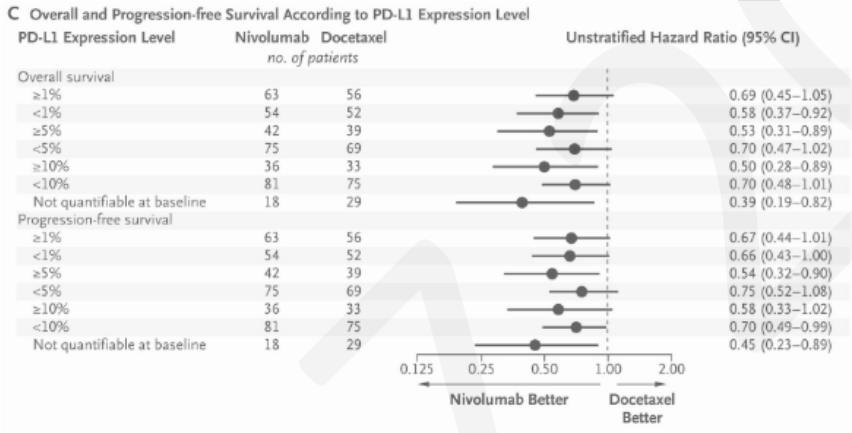


Table 2. Clinical Activity of Nivolumab versus Docetaxel in Patients with Advanced Squamous-Cell Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N=135)	Docetaxel (N=137)
Objective response†		
No. of patients	27	12
% of patients (95% CI)	20 (14–28)	9 (5–15)
Estimated odds ratio (95% CI)	2.6 (1.3–5.5)	
P value	0.008	
Best overall response — no. (%)		
Complete response	1 (1)	0
Partial response	26 (19)	12 (9)
Stable disease	39 (29)	47 (34)
Progressive disease	56 (41)	48 (35)
Could not be determined	13 (10)	30 (22)
Time to response — mo‡§		
Median	2.2	2.1
Range	1.6–11.8	1.8–9.5
Duration of response — mo‡¶		
Median	NR	8.4
Range	2.9 to 20.5+	1.4+ to 15.2+

Combined CheckMate 017 and 057

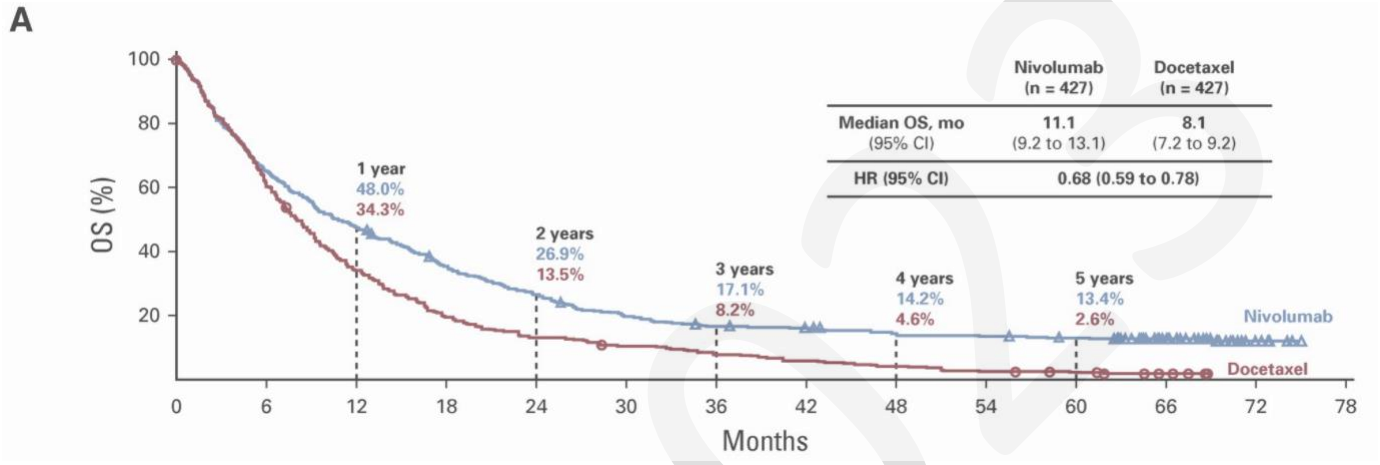
Pooled 854 patients with advanced NSCLC, PS ≤ 1, and progression during or after 1st line platinum chemo | 1. Nivo 3mg/kg q2wk| 2. Docetaxel 75 mg/m² q3wk |. Minimum follow-ups of 64 months both.

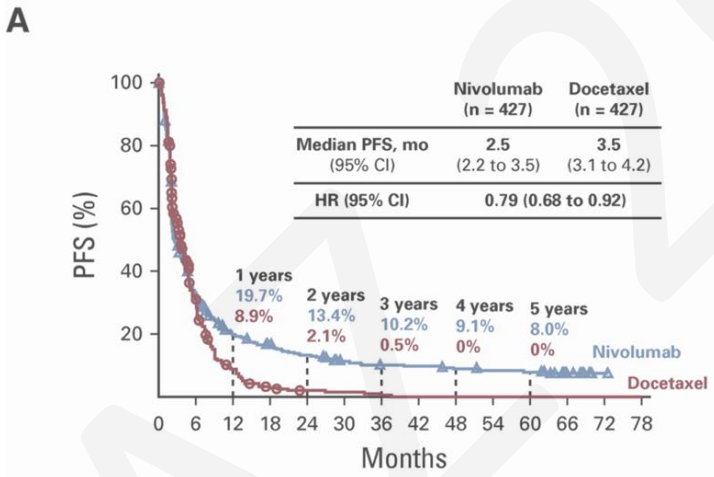
Borghaei, JCO 2021

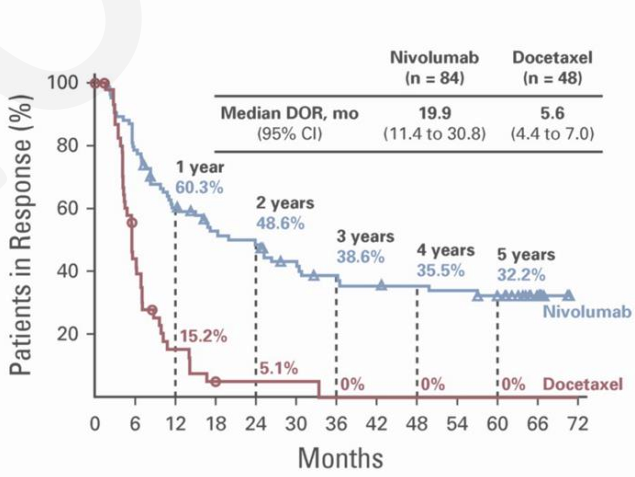
5-year OS 13.4% vs. 2.6% 5-year PFS 8.0% vs. 0%.

Nivolumab patients w/o progression at 2 and 3 years had an 82.0% and 93.0% chance of survival, and a 59.6% and 78.3% chance of remaining +5-year PFS. Treatment-related adverse events (TRAEs) were reported in 8 of 31 (25.8%) nivolumab-treated patients between 3–5 years of follow-up, seven of whom experienced new events; one (3.2%) TRAE was grade 3, and there were no grade 4 TRAEs.

CONCLUSION At 5 years, nivolumab continued to demonstrate a survival benefit versus docetaxel, exhibiting a five-fold increase in OS rate, with no new safety signals. These data represent the first report of 5-year outcomes from randomized phase III trials of a programmed death-1 inhibitor in previously treated, advanced NSCLC.

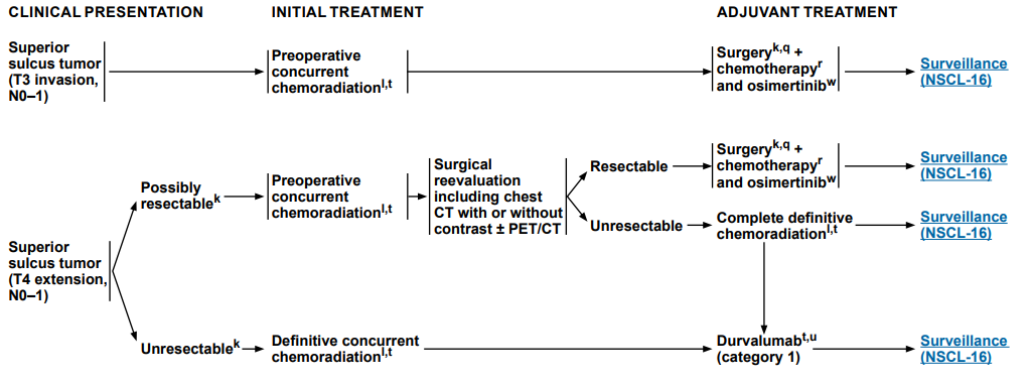






Superior Sulcus (Pancoast)

- Complete resection in 50%, 5-year OS 30%.
- Should be managed differently.



- **Typical Findings:**
  - Horner's Syndrome: miosis (constriction of the pupils), anhidrosis (lack of sweating), ptosis (drooping of the eyelid).
  - Brachial plexopathy
  - Hoarse voice → recurrent laryngeal.
  - SVC Syndrome: facial swelling and dilatation of the neck veins.

SWOG 9416 / Intergroup 0160, 2001 (1995-99) - Phase II. 111 pts. T3-4 N0-1, mediastinoscopy negative. Treated with 2 cycles of cisplatin and etoposide concurrent with 45 Gy RT. Imaging CT 2-4 after tx. Pts who responded or had stable disease underwent resection 3-5 weeks later. Two additional cycles of adjuvant chemotherapy were given.
MUST GET MRI to figure out brachial plexus…SWOG regimen is CIS Etoposide + 45 Gy RT

Rusch, J. Thoracic Carciovasc. Surg. 2001.
Rusch, JCO 2007.

20% not resectable and went for definitive CRT to 60 Gy.
80% were resectablez` (of these 94% had R0 resection)
pCR 29.1% (32/110), microscopic disease left 26.4% (29/110) = COMBINED RATE OF 56%.
5-year OS 44% (if resection) and 54% (if R0).

NOTE: THE RADONC QUESTIONS recommend CT imaging either during the last week of RT or immediately after CRT. But this study had CT imaging 2-4 weeks after. Regardless, you have to plan the entire Tx to 60 Gy even if you stop at 45 due to cord tolerances.

The pattern of recurrence in the Intergroup study was distant (non-brain) only (33%), brain only (33%), local only (17%), local + distant (12%). Despite the extensive local disease, 76% of patients underwent complete resection with pathological CR or minimal microscopic disease seen in 56% of the resection specimens, resulting in low local recurrence rates. In appropriately staged patients with mediastinoscopy (or EBUS + PET-CT), recurrence in nodal regions outside of CTV remains low.

JCO 2007 Paper **5-year OS 44% and 56% for those with complete resection.**

Particle Therapy

Proton IMRT vs. Photon Passive Scatter
All Tx CRT Eligibility: IIB to IIIB NSCLC (or stage IV NSCLC + single brain met or recurrent lung or mediastinal dx after surgery).
V20 ≤ 37% and mean lung dose < 20 Gy.
1-year LC 90% 2-year LC 70%.

Palliation + PCI

Note: Intracranial effect exists with atezolizumab, carboplatin, and pemetrexed.[22] Less than 50% have some response and most progression within 6 months → RT.

Meta-analysis
Background: Prophylactic cranial irradiation (PCI) was compared to observation in several randomized trials (RCTs), and a reduction greater than 50% was shown regarding the incidence of brain metastases (BM). However, none of these studies showed an improvement of overall survival (OS), possibly related to relatively small sample sizes and short follow-up. The aim of this meta-analysis was therefore to assess the impact of PCI on long term OS for stage III non-small cell lung cancer (NSCLC) compared to observation based on the pooled updated individual patient RCT data.
←M→ 4 recent RTC with 924 patients

Witlox, Radiother Oncol 2021 97-month follow-up
Compared to observation, no statistically significant impact of PCI on OS was observed (HR 0.90 [0.76-1.07] p = 0.23, 5-year absolute difference 1.8% [-5.2-8.8]).
PCI significantly prolonged progression-free survival (HR 0.77 [0.66-0.91] p = 0.002) and BM-free survival (HR 0.82 [0.69-0.97] p = 0.02).
The number of patients with high-grade (≥3) toxicity was 6.4% (21/330) for PCI.
Conclusion: No OS benefit by PCI was observed, but PCI prolonged the progression-free survival and BM-free survival at an increased risk of late memory impairment and fatigue.

RTOG 02-14
←R→ 340 LA-NSCLC Stage III | 1. PCI 30 Gy in 15 fractions | 2. Obs.
1^{O} OS. DFS and Brain Mets (BM)

Table 1. Outcome Estimates for Entire Study

	PCI (n = 163)		Observation (n = 177)			
Outcome by Time	No. at Risk	Event Estimate % (95% CI)	No. at Risk	Event Estimate % (95% CI)	PCI vs Observation, HR (95% CI)[a]	*P* Value[b]
Overall survival					0.82 (0.63-1.06)	.12
2 y	90	56.3 (48.3-63.6)	91	53.0 (45.3-60.1)		
5 y	39	24.7 (18.3-31.6)	42	26.0 (19.6-32.8)		
10 y	15	17.6 (12.1-23.9)	11	13.3 (8.4-19.4)		
MST (95% CI)	2.4 y (2.0-2.9)		2.1 y (1.7-2.7)			
No. of events	131		146			
Disease-free survival					0.76 (0.59-0.97)	.03
2 y	58	36.1 (28.7-43.5)	55	31.5 (24.7-38.4)		
5 y	30	19.0 (13.3-25.4)	26	16.1 (11.0-22.0)		
10 y	10	12.6 (8.0-18.3)	7	7.5 (4.0-12.5)		
MST (95% CI)	1.3 y (1.0-1.6)		1.0 (0.9-1.1)			
No. of events	141		159			
Brain metastasis					0.43 (0.24-0.77)	.003
2 y	86	10.9 (6.7-17.6)	81	24.3 (18.1-32.0)		
5 y	39	16.7 (10.6-25.9)	37	28.3 (21.2-37.2)		
10 y	15	16.7 (10.6-25.9)	11	28.3 (21.2-37.2)		
MST (95% CI)	Not reached		Not reached			
No. of events	20		40			

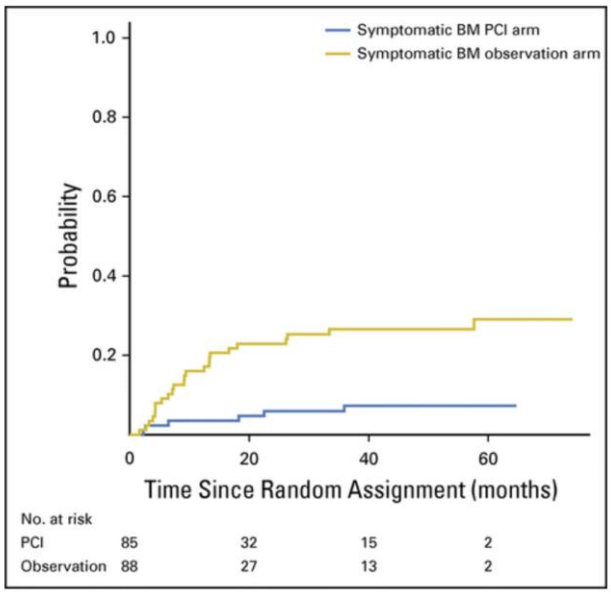
Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; MST, median survival time; PCI, prophylactic cranial irradiation.
[a] From stratified Cox proportional hazard model, stratified by AJCC stage (IIIA vs IIIB); prior surgery (no vs yes); histologic characteristics (nonsquamous vs squamous) and Zubrod performance status (0 vs >0).
[b] From stratified log-rank test, stratified by AJCC stage (IIIA vs IIIB); prior surgery (no vs yes); histologic characteristics (nonsquamous vs squamous) and Zubrod performance status (0 vs >0).

Sun, Jama 2019. 2.1 years
OS (HR 0.82 P = .12)
5-year OS 24.7% vs 26% 10-year OS 17.6% vs 13.3%.
DFS (HR, 0.76; P = .03)
5-year DFS 19% vs. 16.1% 10-year DFS 12.6% vs 7.5%.
BM (HR, 0.43; P = .003) 5-year BM 16.7% vs 28.3%
Patients in the PCI arm were 57% less likely to develop BM than those in the observation arm.
Younger patients (<60 years) and patients with nonsquamous disease developed more BM.
MVA, PCI was associated with decreased BM and improved DFS, but not improved OS.
Multivariable analysis within the nonsurgical arm suggests that PCI effectively prolongs OS, DFS, and BM.
Conclusions and Relevance In patients with stage III LA-NSCLC without progression of disease after therapy, PCI decreased the 5- and 10-year rate of BM and improved 5- and 10-year DFS, but did not improve OS. Although this study did not meet its primary end point, the long-term results reveal many important findings that will benefit future trials. Identifying the appropriate patient population and a safe intervention is critical.

[22] https://ascopubs.org/doi/full/10.1200/JCO.22.02561

PRoT-DM Phase 2
Prospective 84 patients high risk stage IIIB (12%) or IV (88%) NSCLC without baseline BM. With Δs e.g. EGFR, ALK, ↑ CEA. | 1. SoC | 2. PCI (25 Gy in 10 fx) |.

Arrieta, IJROBP 2021.
2-year BM 7% vs. 38% (HR 0.12 SS).
Median OS 19.8 vs. 64.5 mo (HR 0.41, SS).
Conclusions Among a selected population at high risk for developing BM, PCI significantly decreased CBM in addition to increasing progression-free survival and OS. To our knowledge, this is the first study to evaluate PCI in epidermal growth factor receptor mutations, anaplastic lymphoma kinase rearrangements, or elevated carcinoembryonic antigen levels in patients with NSCLC, showing a significant improvement in CBM. This relevant information should be of particular importance in the context of patients without access to third-generation targeted agents. Further studies are warranted to ascertain this effect.
Note: 95% of patients in the PCI arm had actionable EGFR or ALK alterations compared to < 75% of the standard arm.



NVALT-11
←R→ 175 patients Stage III NSCLC tx with curative intent (concurrent/seq CRT w/wo surgery) → |1. Obs | 2. PCI |.
1^{O} development of symptomatic brain metastases at 24 months.

Witlox, Radiother Oncol 2019. Median follow- 48.5 months.
2-year BM 27% vs. 7% (SS).
PCI SS ↑ time to develop symptomatic brain metastases (HR 0.23, P = .0012).
Median time to develop brain metastases was not reached in either arm.
Overall survival was not significantly different between both arms.
Grade 1 and 2 memory impairment (n=7 vs. n=26) and cognitive disturbance (n=3 vs. n=16) were significantly increased in the PCI arm.
Quality of life was only decreased 3 months post-PCI and was similar to the observation arm thereafter.
Conclusion PCI significantly decreased the proportion of patients who developed symptomatic brain metastases with an increase of low-grade toxicity.

Norway Palliative Study
←R→ 421 patients with Stage III/IV, chest symptoms or tumor threatening airway.
| 17/2 (Given 1 week apart) | 42/15 | 50/25 |

Sundstrom, JCO 2004.
QOL and symptom relief comparable. Median OS: comparable 7-8 mo.
Conclusion: Long course RT no improvement over short-term RT

Early Palliative Care Study
Intro: Patients with metastatic non-small-cell lung cancer have a substantial symptom burden and may receive aggressive care at the end of life. We examined the effect of introducing palliative care early after diagnosis on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease.
←R→ 151 newly diagnosed NSCLC metastatic | early palliative care + standard oncologic care | standard oncologic care alone |.
Quality of life and mood were assessed at baseline and at 12 weeks with the use of the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale and the Hospital Anxiety and Depression Scale, respectively. The primary outcome was the change in the quality of life at 12 weeks. Data on end-of-life care were collected from electronic medical records.

Temel, NEJM 2010.
QOL improved with early palliative care (mean score on the FACT-L scale [in which scores range from 0 to 136, with higher scores indicating better quality of life], 98.0 vs. 91.5; P=0.03).
Depression symptoms decreased (16% vs. 38%, P=0.01).
Despite fewer patients in the early palliative received aggressive end-of-life care (33% vs. 54%, P=0.05), **median survival was longer** among patients receiving early palliative care (11.6 months vs. 8.9 months, P=0.02).
CONCLUSIONS: Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival.

Toxicity

Heart

Major Adverse Cardiac Events (MACE) Predictor: https://www.thegreenjournal.com/article/S0167-8140(22)00095-0/fulltext
Cardiac disease, **Hy**pertension, and **L**ogarithmic **L**AD RT dose in lung cancer (CHyLL)

Harvard Heart Substructure and Toxicity Study
RR 701 NSCLC patients between 2003-2014. 50% men. Median age was 65 years.

Atkins, JAMA Network 2020
The optimal cut points for substructure and radiotherapy doses (highest C-index value)
- LAD coronary artery V15 Gy ≥ 10% (0.64)
- left circumflex coronary artery V15 Gy ≥ 14% (0.64),
- left ventricle V15 Gy ≥ 1% greater (0.64)
- mean total coronary artery dose ≥ 7 Gy (0.62).

Adjusting for baseline CHD status and other prognostic factors, LAD V15 Gy ≥ 10% associated with ↑ major adverse cardiac events (MACE) (aHR 13.90; P = .03) and all-cause mortality (aHR 1.58; P = .02).
Among patients without CHD, associations with **↑ 1-year MACE**
- LAD coronary artery V15 Gy ≥ 10% (4.9% vs 0%)
- left circumflex coronary artery V15 Gy ≥ 14% (5.2% vs 0.7%)
- left ventricle V15 Gy ≥ 1% (5.0% vs 0.4%),
- mean total coronary artery dose ≥ 7 Gy (4.8% vs 0%) (all P ≤ .001)

Among patients **WITH** CAD, **↑ 1 year MACE**
- Only left ventricle V15 Gy ≥ 1% (8.4% vs 4.1%; P = .046).

Among patients without CHD, **↑ 2-year all-cause mortality.**
- LAD coronary artery V15 Gy ≥ 10% (51.2% vs 42.2%; P = .009)
- mean total coronary artery dose ≥ 7 Gy (53.2% vs 40.0%; P = .01).

Conclusions and Relevance The findings of this cohort study suggest that optimal cardiac dose constraints may differ based on preexisting CHD. Although the LAD coronary artery V15 Gy greater than or equal to 10% appeared to be an independent estimator of the probability of MACE and all-cause mortality, particularly in patients without CHD, left ventricle V15 Gy greater than or equal to 1% appeared to confer an increased risk of MACE among patients with CHD. These constraints are worthy of further study because there is a need for improved cardiac risk stratification and aggressive risk mitigation strategies.

RTOG 06-17 Re-Evaluation for LAD V15
449 patients NSCLC with LAD dose-volume data and clinical outcomes available after 10 patients were excluded owing to unreliable LAD dose statistics. The median age was 64 years.
Median LAD V15 Gy was 38% (interquartile range, 15%-62%), including 94 patients (21%) with LAD V15 Gy <10% and 355 (79%) with LAD V15 Gy ≥10%.

McKenzie, IJROBP 2022
Adjusting for prognostic factors, LAD V15 Gy ≥10% vs. <10% was associated ↑ all-cause mortality (HR 1.43; P = .037)
Mean heart dose ≥10 Gy vs. <10 Gy was not (aHR, 1.12; P = .36).
Median OS LAD V15 Gy ≥10% versus <10% was 20.2 versus 25.1 month
2-year OS of 47% vs. 67% (P = .004), respectively.
Conclusions In a reanalysis of RTOG 0617, LAD V15 Gy ≥10% was associated with an increased risk of all-cause mortality. These findings underscore the need for improved cardiac risk stratification and aggressive risk mitigation strategies, including implementation of cardiac substructure dose constraints in national guidelines and clinical trials.

RTOG 06-17 AI Machine Learning (2 Studies)

Lee, IJROBP 2023	↑ OS	Left Atrium (LA) V60 Gy < 25.6% Lungs-CTV_PTV_Voverlap < 1.1% Pericardium D30% < 18.9 Gy Right Atrium 55Gy < 19.5%
Ladbury, IJROBP 2023	Pulmonary toxicity thresholds	Lung mean dose >18 Gy (OR, 2.467; P = .038) lung V20 > 37% (OR, 2.722; P = .043)
	Esophageal toxicity thresholds	Esophageal mean dose >34 Gy (OR, 4.006; P < .001) Esophageal V20 > 37% (OR, 3.725; P = .014).
	No significant thresholds were identified for cardiac toxicity.	

Atrial Fibrillation Sinoatrial Node (SAN) DMax Study
RR 560 (239 SCLC and 321 NSCLC) 2008 -2019 → all definitive chemoradiotherapy.
Median (IQR) age was 68 (60-73) years and 67 (61-75) years, and 207 (86.6%) and 261 (81.3%) were men, respectively.

Kim, JAMA Oncol 2022 **32.7 months**
SAN Dmax = highest predictive value for prediction of AF. In SCLC (aHR, 14.91; P < .001) and NSCLC (aHR, 15.67; P = .008).
SAN Dmax was not associated with non-AF cardiac events.
↑ SAN Dmax was significantly associated with ↓ OS SCLC (aHR, 2.68;; P < .001) and NSCLC (aHR, 1.97; P < .001).

3-year OS SAN Dmax of ≥ 53.5 Gy vs. ≤ 53.5 Gy SCLC cohort (30.9% vs. 48.5%; P = .008).
3-year OS SAN Dmax of ≥ 20.0 Gy vs. ≤ 20.0 Gy NSCLC cohort (35.0%; vs 54.5%; P < .001).
Conclusions and Relevance In this cohort study, results suggest that incidental irradiation of the SAN during chemoradiotherapy may be associated with the development of AF and increased mortality. This supports the need to minimize radiation dose exposure to the SAN during radiotherapy planning and to consider close follow-up for the early detection of AF in patients receiving thoracic irradiation.

Cardiotoxicity PORT (retrospective predictor of **post-op Cardiotoxicity**)
284 patients stage III s/p either preoperative or adjuvant chemotherapy.
Lobectomy (81.3%) with R0 (80%). PORT = 54 Gy (70% IMRT).

Shepherd, 2021 J Thoracic Oncology 2021.
Dosimetric variables across a large range of doses to the heart were highly significant ($p < 0.05$) for OS.
Heart V8Gy was the most significant dosimetric variable ($p < 0.001$), and the median HV8 was 35.5 %.
Median OS was 33.2 → 53.6 months ($p < 0.005$) for patients with HV8 below 35.5 %.
MVA, HV8 remained highly significant ($p < 0.001$).
Conclusions The data reveal a strong correlation between increasing heart dose and OS in patients with NSCLC undergoing PORT. Taken together with the recently presented LungART trial, lowering heart dose in PORT patients may help to decrease the risk of morbidity and mortality and improve the therapeutic ratio of PORT.

Japanese Durvalumab Retrospective
RR 113 patients receiving CRT → durvalumab maintenance 2018-2021.

Kashihara, Radiother Oncol 2023 **24 months**
Comment: consider stricter dose constraints for these patients and propose a mean lung dose < 12.2 Gy and lung V20 < 22%.
Comment 2: Interstitial lung abnormalities (ILA) at pretreatment baseline = primary predictor of worse overall and cancer specific survival. 9/17 of these patients discontinued durvalumab early due to pneumonitis as compared to 18% of the remaining patients.
Conclusion: Pretreatment ILA, adenocarcinoma, and performance status may have an impact on OS of LA-NSCLC patients receiving CCRT plus durvalumab.

Indiana University → Liu, Radiother Oncol 2020 (retrospective predictor of **post-SBRT RP**).
Radiation: 48 in 4 fx (46% cases) QoD treatments. ~10% developed symptomatatic RP (4.4% G2, 5% G3, 0.3% G4).
↑ RP patient specific comorbid lung condition, prior lung RT, R sided tumor location.
< 10% risk ≥ G2 RP if Mean Lung Dose – Total Lung < 6 Gy, MLD – IL < 20 Gy, and V20 < 10%.
If 5 fx EQD2 Mean Lung Dose – Total Lung < 7 Gy, MLD – IL < 16Gy.
If you have comorbid lung condition… MLD-TL 4.2 Gy, MLD-IL 6.5 Gy, and V20 6.8% were required for a 10% risk of RP.

Post-op RP → Shepherd, Pract Rad Oncol 2020 (retrospective predictor of **post-op RP**).
285 patients Post-op RT 2004 and 2017 (generally part of trimodality therapy for LN+), symptomatic RP = 12.6%.
Low-range lung dose, heart dose, carboplatin, and patient age were associated with higher risk of RP.
MVA → lung V5 and patient age were significant predictors of RP2.
Conclusions: The incidence of RP after PORT is consistent with the literature. Factors correlated with RP include lung and heart doses, age, and carboplatin chemotherapy. These data also suggest that elderly patients may be more susceptible to lower doses of radiation to the lung. Based on these data, dose constraints to limit the risk of RP2+ to <5% in the setting of PORT include lungV5 ≤65% in patients <65 years old and lungV5 ≤36% in patients 65 years or older.

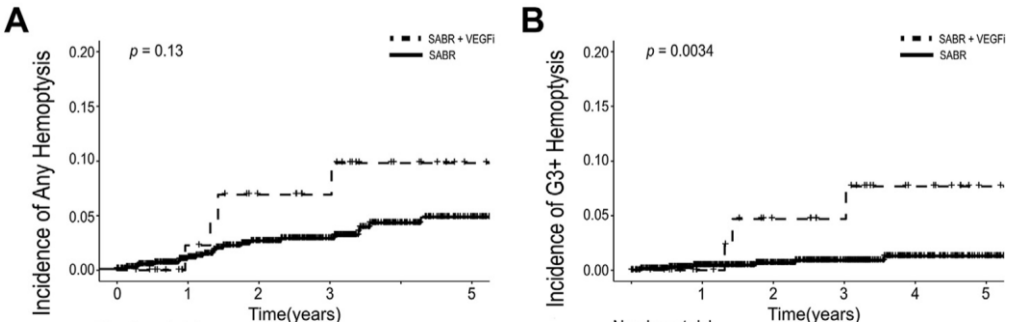
ASPIRE-ILD (Interstitial Lung Disease).
MORTALITY ONLINE TOOL GAP (https://www.mdcalc.com/gap-index-idiopathic-pulmonary-fibrosis-ipf-mortality)
Phase II, 39 patients T1–2N0M0 NSCLC w/ co-existing ILD (NON-SURGICAL candidates). Path diagnosis not required (strongly recommended).
Starting SABR dose 50 Gy in 5 fractions every other day (biologically effective dose: 100 Gy10 or 217 Gy3).
RT dose can be de-escalated up to two times to 50 Gy in 10 fractions daily (75 Gy10 or 133 Gy3) and 45 Gy in 15 fractions daily (58 Gy10 or 90 Gy3).
Dose de-escalation will occur if 2 or more of the first 7 patients in a cohort experiences grade 5 toxicity within 6 months of treatment.
Dose de-escalation also occur if 2 or more of the first 7 patients with a specific subtype of ILD experiences grade 5 toxicity within 6 months of treatment.
1^{O} OS. **Ongoing.**

RP and Location Retrospective.
165 training cohort and 42 validation cohort. Voxel-based analysis of local dose differences.

Bourbonne, Radiother Oncol 2021.
Significant sites of ↑ Mean RT dose posterior right upper and lower lobes for RP (32 Gy) vs. without (15 Gy) pneumonitis.
Mean dose to ipsilateral and bilateral lungs were associated with increased risk of pneumonitis.
Conclusion
Our APT-prediction model was successfully validated in a prospective cohort treated by VMAT. Regional radiosensitivity should be considered in usual lung dose constraints, opening the possibility of easily implementable adaptive dosimetry planning.

RP and Fungal Infections
1746 retrospective patients with NCLSC and symptomatic RP.

Mei, IJROBP 2021.
44.5% of patients with NSCLC and SRP (777 of 1746 patients) were diagnosed with secondary lung infections.
In total, 899 bacterial strains were isolated from these patients, with Acinetobacter baumannii (n = 206; 27%), Klebsiella pneumonia (n = 200; 26.2%), and Pseudomonas aeruginosa (n = 104; 13.6%) being the most common.
Carbapenem and cefoperazone-sulbactam resistance rates of 52.7% and 32.2%, 28.8% and 26.4%, and 23.7% and 20.2% were observed for these isolates, respectively.
Infection-related deaths occurred in 22.4% of patients with SRP. Independent risk factors for infection-related death included poor performance status scores, inappropriate empirical antimicrobial treatment, bacteria/fungal coinfection, and lack of empirical antifungal treatment.
ROC curves showed that the cutoff value of empirical antifungal treatment duration was 9 (area under the curve: 0.819).
Conclusions For patients with SRP and secondary lung infections, appropriate empirical antimicrobial treatment could decrease infection-related mortality, and cefoperazone-sulbactam may be an appropriate antibacterial drug. Empirical antifungal treatment for a minimum of 9 days might contribute to better outcomes. Although this represents a promising treatment approach for patients with SRP and secondary lung infections before antibacterial susceptibility testing, further prospective validation is essential.



SABR + VEGFi (Bevacizumab) → Hemorrhage

Background: Severe pulmonary hemorrhage can occur in patients treated with thoracic stereotactic ablative radiotherapy (SABR) and vascular endothelial growth factor inhibitors (VEGFis). There is limited understanding of which patients are at risk for toxicity with the combination of thoracic SABR and VEGFis or how the risk differs over either therapy alone.

Prospective cohort 690 patients with 818 **pulmonary tumors** → highly conformal SABR.

Types of "pulmonary tumors" = lung mets (59.6%), primary tumor (32.7%), both (7.7%).

11.5% ultracentral lesions. 75% peripheral.

Rates of any-grade and grade 3 plus (G3+) pulmonary hemorrhage were compared between patients treated **with** or **without VEGFi therapy.**

Outcomes were compared between patients treated with SABR plus VEGFi and a propensity-matched cohort of those treated with VEGFi therapy alone.

Lau, Journal of Thoracic Oncology 2023

3-year ≥ G3 pul hemorrhage	VEGFi+SABR vs. SABR alone	ALL	7.9% vs. 0.6% (p < 0.01)
		Central tumors	19.1% vs. 3.3% (p = 0.04).
		Central nonabutting	0.0% vs. 1.3% (NS).
	VEGFi +SABR vs. VEGFi alone	ALL	9.6% vs 1.3% (p = 0.04).

Conclusions The combination of VEGFi and SABR was associated with an increased risk of high-grade pulmonary hemorrhage over either therapy alone. Low rates of toxicity were observed when excluding patients with SABR to ultracentral tumors and applying highly conformal SABR techniques.

Table 1. Baseline Characteristics of Patients Treated With SABR With and Without VEGFi Therapy

Characteristics	SABR	SABR + VEGFi	*p* Value
Location, n (%)			0.17
Peripheral	593 (78.3)	40 (76.9)	
Central nonabutting	129 (16.8)	6 (11.5)	
Ultracentral	44 (5.7)	6 (11.5)	
BED_{10}_Gy, mean (SD)	95.79 (17.73)	100.58 (18.83)	0.06
Fractions planned, n (%)			0.06
1	340 (44.4)	15 (28.8)	
3	30 (3.9)	4 (7.7)	
4	321 (41.9)	26 (50.0)	
5	49 (6.4)	4 (7.7)	
6	1 (0.1)	1 (1.9)	
8	23 (3.0)	2 (3.8)	