ARROCase:
Small Cell Lung Cancer

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Outline

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- Pathology
- Clinical Presentation
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- General Management
- Radiation Treatment Planning

Case Presentation

- CC: Confusion, weight loss, cough.
- HPI: 62 year old woman with 2 month history of weight loss and cough. Brought to emergency department with confusion. No seizures or other focal neuro deficits. Pertinent history includes 50 pack year history of smoking.

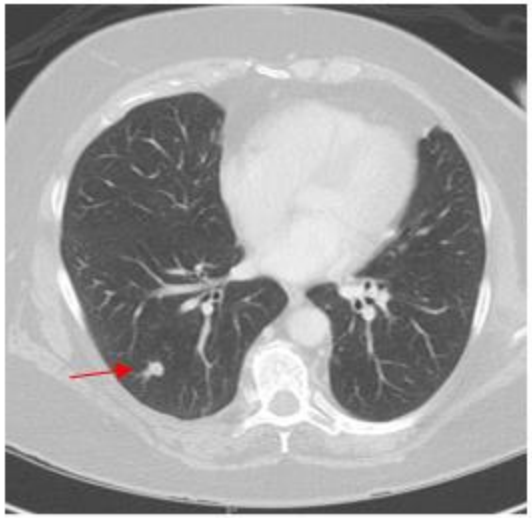
Physical Exam

- Obese-appearing female in no apparent distress. Alert and oriented x 3. Normocephalic with CN II-XII intact. Strength, sensation, and gait are normal. No palpable SCV/ICV/axillary lymphadenopathy. Lungs are clear to auscultation and resonant to percussion bilaterally.

Work-Up

- Chest CT
  - Right lower lobe pulmonary nodule and right hilar and subcarinal lymphadenopathy is concerning for primary lung cancer with lymph node metastasis.
- PET/CT Scan
  - Mildly metabolically active noncalcified right lower lobe pulmonary nodule with bulky right hilar and subcarinal lymphadenopathy. No evidence of distant metastatic disease.
- Head CT w/o con and brain MRI
  - both negative for masses or infarction

Chest CT



Chest CT

PET/CT

Labs

- CBC, BMP, UA, urine toxicologies ordered for her presentation of confusion
- Significant for corrected calcium of 11.6 (high)
- All other labs normal

Pathology

- Endobronchial ultrasound-guided FNA of subcarinal lymph node
  - Small cell carcinoma
    - Malignant epithelial cells with nuclear pleomorphism, dispersed chromatin, increased N:C, and nuclear molding
    - Crush artifact and numerous apoptotic bodies
    - Positive for synaptophysin, chromogranin, CD56, CAM 5.2.

Small Cell Lung Cancer

Introduction

- SCLC is distinguished from NSCLC by its rapid doubling time, high growth fraction, and the early development of widespread metastases
- Although considered highly responsive to chemotherapy and radiotherapy, SCLC usually relapses within two years despite treatment
- Overall, only three to eight percent of all patients with SCLC (10 to 13 percent of those with limited disease) survive beyond five years

Epidemiology

- The American Cancer Society's estimates for lung cancer (including both small cell and non-small cell) in the United States for 2017 are:
  - About 222,500 new cases of lung cancer (116,990 in men and 105,510 in women)
  - About 155,870 deaths from lung cancer (84,590 in men and 71,280 in women)
- Approximately 10-15% of newly diagnosed lung cancer is small cell histology
  - Despite their overall risk of lung cancer being higher, black men are about 15% *less* likely to develop SCLC than are white men, and the risk is about 30% lower in black women than in white women.

SCLC Histology

- SCLC is a "small round blue cell tumor" arising from neuroendocrine cells
- Further classifications:
  - Oat cell (lymphocyte-like), fusiform, polygonal
  - OR classical, large cell neuroendocrine, combined SCLC/NSCLC
- Buzz word: "crush" artifact
- Immunohistochemistry tests:
  - TTF1+ (both adeno & SCLC)

Clinical Presentation

- Almost exclusively in heavy smokers
- Cough in approximately 75%
- Hemoptysis 50%
- Chest pain and dyspnea
- Constitutional symptoms (i.e. weight loss) 15%
- Clubbing
- Pneumonia
- Seizures or focal neurologic deficit

SCLC Paraneoplastic Syndromes

- SIADH
  - Hyponatremia and hypo-osmolality from inappropriate, continued secretion or action of antidiuretic hormone AVP
- Ectopic ACTH production- Cushing's syndrome
- Eaton-Lambert Myasthenic syndrome
  - proximal muscle weakness that *improves* on repetition ("facilitation")
- Hypercalcemia
- Peripheral Neuropathy

Work Up/Diagnosis

- Labs: CBC, BMP, LFTs, LDH
- CT chest/abdomen/pelvis
- Brain imaging (MRI preferred)
  - Up to 30% have brain metastases at presentation
- PET/CT scan (especially if limited stage suspected)
- Biopsy: CT guided or EBUS

General Management – Limited Stage

- Concurrent chemoradiation
  - Chemotherapy: cisplatin/etoposide q3wks
  - Radiation: 150 cGy BID to 4500 cGy (Turrisi)

  OR 180/200cGy QD to 50-70Gy.
- If CR, then consider PCI
  - 2500cGy/10 frx
  - Auperin (NEJM 99)

Radiation Treatment

- Cover primary disease & known positive LNs w/ 1.0-2cm margin.
- For example, from CALGB 30610 using 4D CT simulation:
  - GTV: The primary tumor and clinically positive lymph nodes seen either on the pretreatment CT (> 1 cm short axis diameter) or pretreatment PET scan (SUV> 3) will constitute the GTV. This volume(s) may be disjointed.
  - CTV: Will include the GTV plus potential occult disease as defined below. Potential occult disease: Ipsilateral hilum (i.e., level 10 lymph node station)
  - PTV: If the ITV approach is used, then the PTV margin should account for setup uncertainties and may be individualized but should not be less than 1.0 cm. If daily imaging is used to align the vertebral bodies, then the margins for setup margins may be reduced to 0.5 cm.

Radiation Treatment

- *Elective mediastinal nodes for SCLC?*
  - CALGB 30610: Elective radiation of the mediastinum and supraclavicular fossa is not included in the CTV. Potential occult disease (i.e. level 10) can be included
- Cord limit BID: <36Gy
- Total Lung-CTV V20 < 37%, mean dose <20Gy*
- Heart V50 < 25%*
- *Values for 2Gy QD fractions

General Management – Extensive Stage

- Chemotherapy
- Thoracic radiotherapy in addition to PCI can be considered for all patients with ES-SCLC who respond to chemotherapy*
  - 30 Gy in 10 fractions thoracic RT

*Slotman et al. Lancet. 2015

Turrisi et al. NEJM 1999 – INT 0096/RTOG 8815

- 417 pts with LS-SCLC (excluded effusion, contra hilar/SCV)
  - Arm 1: 45 Gy in 25 QD fractions
  - Arm 2: 45 Gy in 30 BID fractions
  - All received 4 cycles of cisplatin and etoposide q3wks, PCI if CR
  - Fields: bilat mediastinum, ipsi hilum, inf border 5cm below carina or to hilum. No elective ipsi SCV field allowed.
- Outcomes
  - OS better for BID (Median 1.6 vs 1.9 yrs)
  - 2yr OS 41% QD vs 47% BID (SS), 5yr OS 16 vs 26% (SS)
  - 2-year local failure 52% QD vs 36% BID (NS, p=0.06)
  - Grade 3 esophagitis 11% QD vs 27% BID (SS)
  - No difference in grade 4 esophagitis

Faivre-Finn et al. Lancet Oncol 2017 - CONVERT

- 547 patients with LS-SCLC
  - Superiority trial designed to show 12% higher 2-year OS in QD arm
  - Arm 1: 45 Gy in 30 BID fractions
  - Arm 2: 66 Gy in 33 QD fractions
  - All received cis/etop, RT started 2nd cycle, PCI if CR
- Outcomes
  - No difference in OS between arms
  - Median OS 30 months BID vs 25 months QD (NS)
  - 2-year OS 56% BID vs 51% QD (NS)
  - No difference in grade 3-4 esophagitis or pneumonitis
  - More grade 4 neutropenia in BID (49%) vs QD (38%) (SS)

Current Open Protocol: CALGB 30610

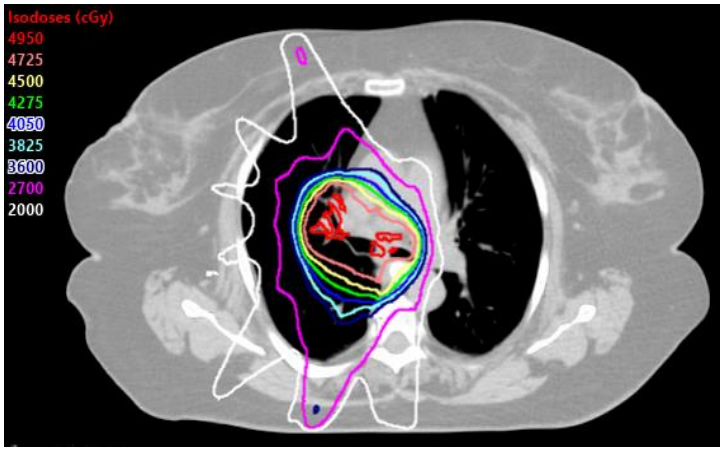
- Phase III superiority trial, opened March 2008
- Arm 1: 45 Gy in 30 BID fractions
- Arm 2: 70 Gy in 35 QD fractions
- Arm 3 (closed as of 3/2013): 61.2 Gy in 34 fractions, QD for first 16 days, then BID for last 9 day
- All get platinum/etoposide, PCI if CR (or “very good PR”)
- Primary endpoint is OS
- Secondary endpoints: CR/PR rates, FFS

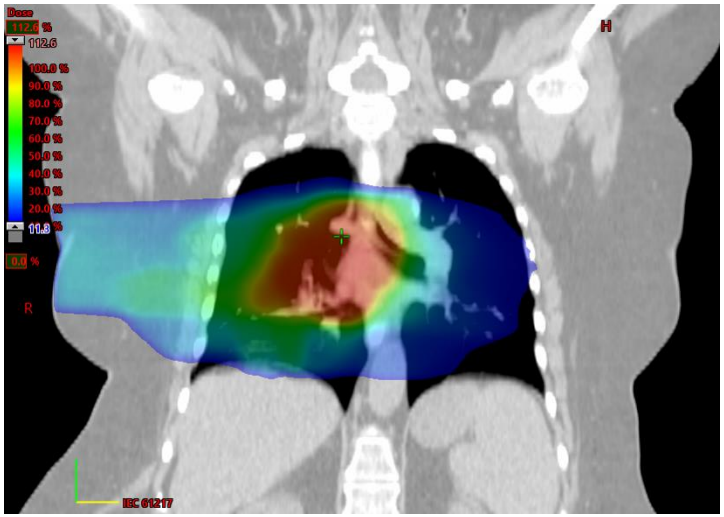
Auperin Meta-Analysis of PCI (NEJM 1999)

- PCI for LS-SCLC if CR after chemo
- Meta-analysis of 7 trials (1965-95)
- Dose Fx: 800cGyx1 to 4000cGy/20
- Improved 3yr OS: 20.7% v 15.3%
- Incidence of brain mets decreased from 58% to 33% at 3 years
- Better if PCI <4mo from chemo start
- No assessment of neurocognitive fxn

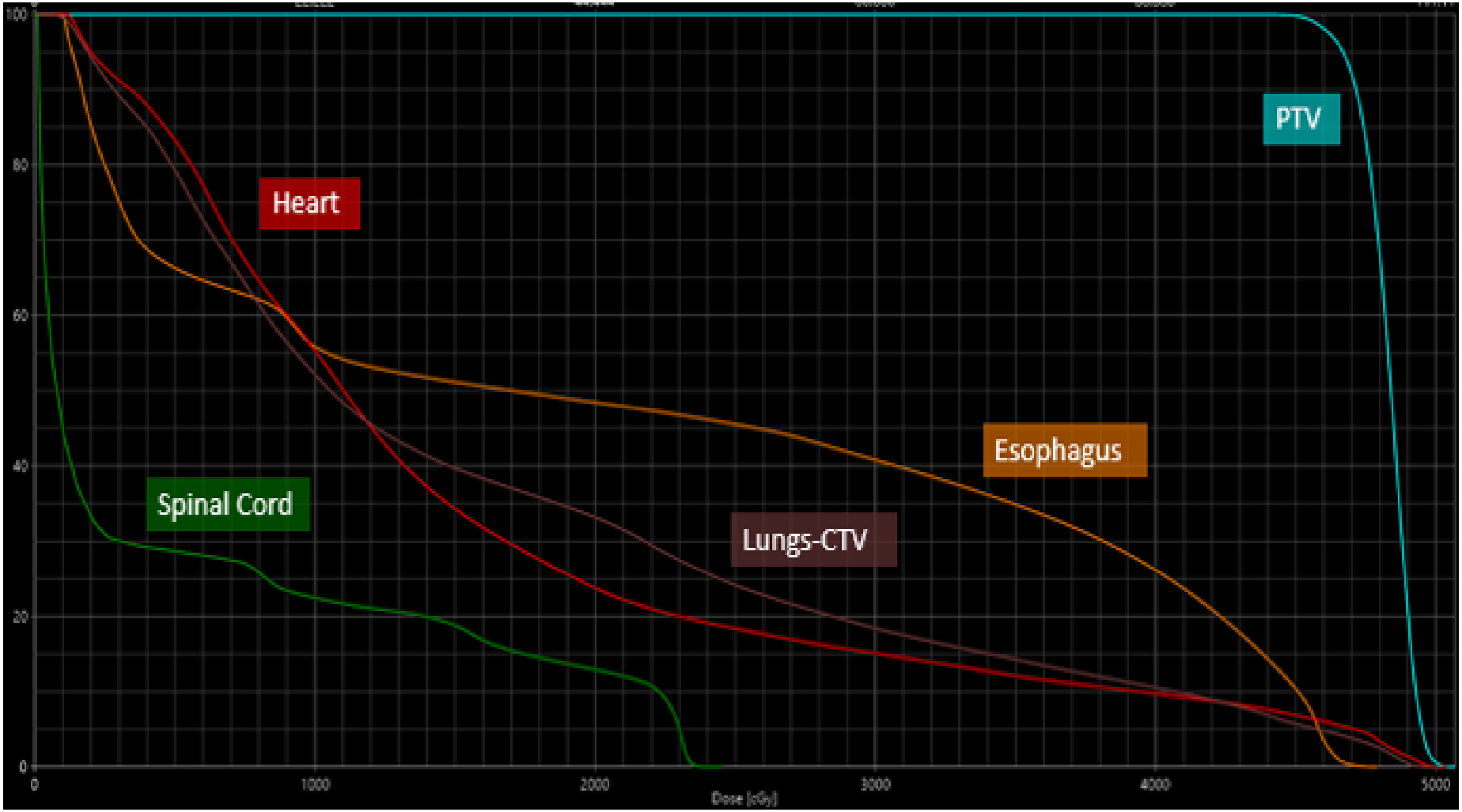
Our patient's treatment

- Enrolled on CALGB 30610
  - Randomized to 45 Gy delivered BID using IMRT with concurrent platinum/etoposide
  - Start RT concurrent with cycle 1 of chemotherapy
  - Will discuss PCI near end of treatment

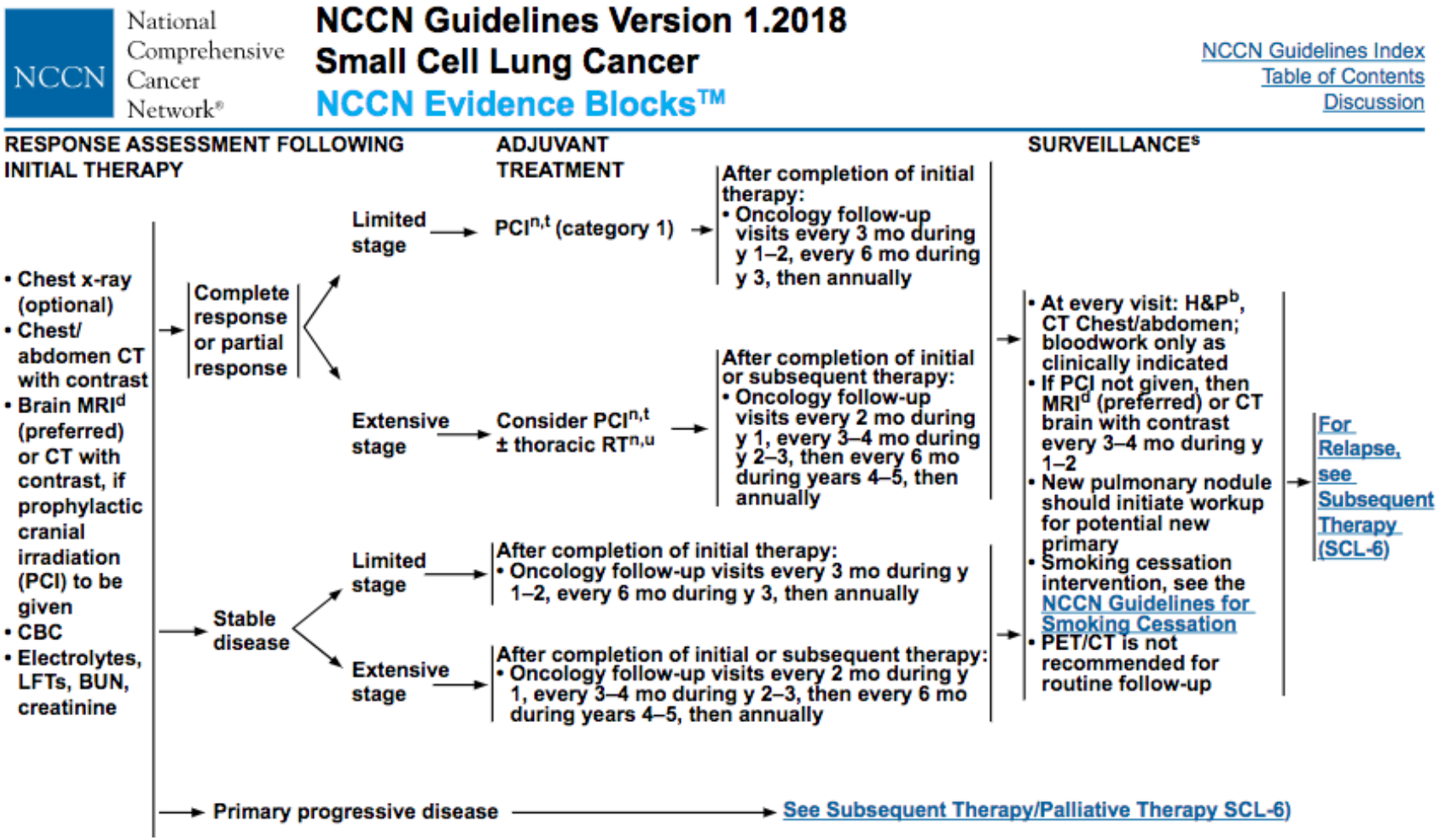




Dose Volume Histogram



Follow-Up


National Comprehensive Cancer Network®
NCCN Guidelines Version 1.2018
Small Cell Lung Cancer
NCCN Evidence Blocks™
NCCN Guidelines Index
Table of Contents
Discussion
RESPONSE ASSESSMENT FOLLOWING INITIAL THERAPY
ADJUVANT TREATMENT
SURVEILLANCE[s]
• Chest x-ray (optional)
• Chest/ abdomen CT with contrast
• Brain MRI[d] (preferred) or CT with contrast, if prophylactic cranial irradiation (PCI) to be given
• CBC
• Electrolytes, LFTs, BUN, creatinine
Complete response or partial response
Limited stage
PCI[n,t] (category 1)
After completion of initial therapy:
• Oncology follow-up visits every 3 mo during y 1–2, every 6 mo during y 3, then annually
Extensive stage
Consider PCI[n,t] ± thoracic RT[n,u]
After completion of initial or subsequent therapy:
• Oncology follow-up visits every 2 mo during y 1, every 3–4 mo during y 2–3, then every 6 mo during years 4–5, then annually
Stable disease
Limited stage
After completion of initial therapy:
• Oncology follow-up visits every 3 mo during y 1–2, every 6 mo during y 3, then annually
Extensive stage
After completion of initial or subsequent therapy:
• Oncology follow-up visits every 2 mo during y 1, every 3–4 mo during y 2–3, then every 6 mo during years 4–5, then annually
• At every visit: H&P[b], CT Chest/abdomen; bloodwork only as clinically indicated
• If PCI not given, then MRI[d] (preferred) or CT brain with contrast every 3–4 mo during y 1–2
• New pulmonary nodule should initiate workup for potential new primary
• Smoking cessation intervention, see the NCCN Guidelines for Smoking Cessation
• PET/CT is not recommended for routine follow-up
For Relapse, see Subsequent Therapy (SCL-6)
Primary progressive disease
See Subsequent Therapy/Palliative Therapy SCL-6)

References

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- Turrisi AT, 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *The New England journal of medicine.* Jan 28 1999;340(4):265-271.
- Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet.* Jan 03 2015;385(9962):36-42.
- NCCN Guidelines Small Cell Lung Cancer

- Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com