SCLC Case Presentation

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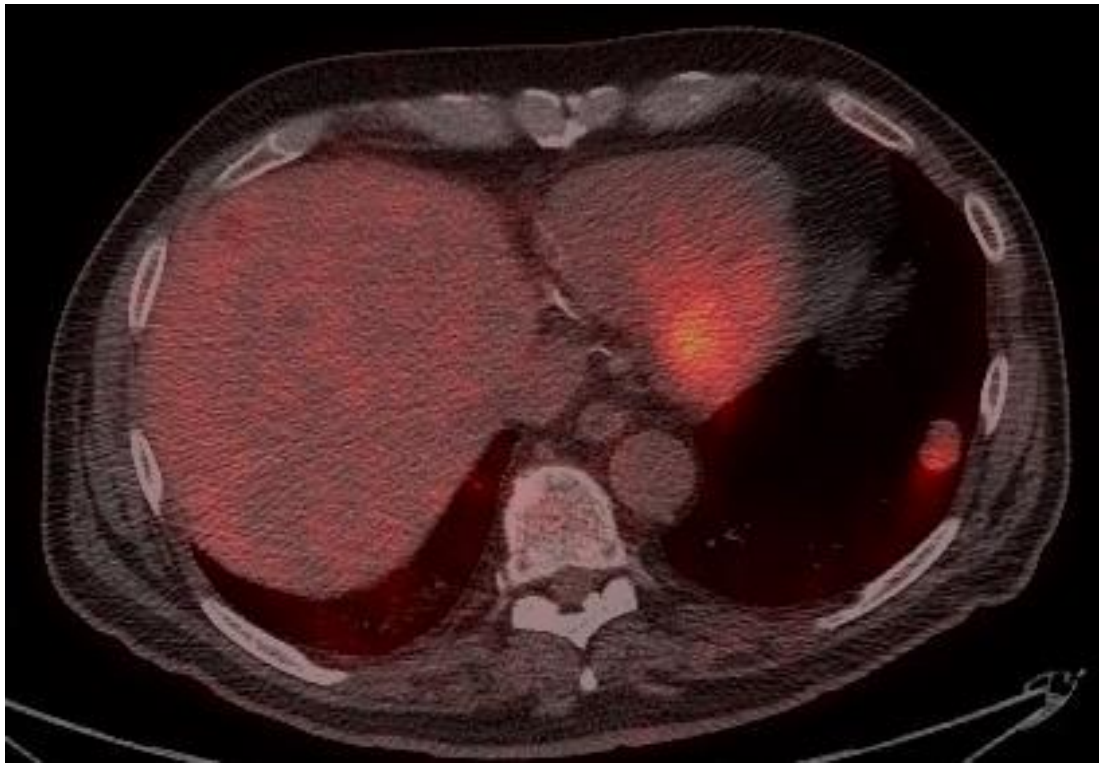
Case*

- 74-year-old male veteran, former pipe smoker x 40 years (quit 2018), h/o undifferentiated ILD (normal PFTs 11/2021), still working managing a construction firm
- Followed by pulmonary clinic for his ILD and was undergoing periodic CT surveillance for lung nodules
- LDCT (8/28/21): solid 17 x 9 mm irregular nodule in LLL (previously 8 mm)
- PET/CT (10/6/21): 17 x 9 mm irregular nodule in LLL without FDG uptake, 4 mm solid nodule in lingula without FDG uptake
- PET/CT (3/2/22): enlarging, newly hypermetabolic solid nodule in LLL, now 18 x 21 mm, concerning for primary malignancy. No mediastinal LN enlargement or SUV uptake. No distant lesions seen.
- Brain MRI: negative for metastases



T1cN0M0 stage IA

*Cases may have been modified for educational purposes

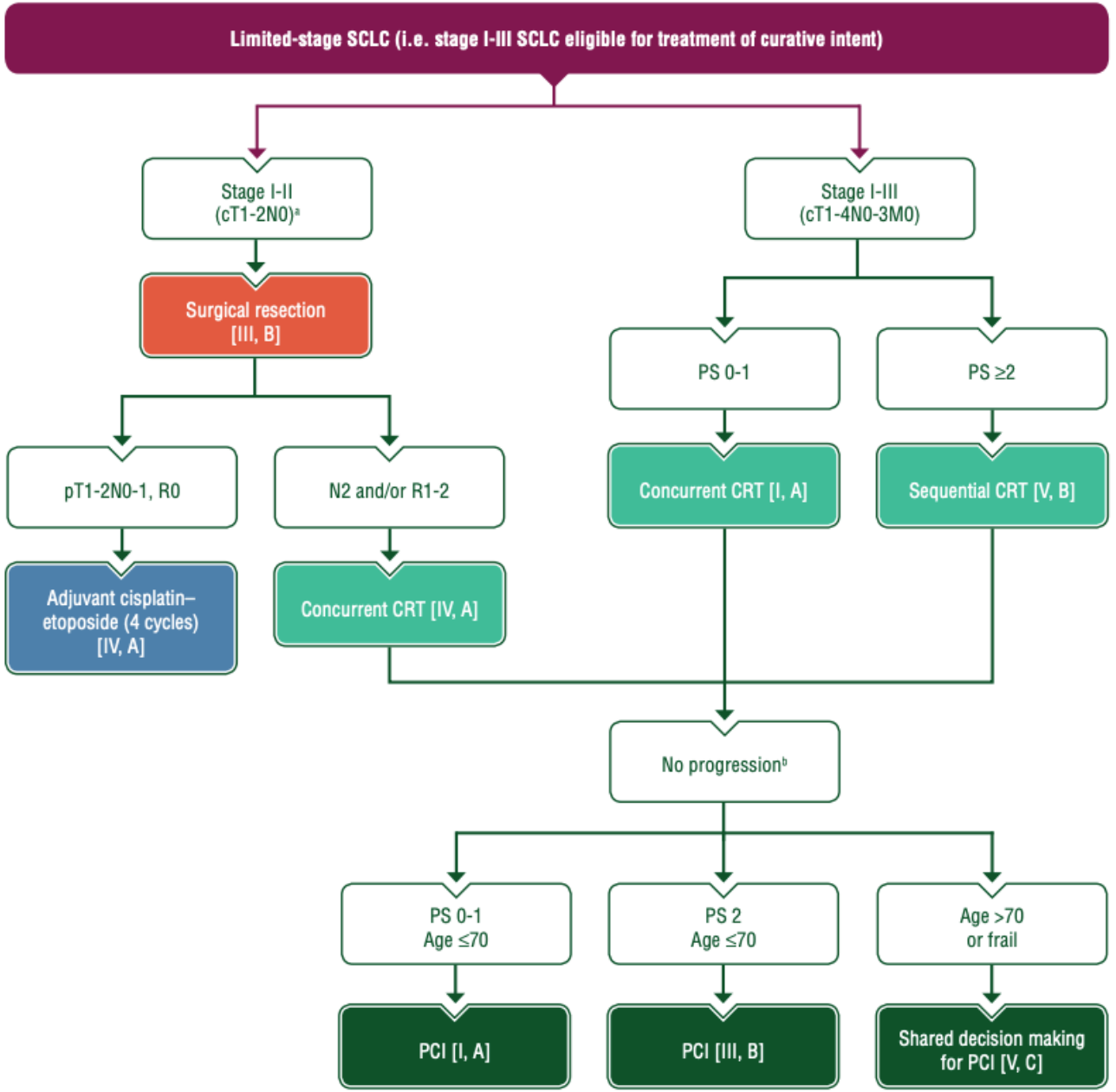
Case/Question

Referred for CT-guided core biopsy of LLL: small cell carcinoma, Ki-67>90%, positive for pankeratin, synaptophysin, chromogranin.

Clinical stage is T1cN0M0 (Stage IA3), Limited Stage SCLC.

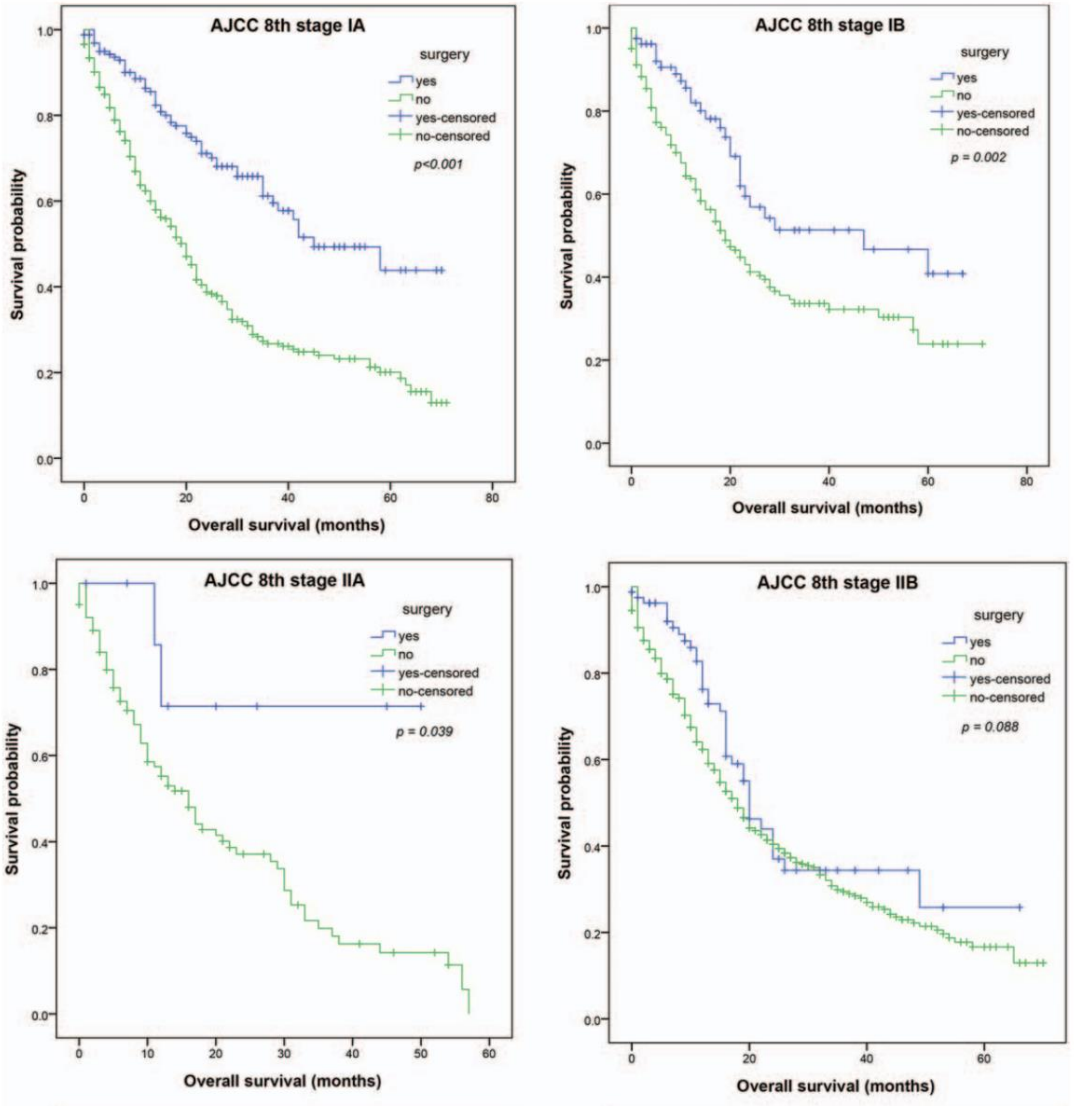
Would you stage the mediastinum in this case. If so, how?

- **No, not necessary for treatment planning**
- **Yes, mediastinoscopy**
- **Yes, EBUS**



Dingemans A-MC, et al. Small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology,* Vol 32(7),pp 839-853

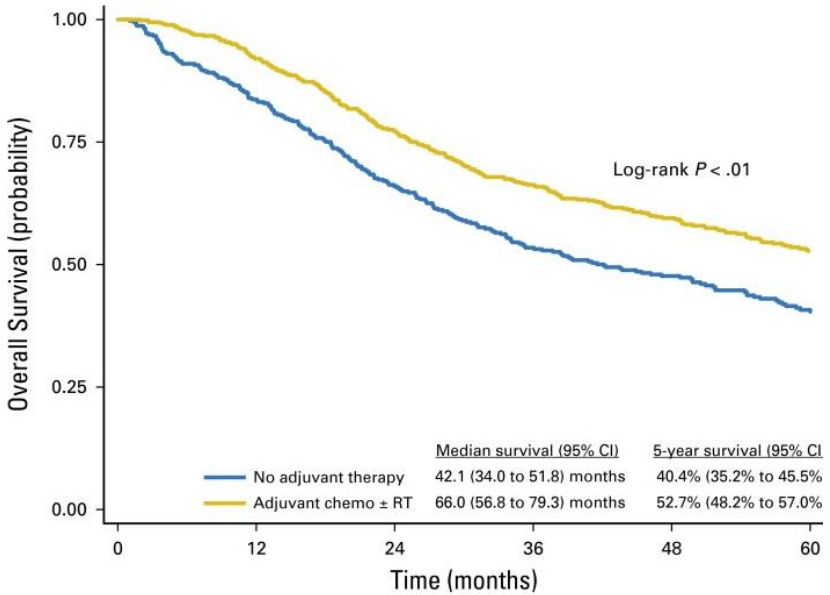
Surgery for Small Cell Lung Cancer: SEER Survey from 2010-2015

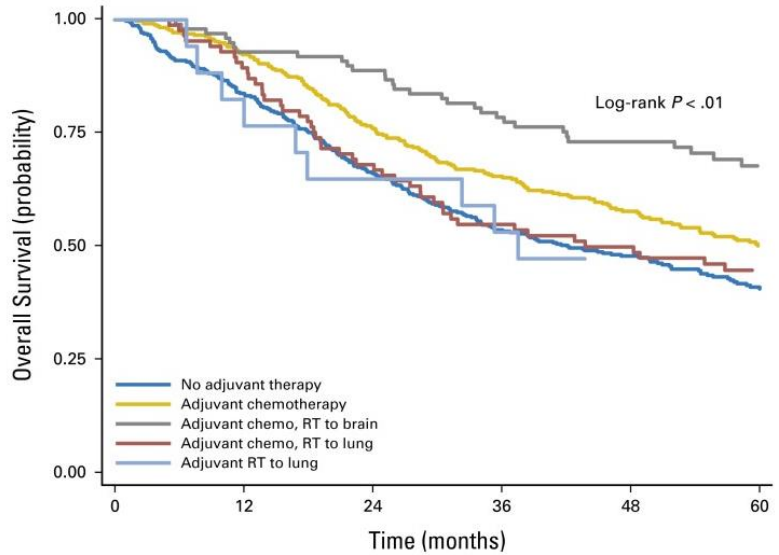


- 26,659 patients included
  - 627 (2.4%) underwent surgery
- Surgery for SCLC was associated with improved OS except for stage IIB
- Multivariate analyses in patients who underwent surgery indicated lobectomy and chemotherapy as independent predictors of improved OS

Xu L, et al. *Medicine.* 2019, 98(40):e17214

Adjuvant Chemotherapy in pT1-2N0M0 SCLC





- No randomized trials
- Observational studies suggest improved outcomes in patients who receive adjuvant chemo
- 1574 patients who underwent surgery for pT1-2N0M0
  - Improved OS for patients who received adjuvant chemo +/- PCI

Yang CF, et al. *J Clin Oncol.* 2016 Apr 1;34(10):1057-64.

Case

- 5/12/22: Tumor Board review with plan for mediastinoscopy and surgical resection followed by adjuvant chemo
- PET/CT (5/20/22): enlarging LLL mass 3.5 x 2.5 cm (SUV 7.8); stable R>L subpleural peripheral GGO within bilateral lower lobes; stable prominent mediastinal LNs with background FDG uptake
- 6/10/22: Taken to OR for consideration of resection of early-stage SCLC; at the time of surgery, was noted to have mediastinal LN involvement

Question

What treatment do you recommend now?

- **No surgery, refer for systemic chemo-IO**
- **No surgery, refer for chemo-RT**
- **No surgery, refer RT alone**
- **Proceed with surgery**

Comparing Daily RT to Twice Daily Thoracic RT

Trial	Daily arm	Twice Daily Arm	Results
[1]Intergroup	45 Gy/25 fractions	45 Gy/1.5 Gy BID	BID radiation improved: Median survival (23 vs 19 months, p=0.04) 2 yr OS (47 vs 41%) 5 yr OS (12.6 vs 16%)
[2]CONVERT	66 Gy/33 fractions	45 Gy/1.5 Gy BID	Median OS 30 months with BID and 25 months with QD (p=0.14)
[3]CALGB 30610	70 Gy/35 fractions	45 Gy/1.5 Gy BID	Median OS 30 months with BID and 25 months with QD (p=0.14)

[1]Turrisi AT, et al. Twice-Daily Compared with Once-Daily Thoracic Radiotherapy in Limited Small-Cell Lung Cancer Treated Concurrently with Cisplatin and Etoposide. *NEJM* 1999.
[2]Faivre-Rinn C, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncology* 2017.
[3]Bogart J, et al. High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538. *J Clin Oncol* 2023.

Ongoing Immunotherapy and ChemoRT Trials in LS-SCLC

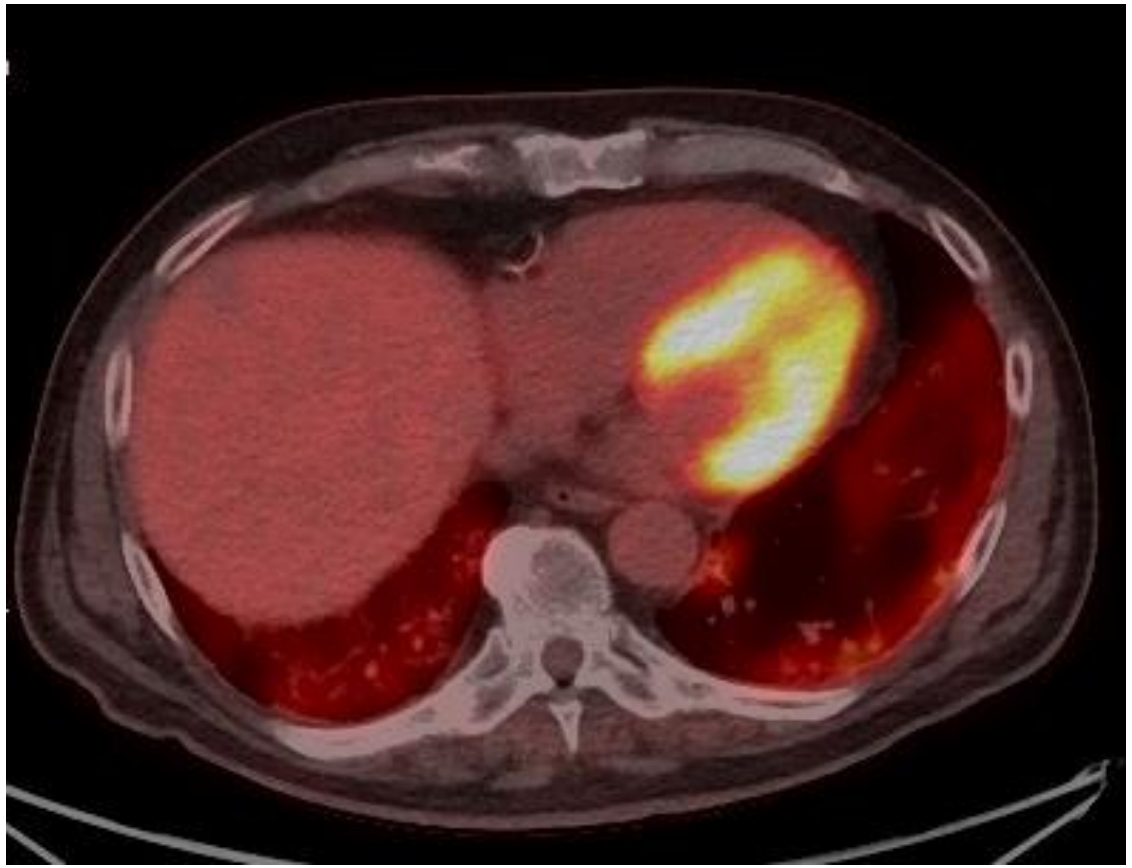
ADRIATIC	Durvalumab +/- tremelimumab	Consolidation
KEYLYNK-013	Pembrolizumab +/- olaparib	Concurrent with chemoRT and as consolidation
NRG LU-005	Atezolizumab	Concurrent with chemoRT and as consolidation
DOLPHIN	Durvalumab	Concurrent with chemoRT and as consolidation

Case

- Pt was felt to have limited stage SCLC, referred for definitive chemoRT
    - Started carbo/etoposide, completed 4 cycles with concurrent XRT on 9/1/22

- 11/28/22: Brain MRI: small foci (5 in number) of abnormal enhancement in the R cerebellar hemisphere and R temporal lobe concerning for new intracranial mets

- 11/28/22: PET/CT: near complete metabolic resolution and significant decrease in size of LLL mass; no change in non-avid mildly prominent mediastinal LNs; R>L subpleural ground glass changes with increasing FDG avidity, could suggest acute on chronic inflammation



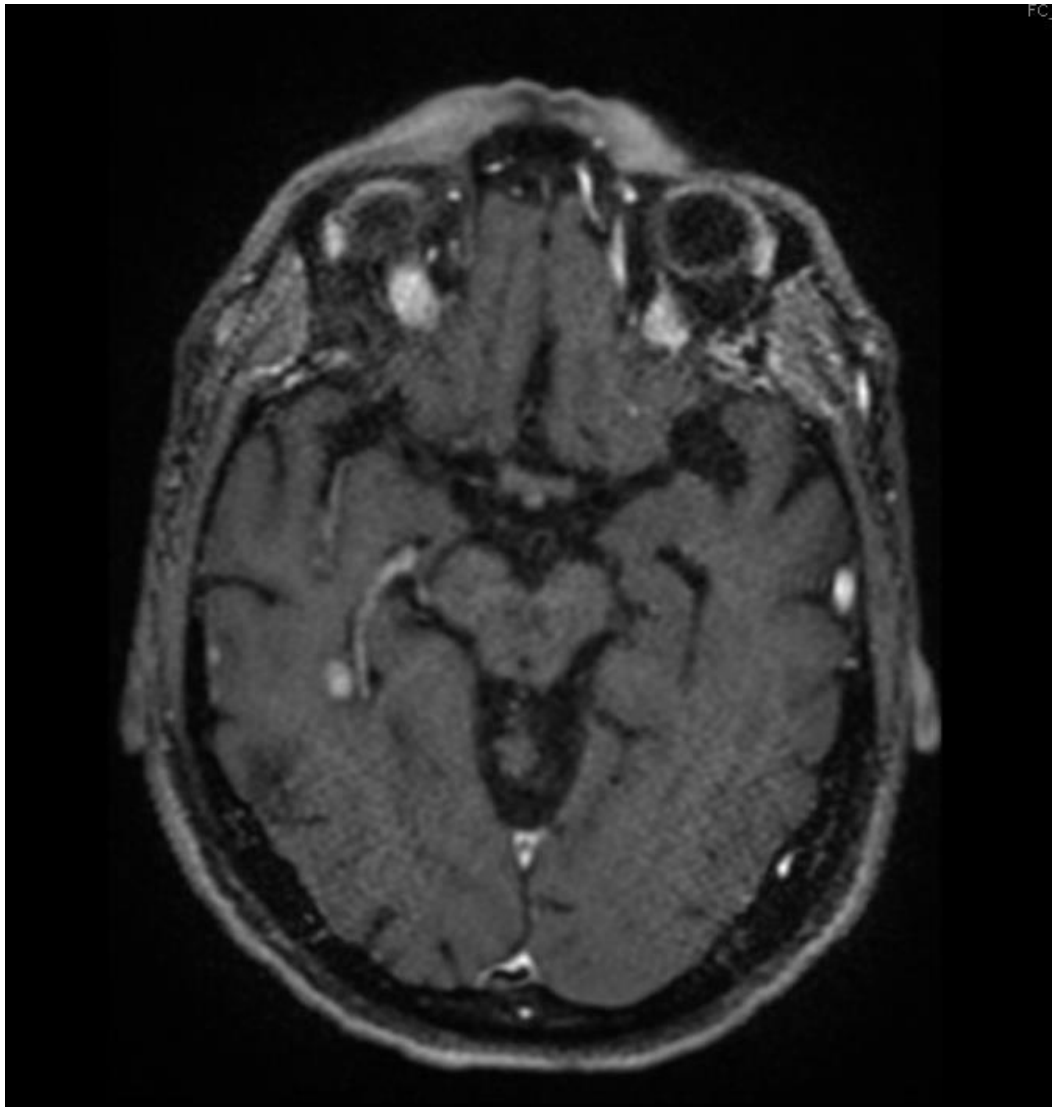
Question

What treatment should this patient receive for the findings noted in the brain?

- **WBRT**
- **Short term brain MRI surveillance**
- **SRS to brain lesions**

Case

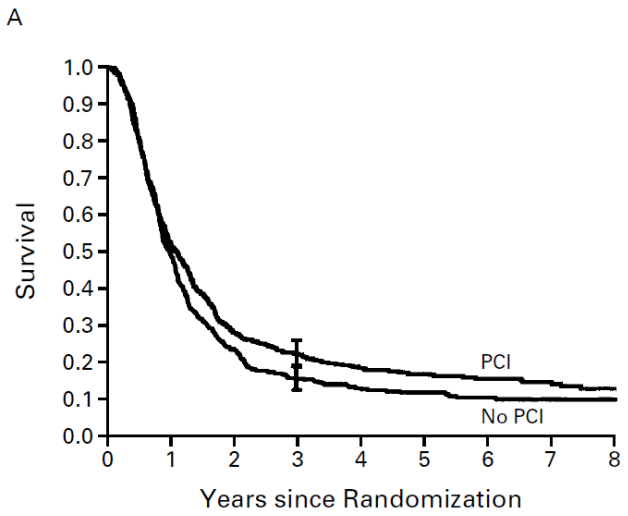
- Thoracic TB review: findings not typical for radiation pneumonitis, more c/w drug reaction or organizing pneumonia; recommend steroids and pulmonary f/u
- Reviewed at Stanford neuro onc TB with recommendation for repeat brain MRI in 6-8 weeks since lesions were felt to be related to possible infarcts, less likely metastatic
- Brain MRI (2/26/23): increased size of intracranial metastases in R cerebellum and R temporal lobe with increased vasogenic edema



PCI for SCLC

Auperin meta-analysis

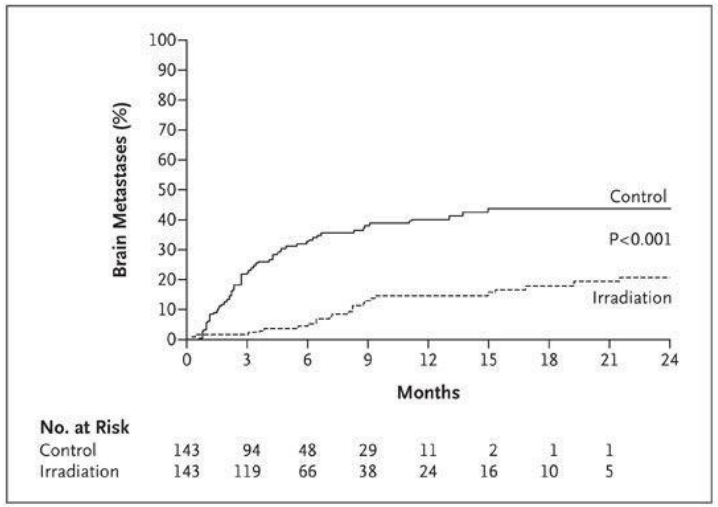
- Analyzed individual data on 987 pts with SCLC in CR enrolled in 7 trials comparing PCI to no PCI
- Relative risk of death in treatment group was 0.84, corresponding to a 5.4% increased survival at 3 years (15.3% vs 20.7%)
- PCI increased DFS and decreased cumulative risk of brain metastases



Auperin A, et al. *NEJM* 1999

Slotman Trial

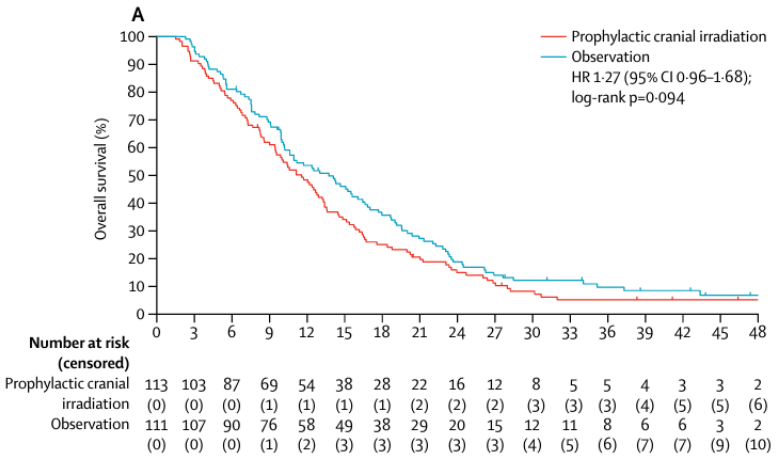
- 286 pts with ES-SCLC
- Eligible pts had any response to chemotherapy and no clinical evidence of brain mets (CNS imaging NOT required)
- Randomized to PCI vs observation
- 1 yr OS 27% vs 13% favoring PCI



Slotman B, et al. *NEJM* 2007

Takahashi Trial

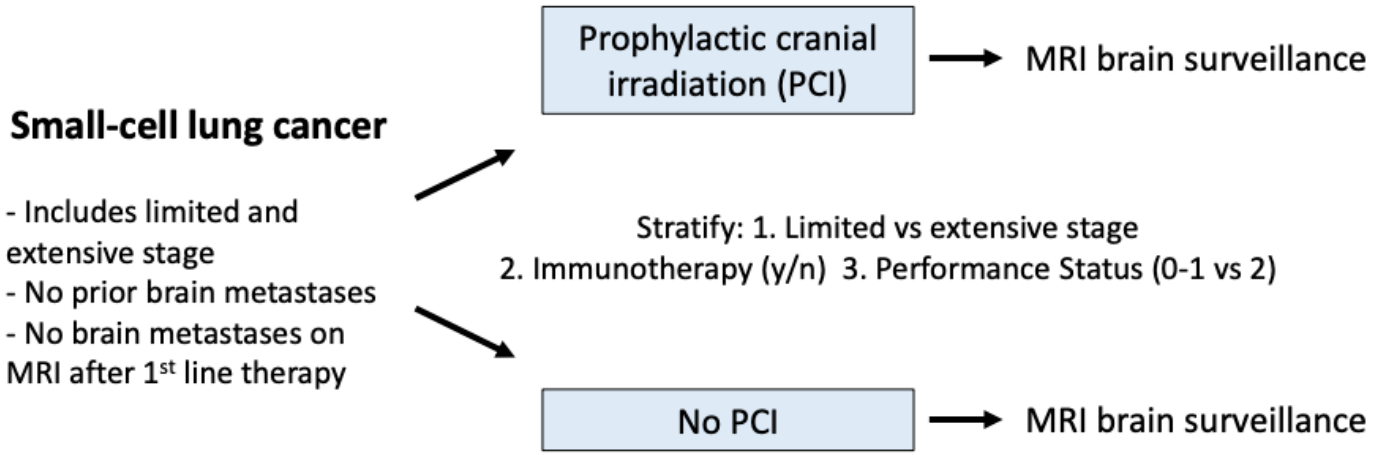
- Randomized ES-SCLC pts with any response to platinum chemo to PCI (25/10) vs no PCI
- Mandated MRI brain prior to PCI
- Terminated early after interim analysis showed futility (163 pts)
- Median OS 11.6 months (PCI) vs 13.7 months (no PCI) (p=0.094)



Takahashi T, et al. *Lancet Oncology* 2017

MAVERICK: Ongoing Ph III trial of MRI Surveillance vs PCI in SCLC

MAVERICK (SWOG 1827): MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation: A Randomized Phase III Trial in Small-Cell Lung Cancer



Primary Endpoint
- Overall survival (non-inferiority)

Secondary Endpoints
- Cognitive function
- QOL
- OS in limited and extensive stage
- Brain metastases free survival
- Toxicity

Translational Endpoints
-Longitudinal brain MRI changes
-ctDNA correlation to PFS, OS

Accrual goal: 668 patients

- MRI brain surveillance scheduled at 3, 6, 9, 12, 18, 24 months
- Radiation therapy is recommended at the time of brain metastases (WBRT and SRS allowed)
- Hippocampal-avoidance PCI and WBRT are allowed
- Patients managed with any/all NCCN-acknowledged first-line treatment strategies are eligible

PIs Chad Rusthoven and Paul Brown

Clinical trials 2023. https://classic.clinicaltrials.gov/ProvidedDocs/47/NCT05223647/Prot_000.pdf

Case/Question

PET/CT (2/6/23): new FDG avid R adrenal mass; continued metabolic resolution of LLL pulmonary mass; mildly increased size of mediastinal LNs with low FDG uptake

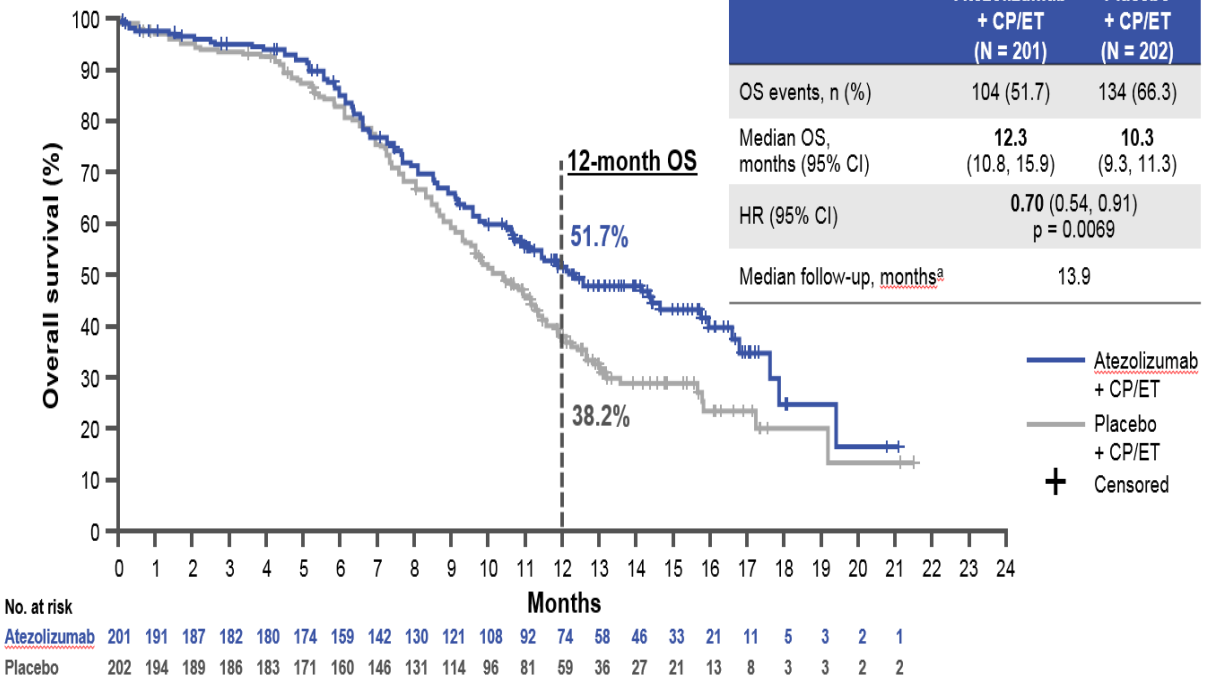
TB review: systemic therapy given concern for evidence of disease progression in brain, adrenal, and possibly LNs; can consider consolidative XRT if good response

What systemic treatment do you recommend?

- **Platinum/etoposide**
- **Platinum/etoposide/nivolumab/ipilimumab**
- **Platinum/etoposide/atezolizumab OR durvalumab**
- **Nivolumab/ipilimumab**

Combining platinum-etoposide + immunotherapy changed the frontline treatment for ES-SCLC after decades

IMpower133 carboplatin/etoposide +/- atezolizumab



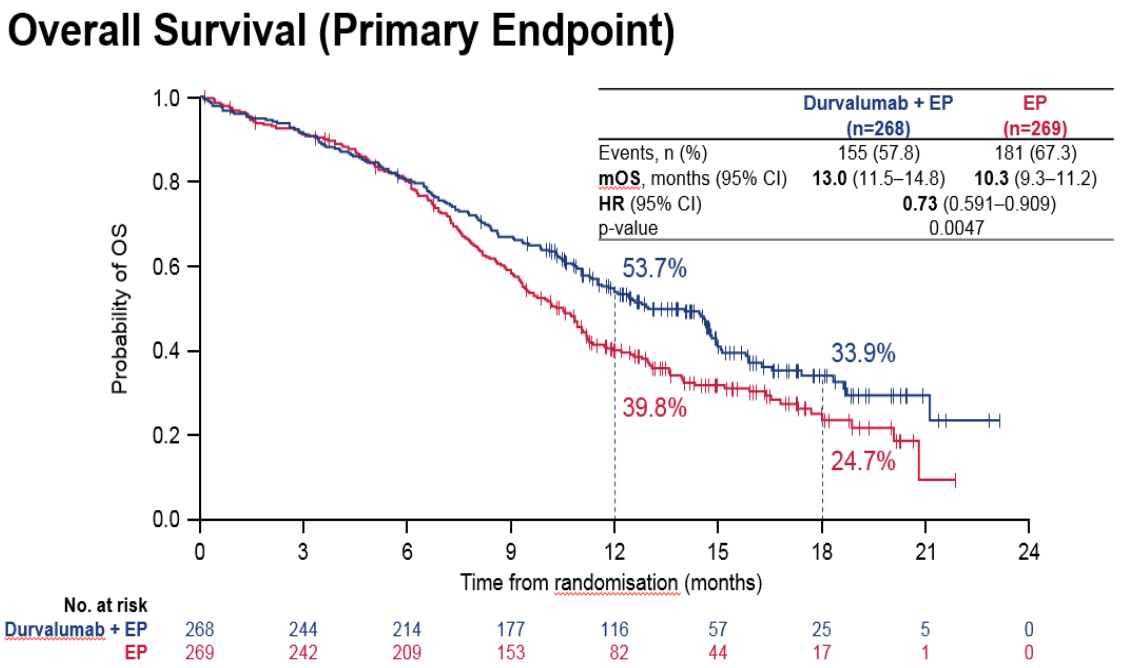
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

No. at risk																					
Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

March 2019: FDA approved atezo for first line treatment of ES-SCLC

Horn L, et al. *NEJM*. 2018 Dec 6; 379(23):2220-2229

CASPIAN cis/carboplatin/etoposide +/- durvalumab



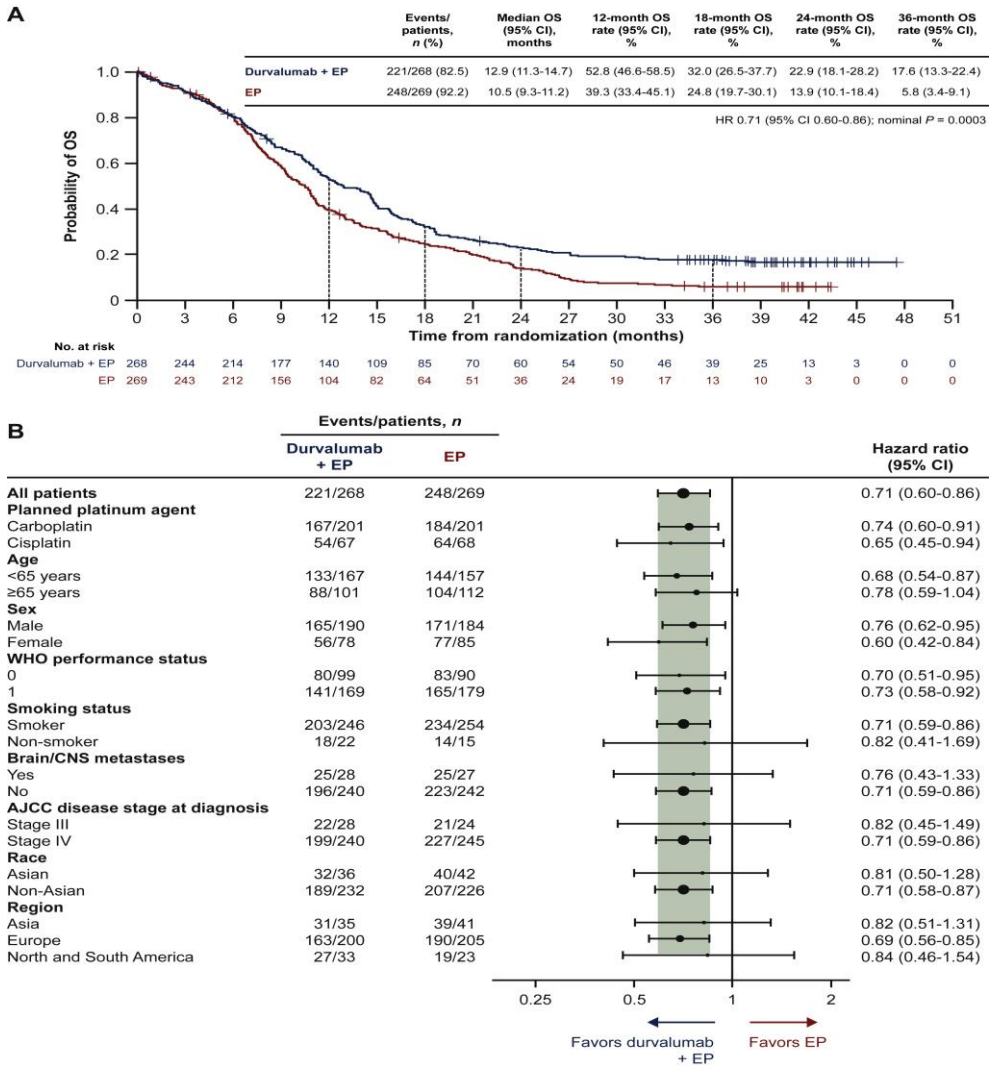
	Durvalumab + EP (n=268)	EP (n=269)
Events, n (%)	155 (57.8)	181 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.591–0.909)	
p-value	0.0047	

No. at risk									
Durvalumab + EP	268	244	214	177	116	57	25	5	0
EP	269	242	209	153	82	44	17	1	0

March 2020: FDA approved durva for first line treatment of ES-SCLC

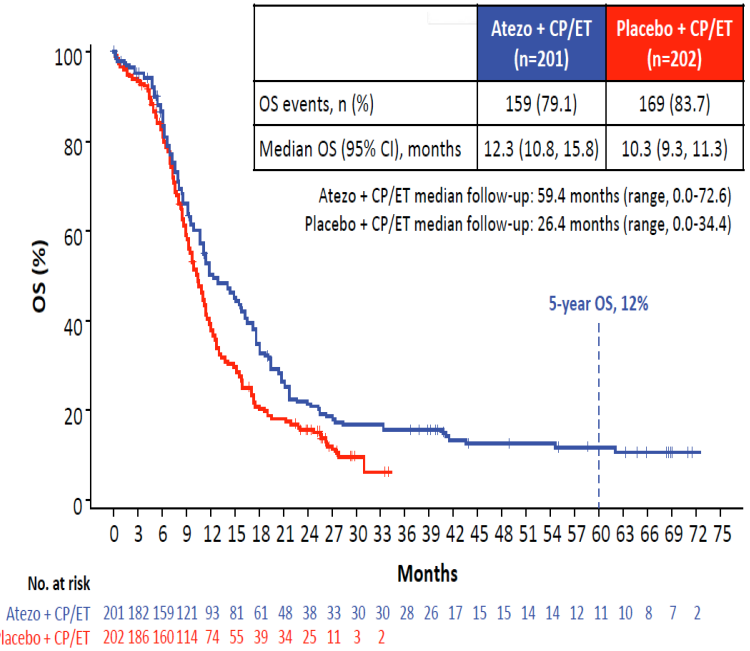
Paz-Ares L, et al. *Lancet*. 2019 Nov 23;394(10212):1929-1939

3-year updated OS: CASPIAN



5-year OS: IMpower133 and IMbrella A

IMpower133 and IMbrella A: long-term OS

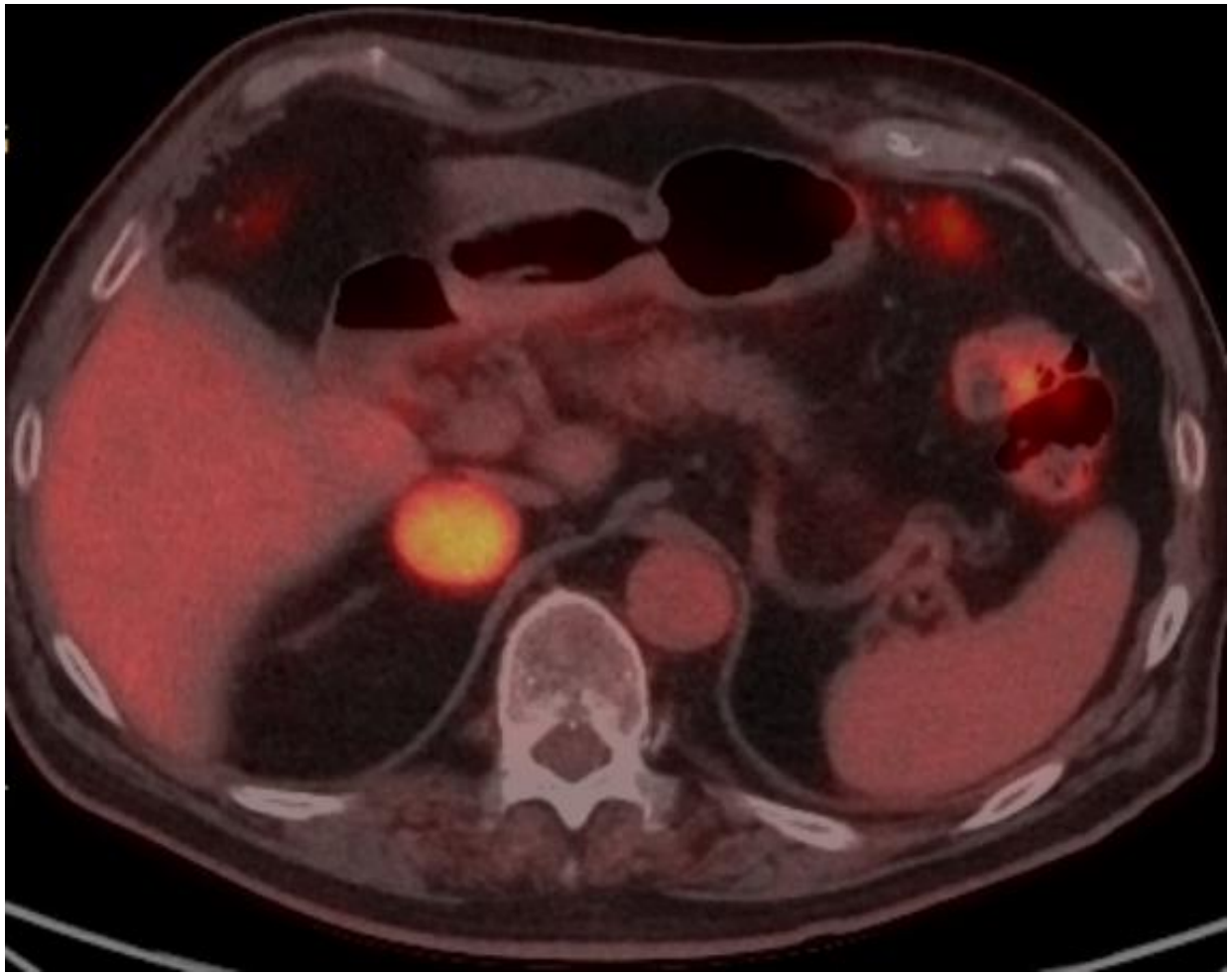


OS rate (95% CI), %	IMpower133 and IMbrella A Atezo + CP/ET (n=201)	IMpower133 only Placebo + CP/ET (n=202)
1-year	52% (45-59)	39% (32-46)
2-year	22% (16-28)	16% (11-21)
3-year	16% (11-21)	NE[a]
4-year	13% (8-18)	NE[a]
5-year	12% (7-17)	NE[a]

Paz-Ares L, et al. *ESMO Open*. 2022 Apr;7(2):100408; Liu SV, et al. *J Clin Oncol* 2021; 39:619-30.

Case

- Received carbo/etop/durva x 4 cycles, then started on maintenance durvalumab
- Received SRS to brain lesions
- After 3 cycles of maintenance durvalumab:
  - PET/CT (8/21/23): increased size and avidity of R adrenal metastasis
  - Brain MRI (8/21/23): interval development of multiple supratentorial and infratentorial metastases (largest is 11 mm in L temporal lobe); some lesions demonstrate intralesional hemorrhage
- TB review: recommend WBRT; XRT to growing adrenal lesion given oligoprogressive disease and continuation of maintenance IO



Takeaways

- Surgery or SBRT can be considered for stage I SCLC followed by adjuvant platinum/etoposide
- Limited stage: chemotherapy (platinum/etoposide) with concurrent radiation (daily or BID)
- Extensive stage: platinum/etoposide + atezolizumab or durvalumab, regardless of PD-L1
- PCI with more evidence in LS than ES but benefit in either setting is questioned
  - Consider brain MRI surveillance instead
- Important ongoing trials investigating IO in LS and role of PCI vs. brain MRI surveillance