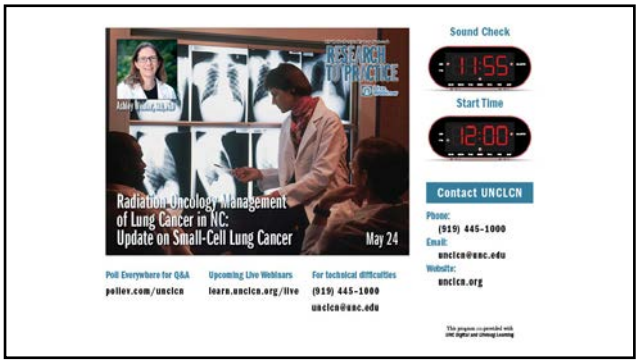

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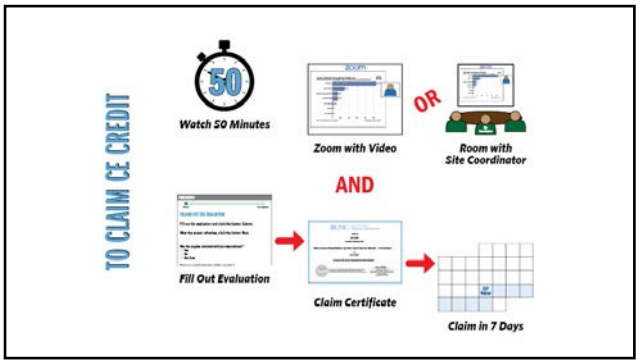

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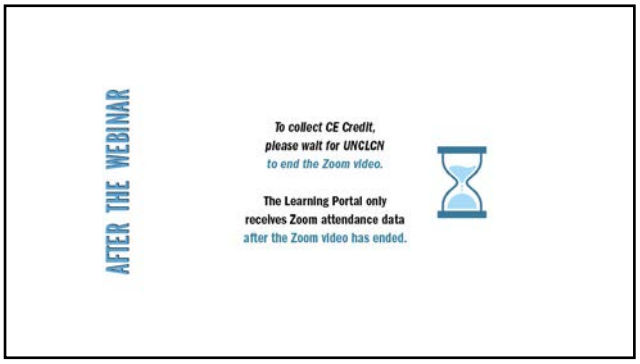

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Ashley Weiner, MD, PhD

Ashley Weiner, MD, PhD, is a radiation oncologist at UNC Hospital in Chapel Hill. Her clinical focuses are thoracic malignancies (primarily non-small cell and small cell lung cancer) and gynecologic malignancies (primarily endometrial and cervical cancer). She received a bachelor's degree from Duke University and her PhD from Vanderbilt University, both in biomedical engineering.

She also received her MD degree from Vanderbilt University School of Medicine. She completed residency training in radiation oncology at Washington University in St. Louis.

At UNC, she is the clinic medical director, director of the residency program in radiation oncology, and the course director of the medical student clerkship. Her passions are medical education, patient-reported outcomes, and improving clinical workflow in radiation oncology

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5. Ashley Weiner, MD, PhD, is a radiation oncologist at UNC Hospital in Chapel Hill.

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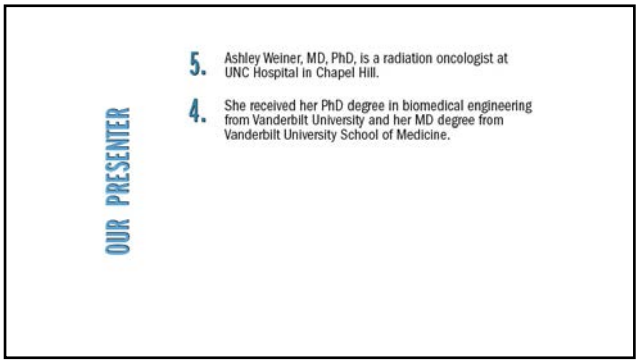

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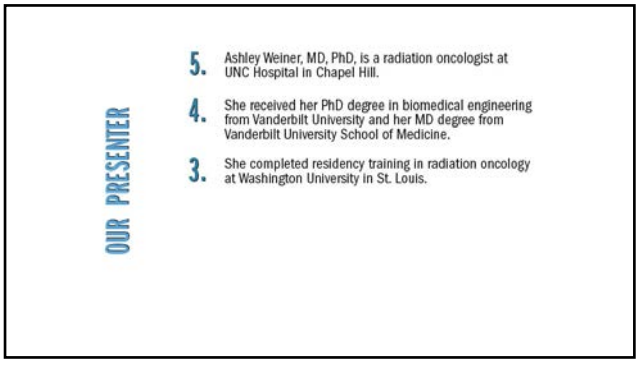

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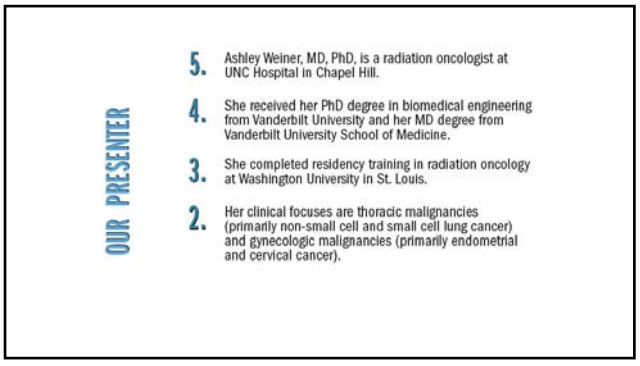

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5. Ashley Weiner, MD, PhD, is a radiation oncologist at UNC Hospital in Chapel Hill.
4. She received her PhD degree in biomedical engineering from Vanderbilt University and her MD degree from Vanderbilt University School of Medicine.
3. She completed residency training in radiation oncology at Washington University in St. Louis.
2. Her clinical focuses are thoracic malignancies (primarily non-small cell and small cell lung cancer) and gynecologic malignancies (primarily endometrial and cervical cancer).
1. At UNC, she is the clinic medical director, director of the residency program in radiation oncology, and the course director of the medical student clerkship.

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Respond at PollEv.com/unclcn
Text UNCLCN to 22333 once to join, then text your message

What one word comes to mind when you hear the phrase "radiotherapy for small cell lung cancer"?

Powered by Poll Everywhere

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DISCLOSURES

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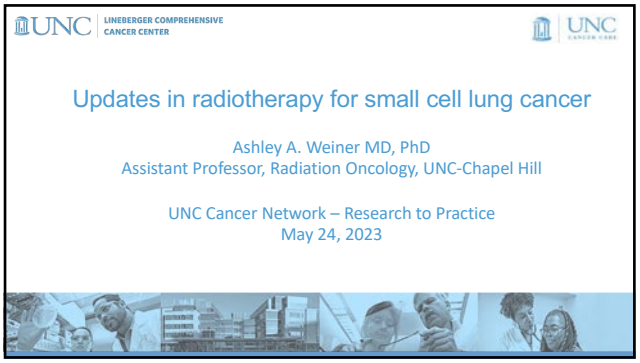

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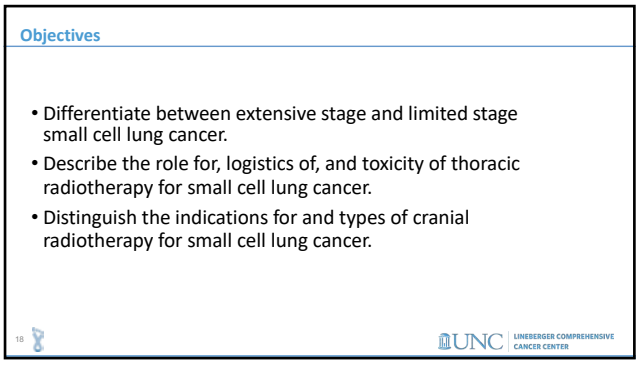

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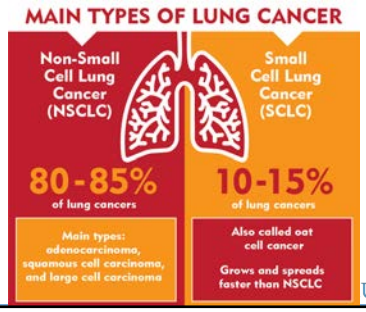
Small Cell Lung Cancer (SCLC)



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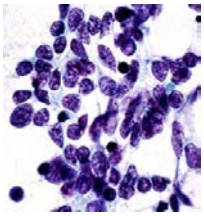
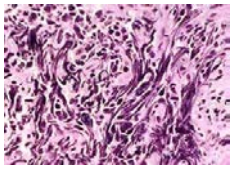
SCLC – Small round, blue cells





High Ki67
Chromogranin, Synaptophysin, TTF-1

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SCLC - Epidemiology

- > 95% of cases are related to smoking

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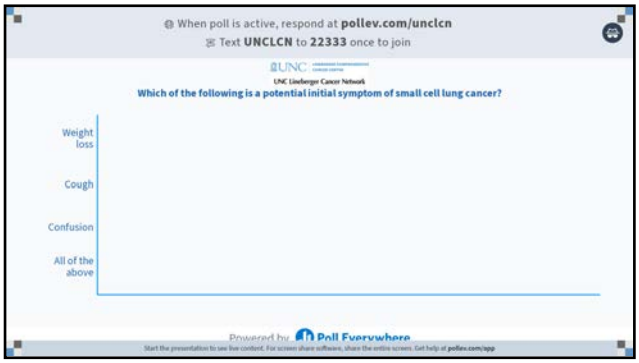

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SCLC – Initial Presentation

- Cough
- Shortness of Breath
- Weight loss
- Paraneoplastic Syndromes
  - SIADH (7-16% of patients)
    - Cramping, nausea, vomiting, confusion
  - Lambert-Eaton Syndrome (3% of patients)
    - Muscle weakness

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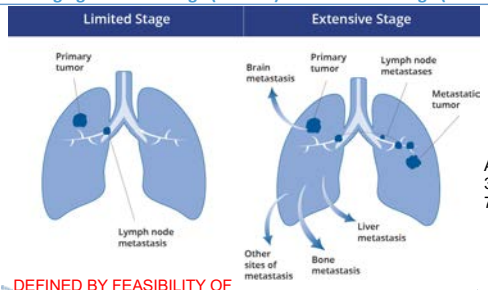
SCLC Staging – Limited Stage (LS-SCLC) and Extensive Stage (ES-SCLC)



At diagnosis:
30% LS-SCLC
70% ES-SCLC

DEFINED BY FEASIBILITY OF RADIATION FIELD

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Staging can be controversial

- What can truly fit in a “radiation port”?
- Supraclavicular LN (ipsilateral and/or contralateral)
- Contralateral mediastinal LN
- Pleural effusion

- With more modern techniques, larger radiation ports are feasible

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Prognosis

- Age
- Performance status
- Weight loss
- Gender
- Disease extent
- Serum markers: hyponatremia, elevated alkaline phosphatase, elevated LDH

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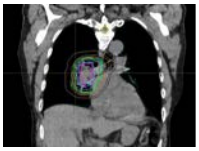
Treatment of SCLC

- SCLC is though to be somewhat of a ”systemic” disease
- Systemic therapy (chemotherapy) is the mainstay of therapy
- Radiation (and surgery) are “local” treatments



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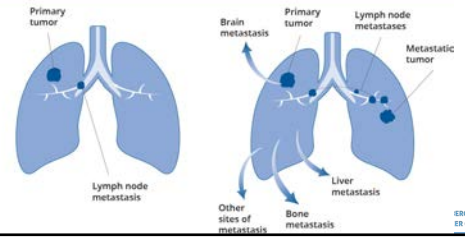
Treatment Paradigms – LS-SCLC and ES-SCLC

SYSTEMIC THERAPY + LOCAL THERAPY

SYSTEMIC THERAPY LOCAL THERAPY ON CASE-BY-CASE BASIS

Limited Stage	Extensive Stage



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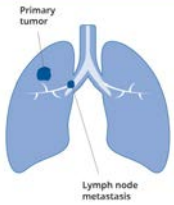
Limited Stage



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Treatment of Stage I SCLC (LS-SCLC with negative lymph nodes)

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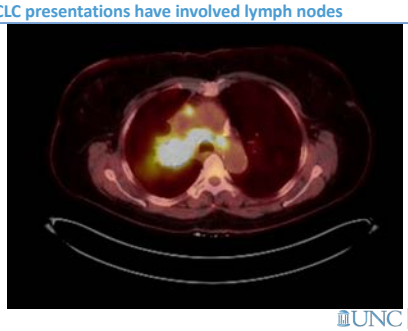
Most LS-SCLC presentations have involved lymph nodes



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Treatment of LS-SCLC (with positive lymph nodes)

- Concurrent chemoradiation
- Chemotherapy = cisplatin and etoposide
  - Cisplatin Day 1, Etoposide Day 1-3
  - Repeat every 3 weeks for 4 cycles
- Radiotherapy
  - What is radiation?

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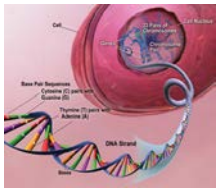
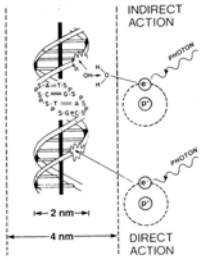
What is radiation? - RT Causes DNA Damage



National Institute on Aging/National Institutes of Health



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What is radiation? – Cells die by mitotic death

- The cells are not "burned"
- DNA strand breaks → eventual mitotic cell death

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What is radiation? The patient pathway

35

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Reasons to do radiation

- **Palliative – to help with a symptom (extensive stage)**
- **Definitive – curative intent without surgery (limited stage)**
- **Adjuvant – after surgery (rare for SCLC)**
- **Prophylactic – radiation without visible disease (RARE for other disease sites, but considered for SCLC)**

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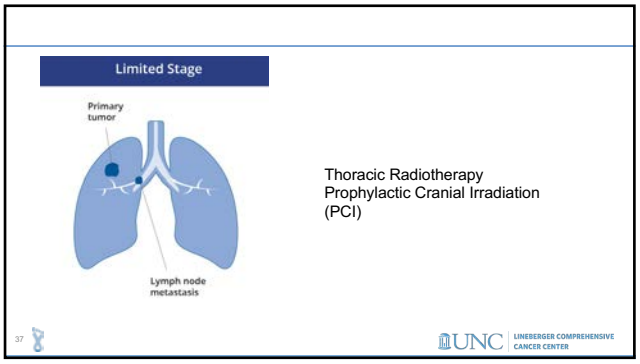

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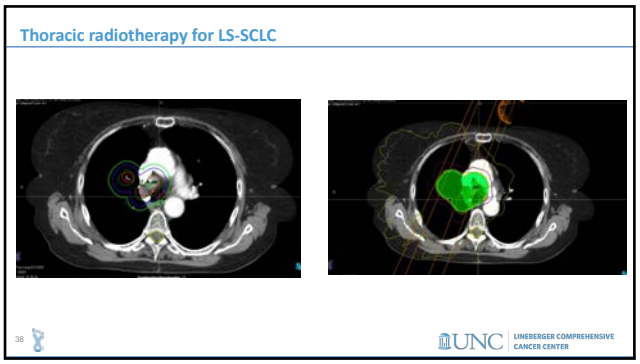

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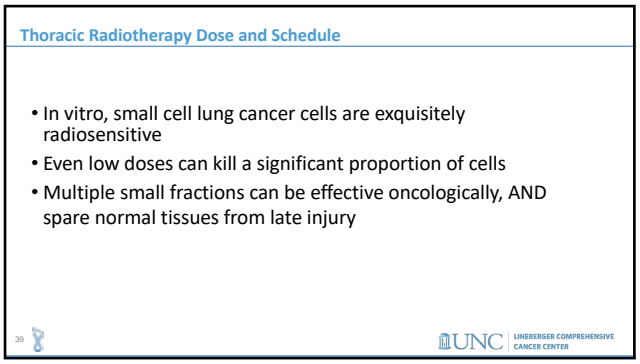

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Radiotherapy Dose and Schedule – BID (Twice daily radiotherapy)

CONVENTIONAL-VS. ACCELERATED - FRACTIONATION

Turrisi, A. et al. NEJM 340: 265-271, 1999.

417 patients
Stratify
PS 0-1 vs. 2

Sex: male vs. female

Wt loss: ≤5% vs. > 5%

RANDOMIZE

CRT: 45 GY/ 25 FX/ 5 WKS + CE X 4 CYCLES

AFX: 45 GY/ 30 FX/ 3 WKS + CE X 4 CYCLES

RT begins on day 1
Cisplatin 60mg/m2 d1
Etoposide 120 mg/m2 d1-3
PCI 25Gy/10 fx for patients with CR

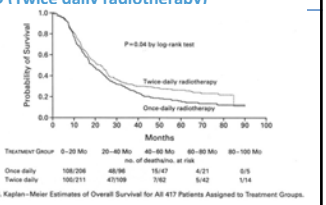

Figure 1. Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

End point	QD-TI	BID-TI	P-value
Med Survival	19 mo	23 mo	0.04
5-yr Survival	16%	26%	0.04
LF alone	52%	36%	0.06
G≥3 Esophagitis	16%	32%	<0.001

40

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CALGB 30610

LS-SCLC stratified by
- Gender
- Weight loss > 5%
- Performance status

RANDOMLY ASSIGNED

45 Gy BID/EP x 4* (1.5 Gy/Fx in 3 wks) → Control

70 Gy QD/EP x 4* (2.0 Gy/Fx in 7 wks)

61.2 Gy QB/EP x 4* (1.8 Gy/Fx in 5 wks)

Reassess → Experimental TRT/EP x 4

41

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CALGB 30610

– Phase III study for LS-SCLC– 638 patients
– 45 Gy in 1.5 Gy BID versus 70 Gy in 2 Gy fractions with concurrent cisplatin-etoposide chemotherapy Q3 wks
– Median OS 28.5 months vs 30 months for BID vs QD arm
– 5-year OS 29% vs. 32% for BID vs. QD arm (not SS)
– No difference in grade 3-4 esophageal or thoracic toxicity in BID vs. QD arm
– Conclusion: no difference in survival outcome between BID vs. QD chemoRT for limited stage SCLC with similar and lower than expected toxicities in both arm

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CONVERT

– Phase III study for LS- SCLC– 547 patients
– 45 Gy in 1.5 Gy BID versus 66 Gy in 2 Gy fractions with concurrent cisplatin-etoposide chemotherapy Q3 wks
– Median OS 30 months vs 25months for BID vs QD arm (HR 1.18, p=0.14)
– 2-year OS 56% vs. 51% for BID vs. QD arm (not SS)
– 5-year OS 34% vs. 31% for BID vs. QD arm (not SS)
– No difference in grade 3-4 esophageal or thoracic toxicity in BID vs.QD arm
– Conclusion: no difference in survival outcome between BID vs. QD chemoRT for limited stage SCLC with similar and lower than expected toxicities in both arm
– Powered for superiority(vs. non-inferiority),thus concluded BID should still be standard

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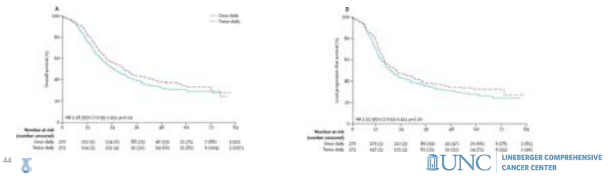
CONVERT

- RT began with chemo cycle 2
- Most 3D-CRT, some IMRT, no elective nodal RT
- ~80-85% with PCI



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Gronberg Phase II trial

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

– Phase II study for LS- SCLC– 170 patients
– 45 Gy in 1.5 Gy BID versus 60 Gy in 1.5 Gy BID with concurrent cisplatin-etoposide chemotherapy Q3 wks
– Median OS 22.6 months vs 37 months (HR 0.67, p=0.012)
– 2-year OS 48 % vs. 74%
– No difference in median PFS (18.6 vs 10.6 months)
– No difference in esophagitis (18% vs 21%)
– Conclusion: Improved OS without PFS, worth pursuing in Phase III study

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Timing of Thoracic RT

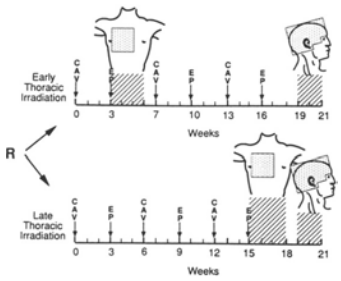

Fig 1. Study schema.

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Timing of Thoracic RT

Murray, N. et al. JCO 11:336-44, 1993

Endpoint	Early TI	Late TI	*p*-value
Median Survival	21 mo.	16 mo.	
5 yr-OS	20%	11%	0.008
G3-4 Esophagitis	15%	8%	0.05
G3 Dermatitis	6%	2%	0.02

TI: Thoracic irradiation, OS: overall survival, G: grade, NS: not significant

Note that Late RT becomes more "sequential-like"

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Timing – SER (start of treatment to end of radiotherapy)

Table 1. Summary of the Selected Phase III Trials Investigating Chest Radiation Schedules Combined With Chemotherapy for Limited-Stage Small-Cell Lung Cancer

Study	No. of Patients	Radiation Schedule	Day That RT Was Started	Concurrent CT	5-Year % LC*	5-Year Survival Rate (%)	Severe Pneumonitis (%)	Severe Esophagitis (%)	SER (days)	$EQD_{2,2}$ (Gy)
Murray et al[28]	155	40 Gy/15 f/19 d	21	Yes	45	20	3.2	15	40	47.13
	153	40 Gy/15 f/19 d	105	Yes	45	11	0.7	7.5	166	47.13
Jeremic et al[27]	52	54 Gy/36 f/26 d	1	Yes	58	30	1.9	29.8	26	51.75
	51	54 Gy/36 f/26 d	42	Yes	35	15	0	25.4	61	51.75
Turrisi et al[23]	211	45 Gy/30 f/19 d	1-19	Yes	64	26	NR	33	19-38	48.02
	206	45 Gy/25 f/33 d	1-19	Yes	48	16	NR	16	33-62	39.35
Takada et al[24]	114	45 Gy/30 f/19 d	2	Yes	82	24	NR	9	20	48.02
	114	45 Gy/30 f/19 d	84	No	82	18	NR	4	103	48.02

Abbreviations: RT, radiotherapy; CT, chemotherapy; LC, local tumor control; SER, the time from the start of any treatment to the end of chest irradiation; f, fractions; NR, not reported; $EQD_{2,2}$, equivalent dose at 2 Gy corrected for overall treatment time of radiotherapy.
*Cumulative % LC except for Takada et al[24] (first site of recurrence).

Improved OS with decreased SER
Each week of increase in SER associated with 1.8% decrease in 5 y OS
De Ruysscher JCO 2006

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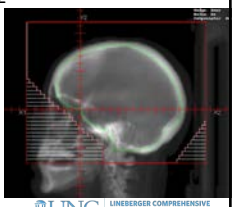
Limited -stage SCLC – Prophylactic Cranial Irradiation (PCI)

- Prophylactic = treatment in the absence of know disease to prevent disease occurrence
- Incidence of brain metastases is 30-80% at 2 years
- PCI can be given (25 Gy in 10 fractions)
- PCI might improve survival, does decrease incidents of brain metastases
- PCI is associated with decline in memory
- Old studies did NOT include MRI



Auperin NEJM 1999.

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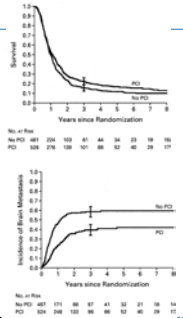
PCI in LS-SCLC

- Individual data of 987 pts in 7 trials ('65-95).
- Median follow up: 3.5-18.5 years
- RR of death : 0.84 (p= 0.01) favoring PCI.
- 5.4% absolute increase in 3-yr survival (20.7vs. 15.3%).



Auperin NEJM 1999.

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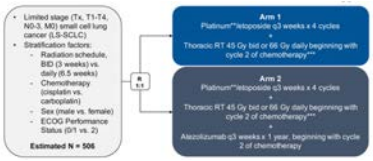
Upcoming Trials in LS-SCLC

- NRG LU-005



- ADRIATIC (NCT03703297)
  - Standard CRT followed by consolidation Durvalumab or Durvalumab + Tremelimumab or placebo
- S1827 Maverick – MRI surveillance vs PCI for LS- and ES-SCLC

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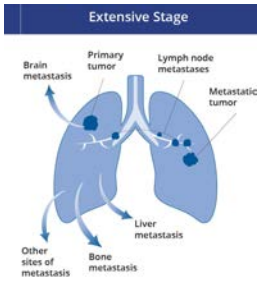

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Reasons to do radiation

- Palliative – to help with a symptom (extensive stage)
- Definitive – curative intent without surgery (limited stage)
- Adjuvant – after surgery (rare for SCLC)
- Prophylactic – radiation without visible disease (RARE for other disease sites, but considered for SCLC)

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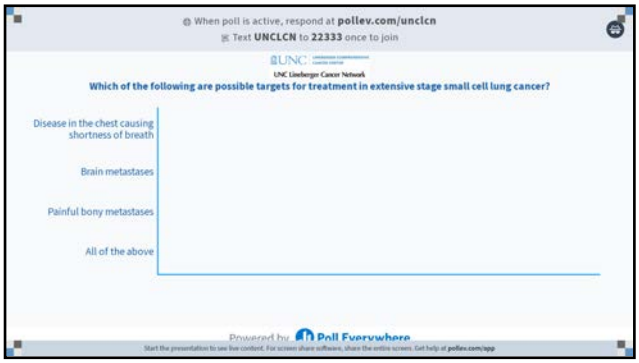

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Radiation for ES- SCLC?



TARGET CAN BE ANYWHERE THAT CANCER IS CAUSING A SYMPTOM

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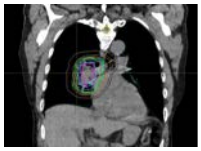
Consolidative thoracic radiation

- Standard of care for ES-SCLC is chemotherapy + immunotherapy
- In the pre-immunotherapy era, consolidative thoracic radiation potentially had an overall survival benefit at 2 years (3% vs 13%)
  - Only benefit in patients with residual disease in chest
  - Outcomes better in patients with 2 or fewer metastases
  - Did NOT meet primary endpoint of 1 year OS



Slotman, Lancet 2015, 2017.

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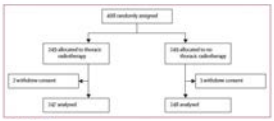
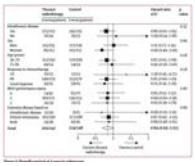
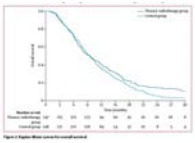
CREST – Consolidative Thoracic Radiation in ES-SCLC







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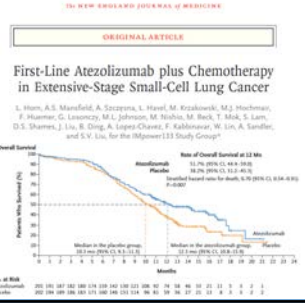
Immunotherapy in ES-SCLC – IMPower133



- Ph 3 carbo/etop +/- atezo in 1st line ES SCLC
- 201 pt, 1:1 randomization
- Median f/u 13.9 mos
- Median OS +/- atezo: 12.3 mos vs. 10.3 mos (SS)
- Median PFS +/- atezo: 5.2 mos vs. 4.3 mos (SS)
- No concerning safety signals

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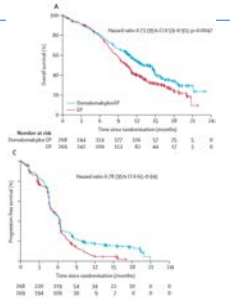
Immunotherapy in ES-SCLC - CASPIAN

- Ph 3: durva + EP vs. durva + tremi + vs. EP alone (1:1:1)
- PCI allowed, but no thoracic RT
- 537 pts total in 2 arms
- Median OS +/- durva: 13.0 mos vs. 10.3 mos (S)
- No difference in Gr 3/4 AEs 62%
- No difference in Gr 5 toxicities: 5% vs. 6%



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Consolidative Thoracic Immunotherapy in the Immunotherapy Era for ES-SCLC

- No prospective data
  - IMPower133 and CASPIAN did NOT allow thoracic radiotherapy
- Potential increased toxicity risk (pneumonitis)
- Consider with bulky residual thoracic disease

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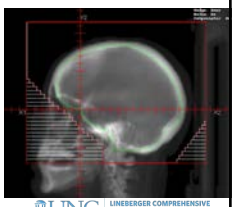
Prophylactic Cranial Irradiation (PCI) in ES-SCLC

- Old studies with overall survival benefit to PCI in ES-SCLC (13 vs 27% at 1 year)
- Modern study with:
  - MRI at baseline, and MRI every 3 months
  - Randomization to PCI or no PCI
  - Decreased incidence of brain mets 69 vs 48%
  - No difference in survival (13.7 mo vs 11.7 mos)



62 Slotman, NEJM 2007, Takahashi, Lancet 2017.

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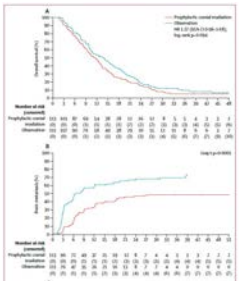
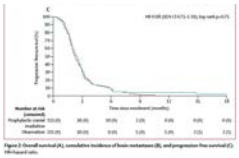
PCI vs MRI surveillance for ES-SCLC





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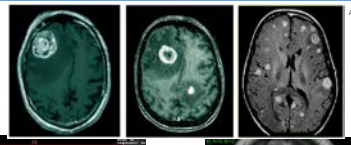
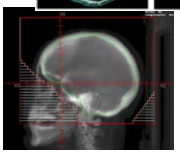
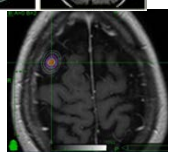
How is radiation used for ES-SCLC? – brain metastases – WBRT vs SRS



Alsidawi, Int J. Mol. Sci. 2014

Whole Brain Radiation





Stereotactic Radiosurgery – Does SRS make sense in a population who could get PCI?

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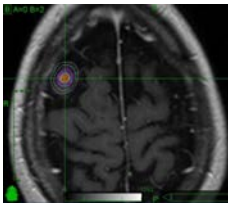
How is radiation used for ES-SCLC? – brain metastases – WBRT vs SRS

- FIRE-SCLC
  - Multicenter cohort – SRS for SCLC
  - 700 patients
  - Median survival 8.5 months after SRS
  - Matched WBRT patients were less likely to have CNS progression, no difference in survival
- Best outcome with < 5 brain mets



65 Rusthoven JAMA Onc 2020, Wang Adv Rad Onc 2023

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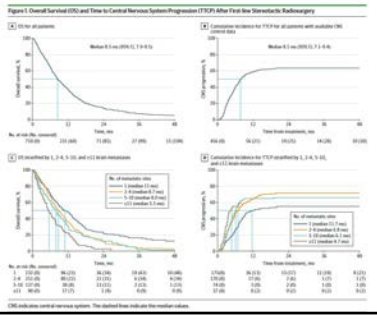
FIRE-SCLC



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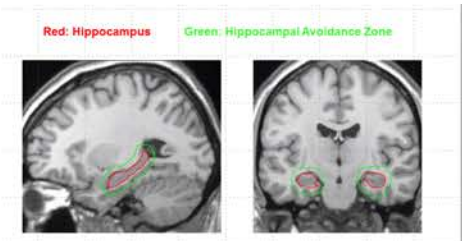
How is radiation used for ES-SCLC? – brain metastases – hippocampal avoidance



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PREMER study – Randomized Phase III – PCI vs HA-PCI

- SCLC (73% LS-SCLC)
- Improved neurocognitive function, no impact on QOL, incidence of brain mets, OS

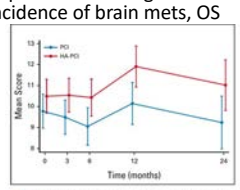

FIG 2. Mean scores of FCSRT-delayed free recall over time. FCSRT, Free and Cued Selective Reminding Test; HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

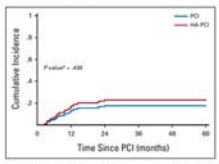

FIG 3. Cumulative incidence of brain metastases. *Pepe and Mori test comparing the cumulative incidence of two groups of arm. HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

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Rogriguez de Dios JCO 2021

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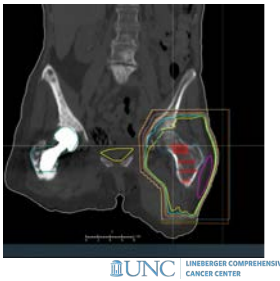
How is radiation used for ES-SCLC? – bone metastases



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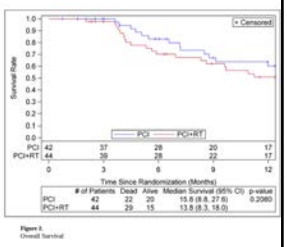
How is radiation used for ES-SCLC? – oligometastatic disease (4 or fewer sites)

- RTOG 0937
- Patients with ES-SCLC (4 or fewer sites), initial response to initial chemotherapy
- Randomized PCI vs RT to all sites + PCI
- PCI 25 Gy in 10 fx
- Other sites 45 Gy in 15 fx
- Outcomes much higher than predicted
- No difference in 1 year survival ~50%
- G3+ toxicity 23% vs 36%



Gore JTO 2018

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What is the current role of radiation in SCLC?

- LS-SCLC
  - Definitive thoracic radiotherapy (BID or QD)
  - PCI?
- ES-SCLC
  - Palliation of symptomatic sites of disease
  - PCI still considered in some practices
  - SRS acceptable for brain metastases14

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Upcoming Trials in SCLC

- NRG LU005 and ADRIATIC – adding immunotherapy to chemoradiation for LS-SCLC
- NRG CC-003 HA-PCI for SCLC
- NRG CC-009 SRS vs HA-WBRT for SCLC brain metastases
- S1827 Maverick – MRI surveillance vs PCI for LS- and ES-SCLC

- Advances in systemic therapy must always be considered when considering advances in radiation

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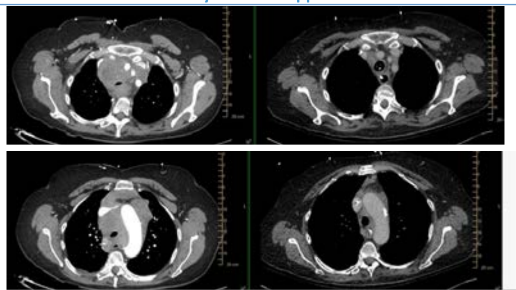
Radiation works for SCLC! Many different approaches!



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ANY QUESTIONS?

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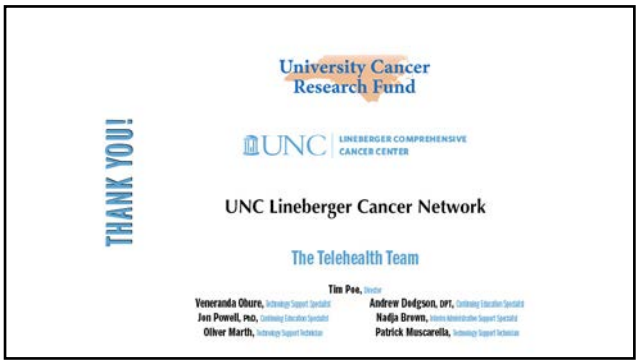

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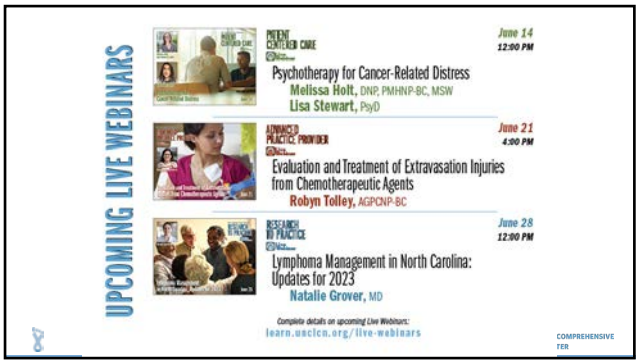

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