

Behandling av småcellet lungekreft

Åslaug Helland, OUS-Radiumhospitalet

- Hva er SCLC
- Epidemiologi
- Behandling
 - Begrenset sykdom
 - Utbredt sykdom
- Utvikling

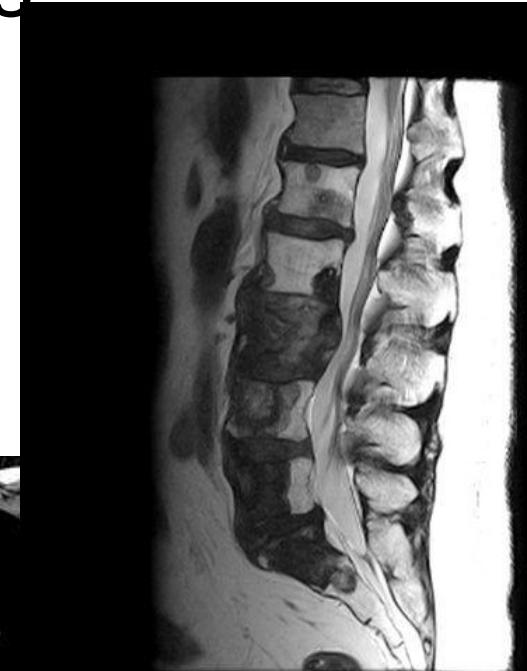
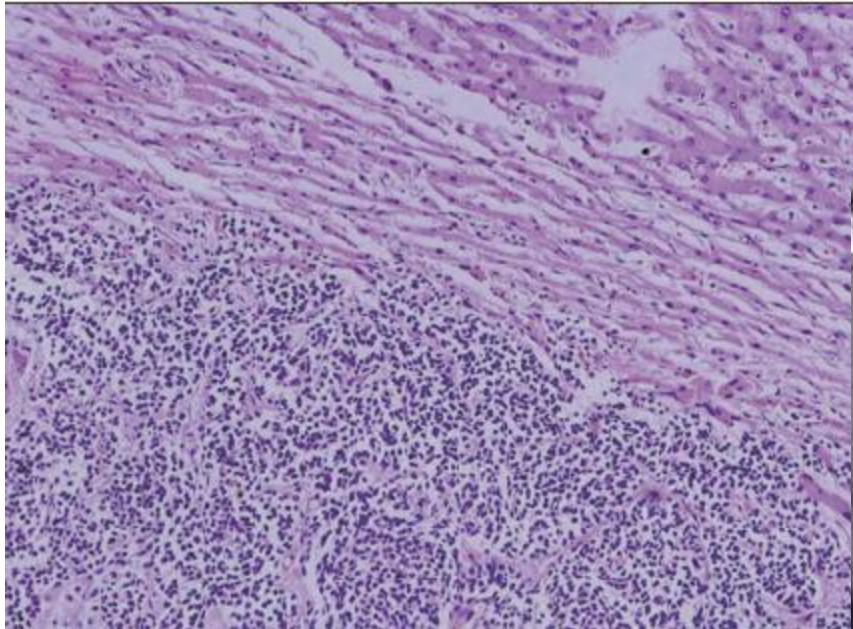


DO YOU REMEMBER (SNEEZE) WHEN ALL SMOKING
GAVE YOU WAS LUNG CANCER?

Hva kjennetegner SCLC?

- Definert som egen subtype ca 1960
- 1968: skille mellom "Limited" og "Extensive Disease"
- Neuroendokrin tumor
- Ca 15% av alle lungekrefttilfeller
- Kjemosensitiv

- Histologisk diagnose - Kjennetegnes ved små celler
- Metastaserer raskt



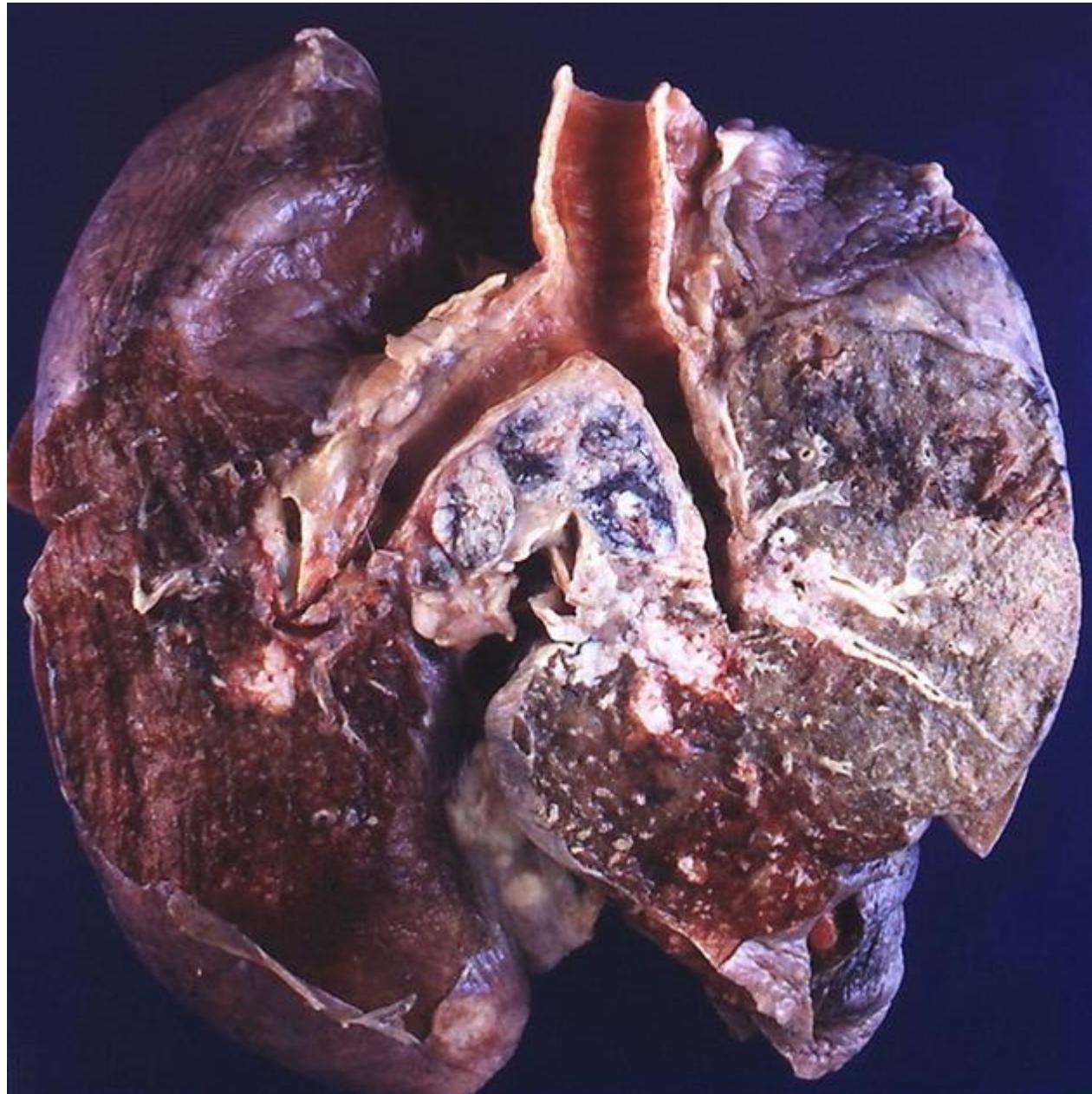
SCIENCEphoto

Bilateral adrenal gland metastases in a 45-year-old woman with shortness of breath.



Johnson P T et al. Radiographics 2009;29:1319-1331

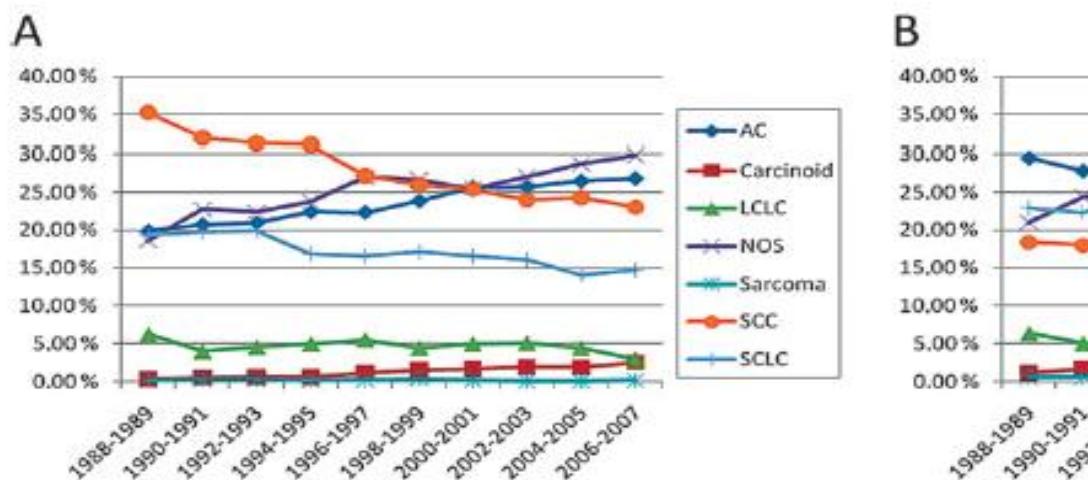
RadioGraphics



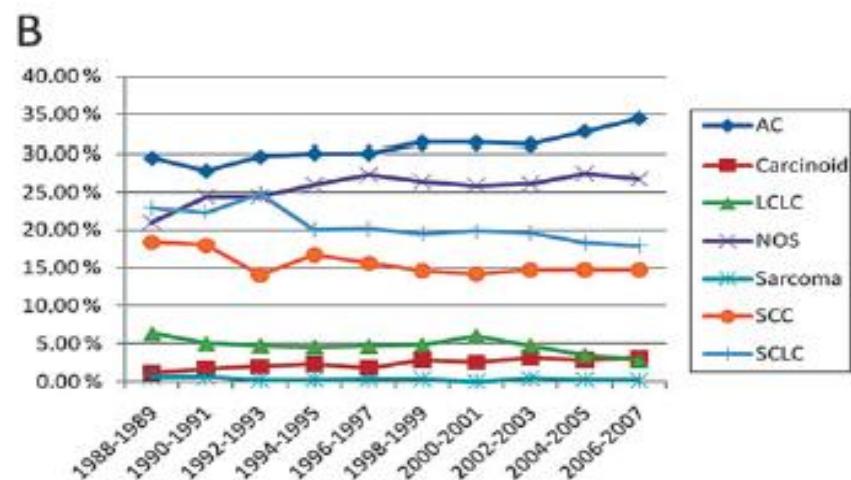


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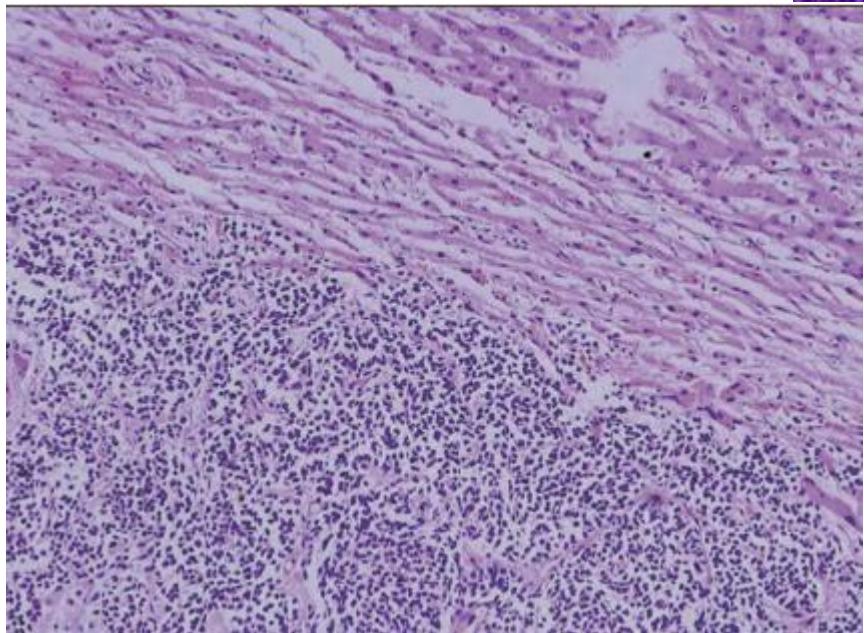
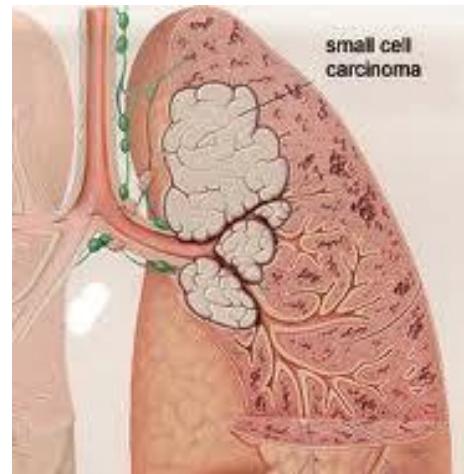
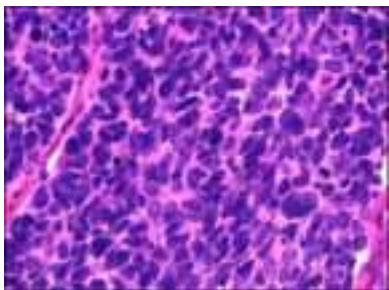
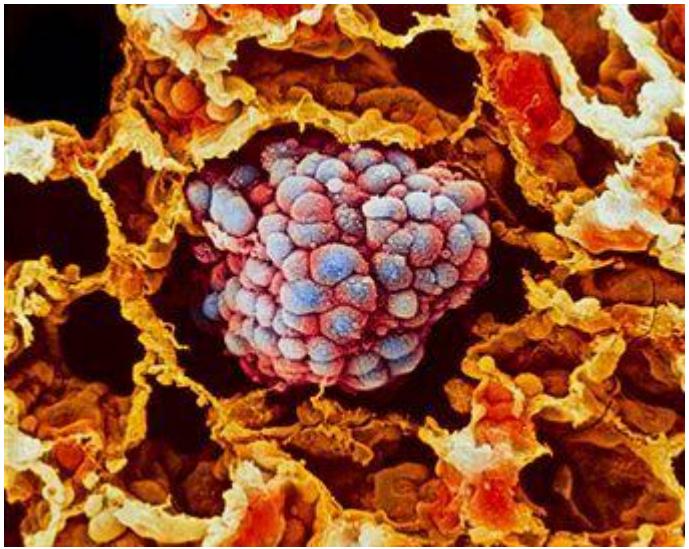


Kvinner



Sagerup et al, 2011

- >95% av pasientene er røykere
- Ubehandlet : overlevelse 2-4 mnd
- God respons på behandling
- Kortvarig respons - raskt tilbakefall
- Systemsykdom
- Begrenset sykdom (35%)
 - "Alt inn i ett strålefelt"
- Utbredt sykdom (65%)
 - Fjernspredning



Symptomer

- Feber
- Vekttap
- Asteni
- Hoste
- Hemoptyse
- Dyspnoe
- Dysfagi
- Heshet
- Stridor
- Smertor
- Paraneoplastiske symptomer
-

Paraneoplastiske symptomer

- Hyponatremi
- Kløe / utslett
- Smertesymptomer
- ..

- Prognostiske faktorer
 - Performance status (ECOG, WHO, Karnofsky)
 - Vekttap
 - Tumorvolum
 - Kjønn
 - LD
 - CNS affeksjon => dårlig prognose

Kasuistikk 1

- Kvinne født 1961
- Helsearbeider
- Røykt ca 20 sig/d
- "Energitap" siste halvår
- Flere pneumonier siste måned, nattesvette
- Dyspnoe, og venetegninger på overkropp siste uke

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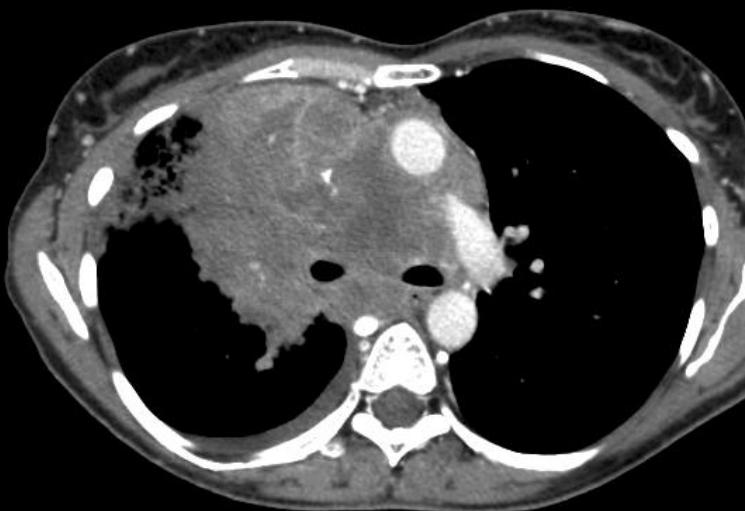
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046Y
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A80

SE: 1
IM: 41

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1
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P265

Tilsendt us, CT thorax
W: 300, C: 40
MAG: 122%

7.0:1

Sykehuset Buskerud

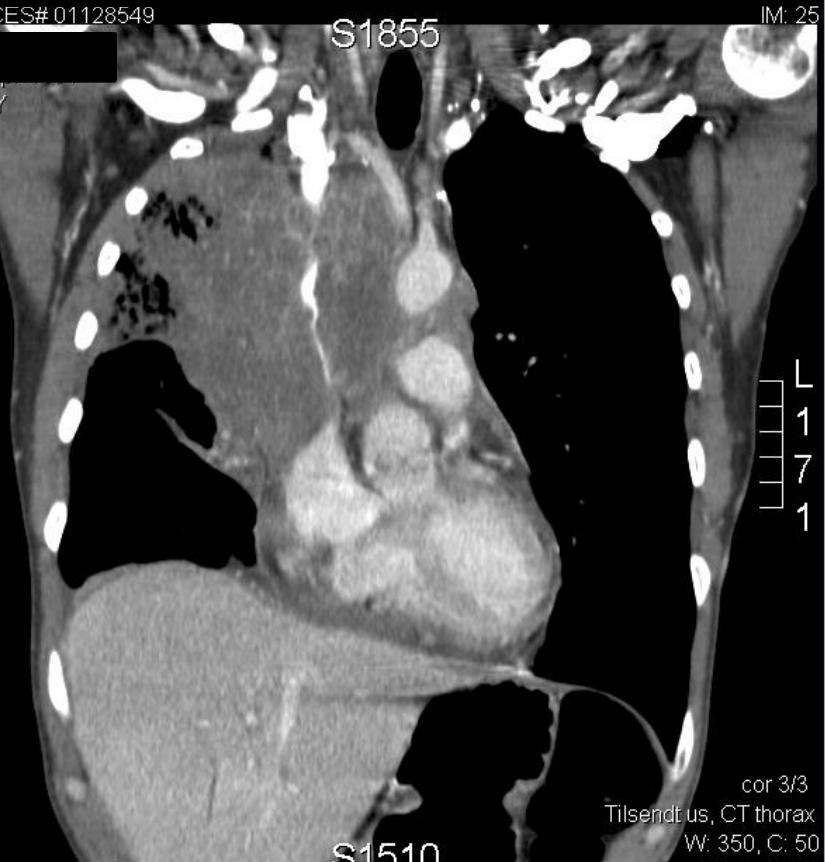
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ACCES# 01128549

SE: 2
IM: 25

046Y
F

R
1
7
4



S1510

cor 3/3
Tilsendt us, CT thorax
W: 350, C: 50
MAG: 122%

5.8:1

Viser bilder...

Brukernavn : otr, Gruppe : unrestricted_team

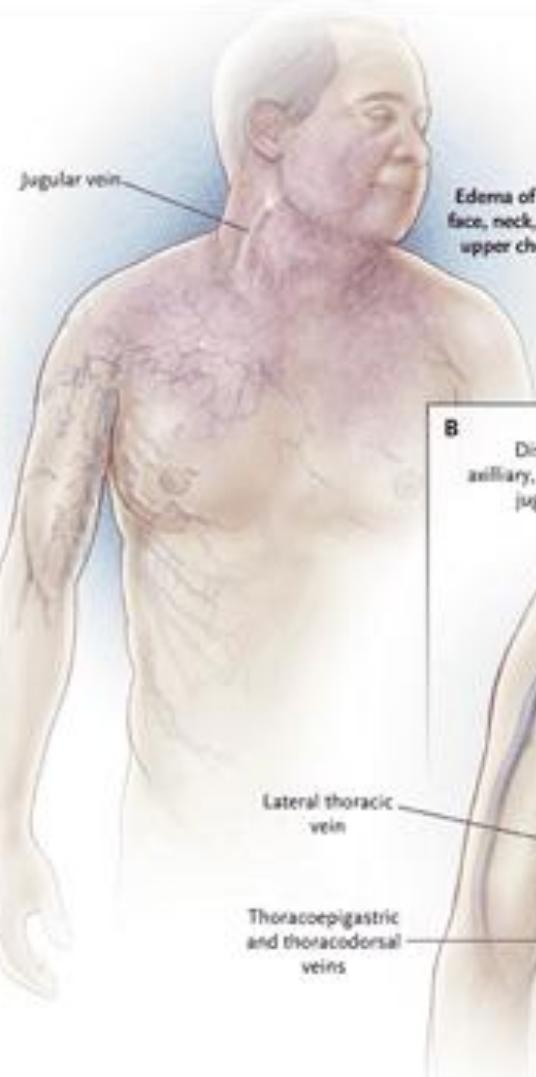


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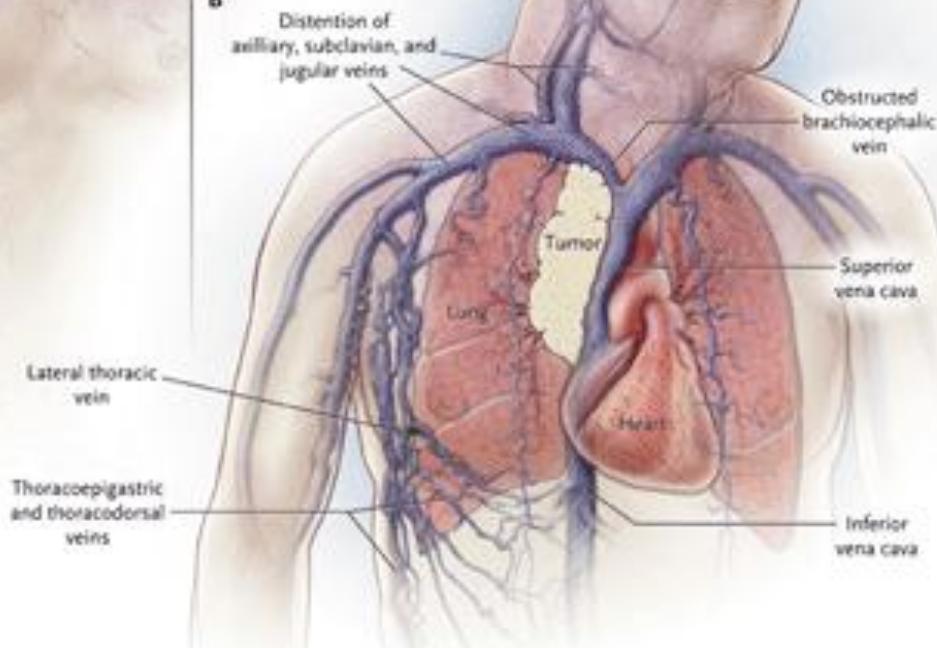
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VCSS

A



B



A



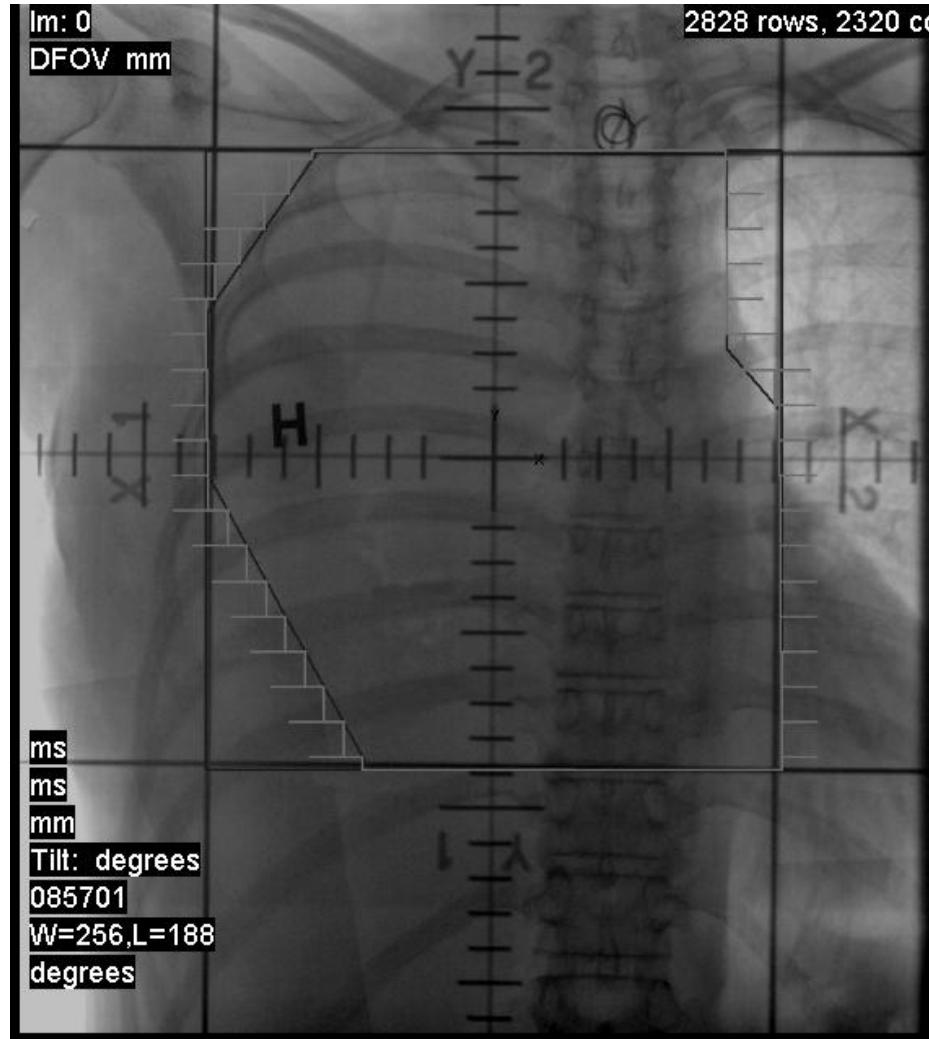
C



Kasuistikk

- Lymfom?
- Biopsi: småcella carcinom
- Først cellegift som kunne dekke begge diagnosene
- Lite effekt etter to dager, starta med strålebehandling

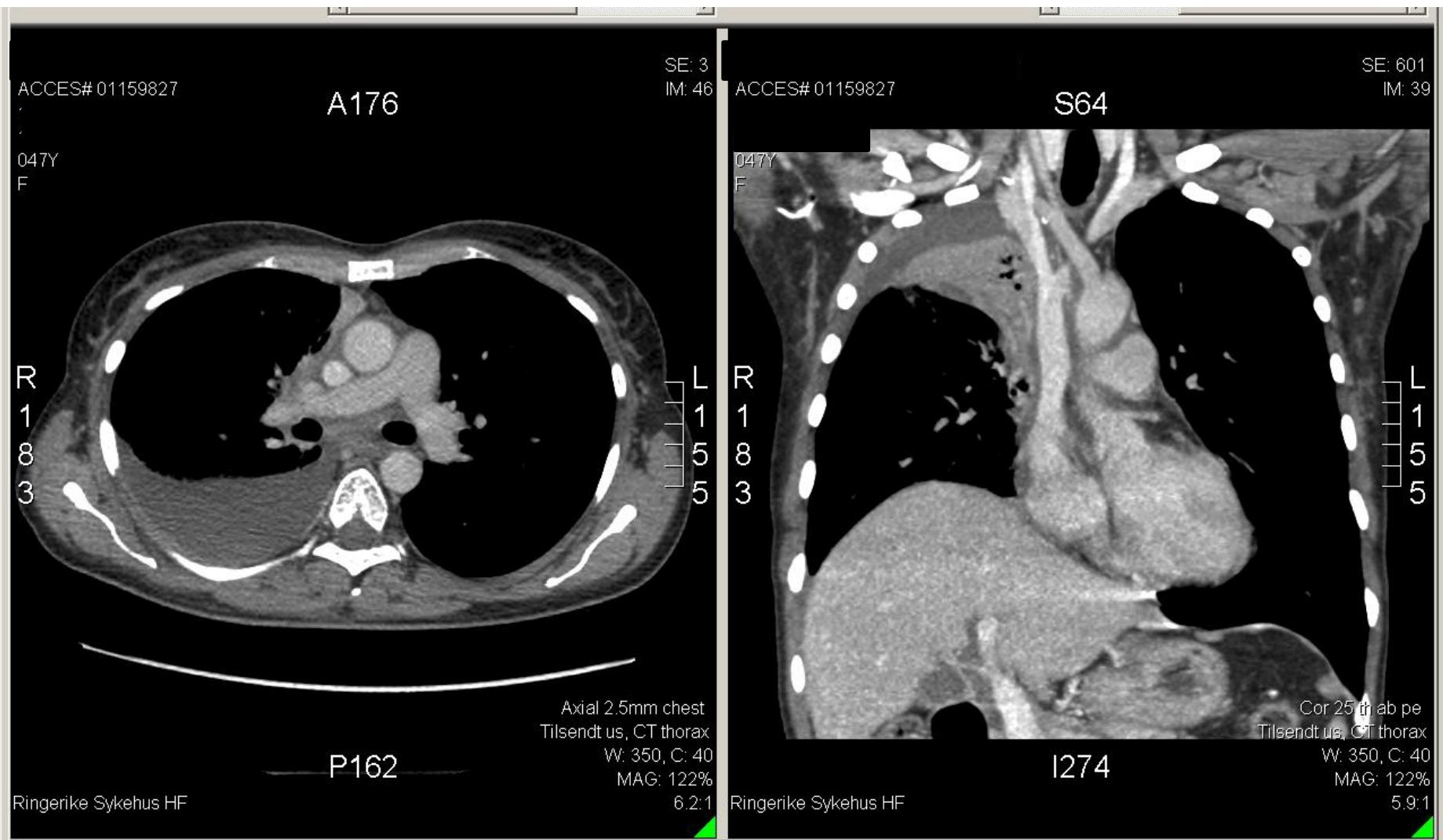
Strålefelt



Kasuistikk

- Etter 4 strålefraksjoner tydelig effekt, redusert ødem i ansikt/armer
- Tre uker strålebehandling
- Infeksjonsproblematikk
- Deretter kjemoterapi, 3 kurer, lokalt

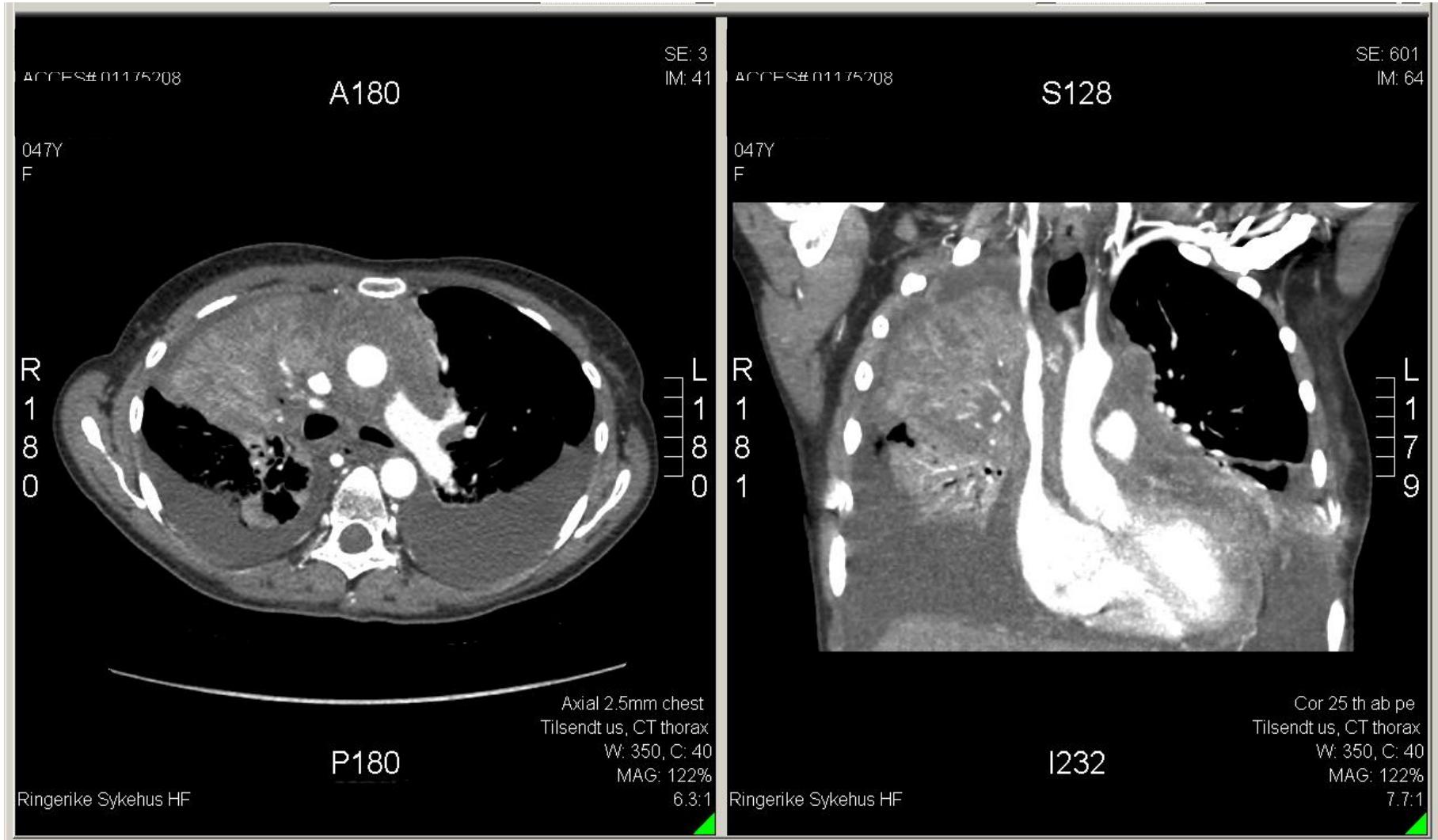
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Kasuistikk

- Fikk så profylaktisk strålebehandling mot hjerne
- Innlagt lokalsykehus i juli, økende dyspnoe, og re-vekst på rtg
- CT-bildene oversendt DNR

230708

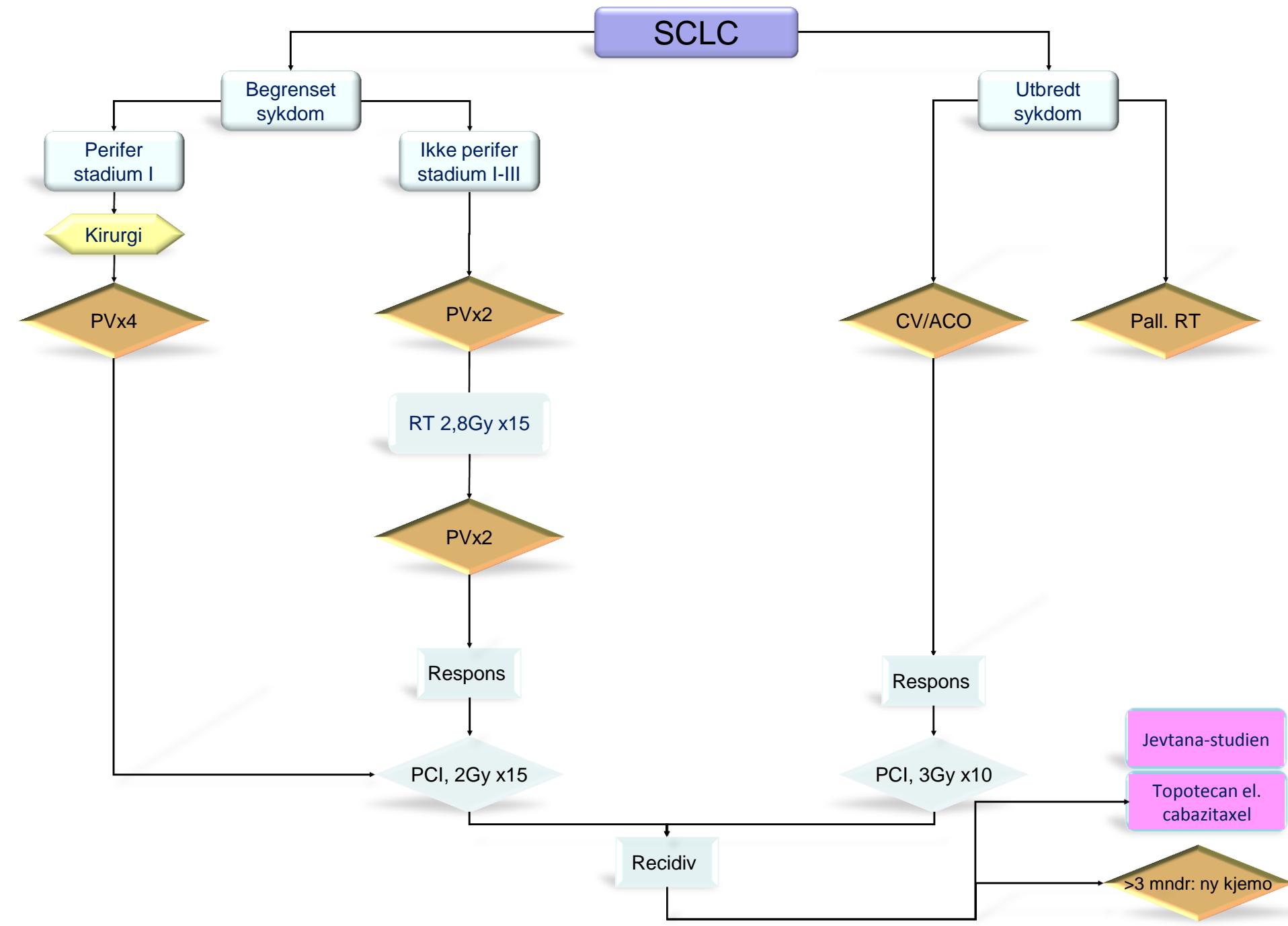


Kasuistikk

- Døde ila få dager

Inndeling av SCLC

- Begrenset sykdom:
 - median levetid 10-18 mnd
 - 5-10% lever 3 år
 - 3-5% kurert
- Utbredt sykdom
 - Median levetid 6-10 mnd
 - Langtidsoverlevere nesten ingen



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**"We've found a mass. The good news is
we have weapons of mass destruction."**

Begrenset sykdom

- T1-T2N0M0: vurdere operasjon
- 4 PV-kurer
 - Cisplatin 75mg/m² iv dag 1
 - Etoposid 100 mg/m² iv dag 1-3
- Interponert strålebehandling etter 2. kur
 - 2.8 Gy x 15
- Profylaktisk hjernebestrålning
 - 2 x Gy 15

Kjemoterapi

- Angriper celler som deler seg raskt
 - Også friske celler i rask deling
- Alvorlige bivirkninger er en kalkulert risiko

Kjemoterapi

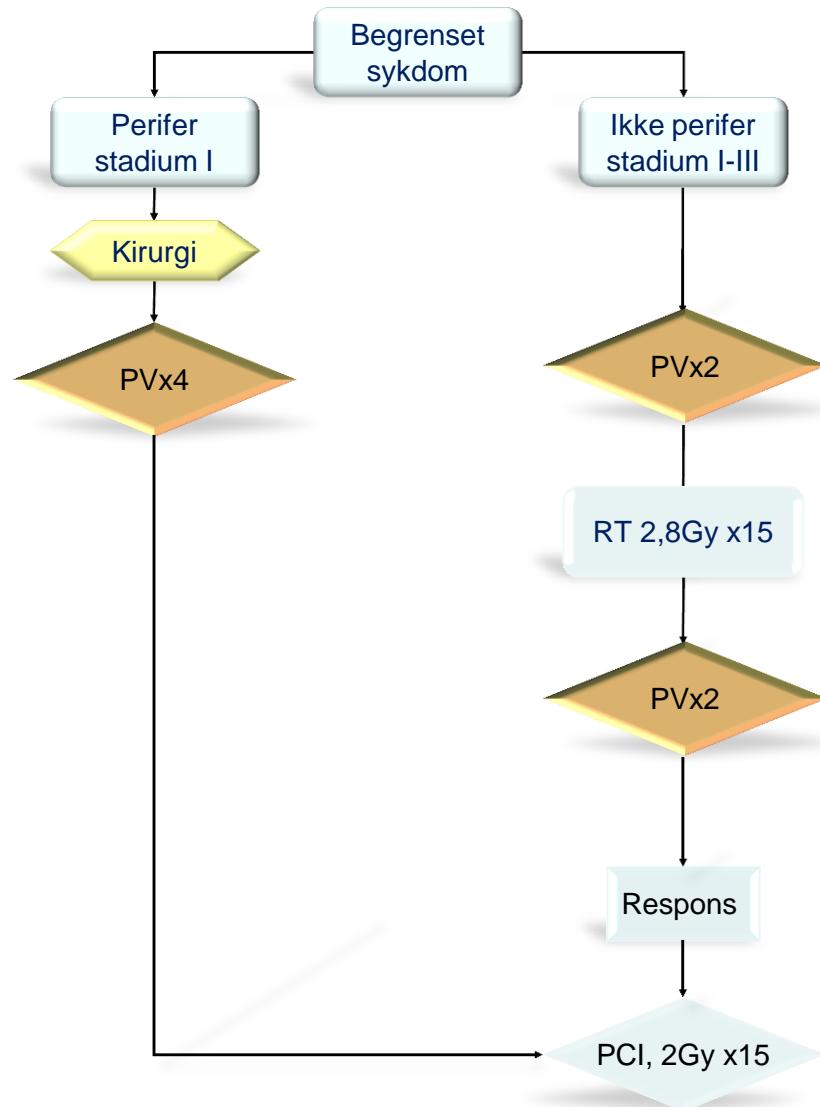
- påfører DNA-skade
- kreftceller dårligere til å reparere enn normale
- virker mest på celler med høy delingsaktivitet
 - blodceller, hårceller, tarmceller

Bivirkninger ved kjemoterapi

- kvalme/oppkast
- hårvfall
- slimhinne-/munnsårhet
- beinmargssvekkelse
- diarre/obstipasjon
- redusert nyrefunksjon
- kjønnskjertelpåvirkning
- slitenhet
- psykiske reaksjoner

Kjemoterapi ved SCLC

- "PV": cisplatin (75 mg/m² d 1) og etoposid (100mg/m² d1-3)
- "CE": carboplatin (AUC 5) og etoposid (100 mg iv d 1 og 200 mg po d 2-4)
- "ACO": adriamycin (50 mg/m²), cyclofosfamid (1000 mg/m²) og oncovin (2 mg)
- Topotecan (Hycamtin kpsl) (2,3 mg/m² d 1-5)
- Bendamustin?



TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY
IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY
WITH CISPLATIN AND ETOPOSIDE

ANDREW T. TURRISI, III, M.D., KYUNGMAN KIM, PH.D., RONALD BLUM, M.D., WILLIAM T. SAUSE, M.D.,
ROBERT B. LIVINGSTON, M.D., RITSUKO KOMAKI, M.D., HENRY WAGNER, M.D., SEENA AISNER, M.D.,
AND DAVID H. JOHNSON, M.D.

Methods We studied 417 patients with limited small-cell lung cancer. All the patients received four 21-day cycles of cisplatin plus etoposide. We randomly assigned these patients to receive a total of 45 Gy of concurrent thoracic radiotherapy, given either twice daily over a three-week period or once daily over a period of five weeks.

NEJM 1999

TABLE 1. CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO ASSIGNED TREATMENT.

CHARACTERISTIC	ONCE-DAILY RADIOThERAPY (N=206)	TWICE-DAILY RADIOThERAPY (N=211)	P VALUE
Age			0.07
Median (yr)	63	61	
Range (yr)	34–80	30–82	
≤65 yr (%)	60	69	
>65 yr (%)	40	31	
Sex (%)			0.84
Male	59	58	
Female	41	42	
Race (%)			0.97
White	90	89	
Black	7	8	
Other	3	3	
Performance status (%)			0.48
0	43	39	
1	51	55	
2	5	5	
Weight loss (%)			0.93
None	54	57	
<5%	26	24	
5–10%	15	13	
>10%	5	5	
Morphologic features (%)*			1.00
Classic	98	98	
Variant	2	2	
Disease site (%)†			
Ipsilateral lung	49	55	0.24
Mediastinum	59	62	0.62
Ipsilateral supraclavicular fossa nodes	3	5	0.47

*Data on morphology were available for 175 patients receiving once-daily radiotherapy and 181 patients receiving twice-daily radiotherapy.

†Patients could have disease in more than one site.

Conclusions Four cycles of cisplatin plus etoposide and a course of radiotherapy (45 Gy, given either once or twice daily) beginning with cycle 1 of the chemotherapy resulted in overall two- and five-year survival rates of 44 percent and 23 percent, a considerable improvement in survival rates over previous results in patients with limited small-cell lung cancer. (N Engl J Med 1999;340:265–71.)

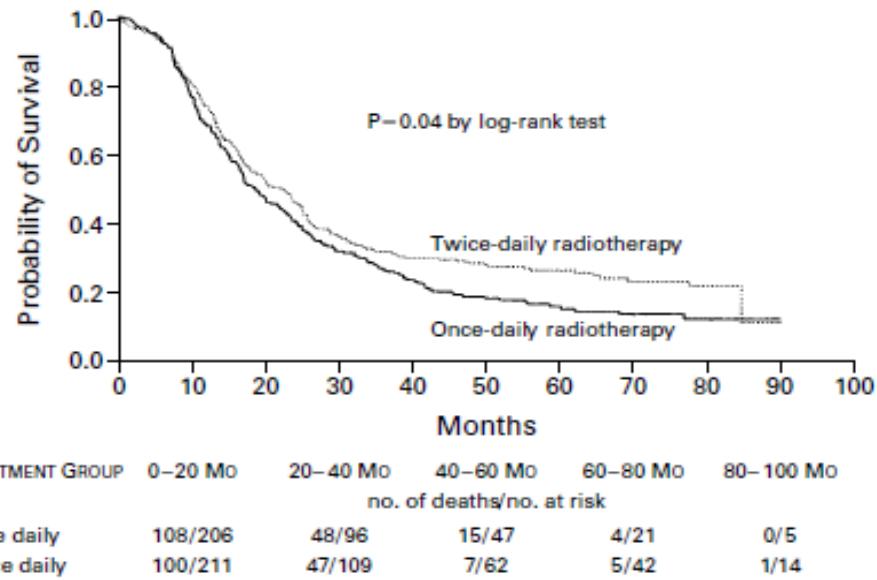


Figure 1. Kaplan-Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

NEJM 1999

HAST-studien

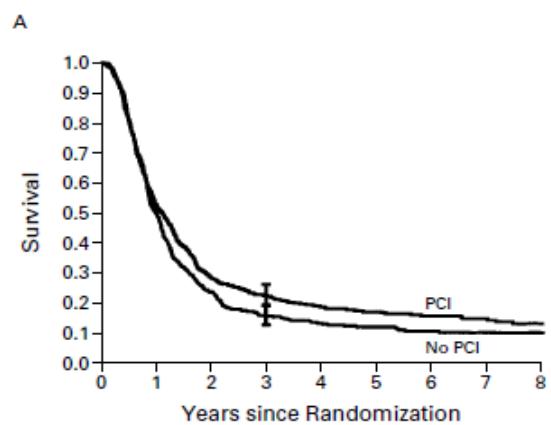
- Undersøkt om 2.8 Gy x 15 er like bra som 1.5 x 2 x 15
- Inkludert 170 pasienter i Norge
- Oppfølgingsdata underveis

Profylaktisk hjernebestråling - PCI

- 2 Gy x 15 etter avsluttet PV + strålebehandling thorax
- Innen 6 uker etter siste kur

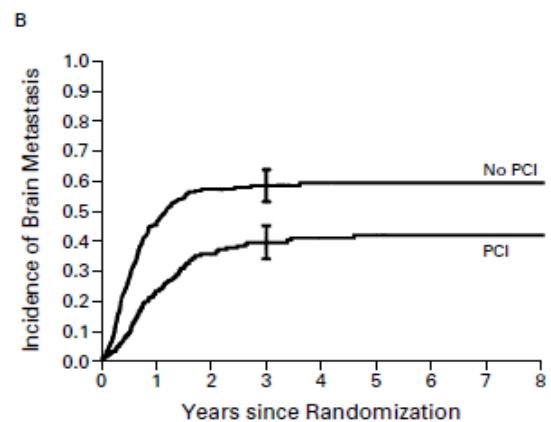
TABLE 2. CHARACTERISTICS OF THE 987 PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION.

CHARACTERISTIC	GROUP TREATED WITH PROPHYLACTIC CRANIAL IRRADIATION (N=526)	CONTROL GROUP (N=461)
Male sex — no. (%)	403 (77)	352 (76)
Age		
Median — yr	59	59
Range — yr	26–80	21–79
<55 yr — no. (%)	147 (28)	158 (34)
55–64 yr — no. (%)	250 (48)	185 (40)
≥65 yr — no. (%)	129 (25)	118 (26)
Performance status — no. (%)*		
0	212 (67)	215 (66)
1	96 (30)	105 (32)
2–3	7 (2)	6 (2)
Extensive initial disease — no. (%)†	62 (12)	78 (17)
Induction treatment with chemotherapy plus thoracic radiotherapy — no. (%)‡	314 (77)	248 (74)
Time between start of induction therapy and randomization — no. (%)§		
<4 mo	84 (27)	77 (24)
4–6 mo	127 (41)	152 (48)
>6 mo	102 (33)	91 (28)



NO. AT RISK

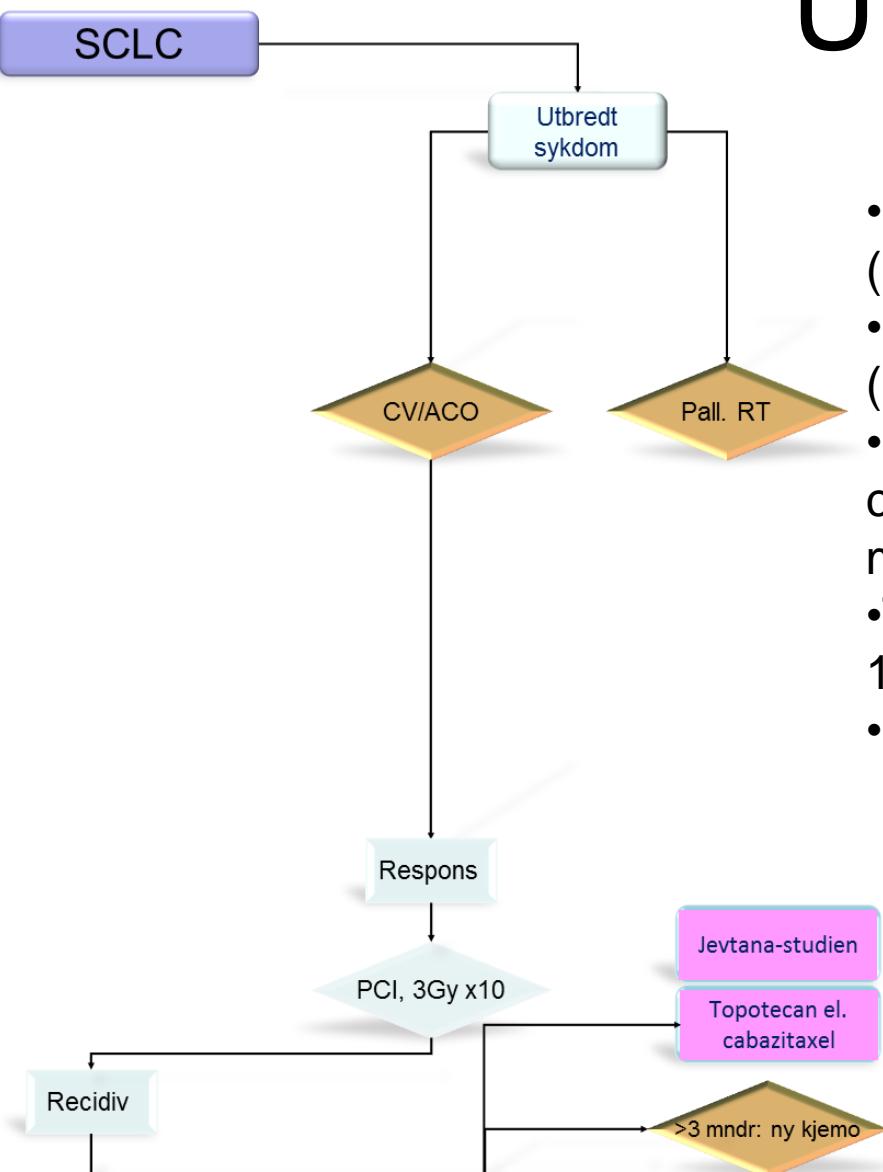
Time	No PCI	PCI
22 August 12, 1999	461	526
27	27	27
	23	40
	19	29
	15	17



NO. AT RISK

Time	No PCI	PCI
171	457	524
133	171	248
96	88	133
66	57	96
40	41	66
20	32	52
18	21	40
14	18	29
	14	17

Utbredt sykdom

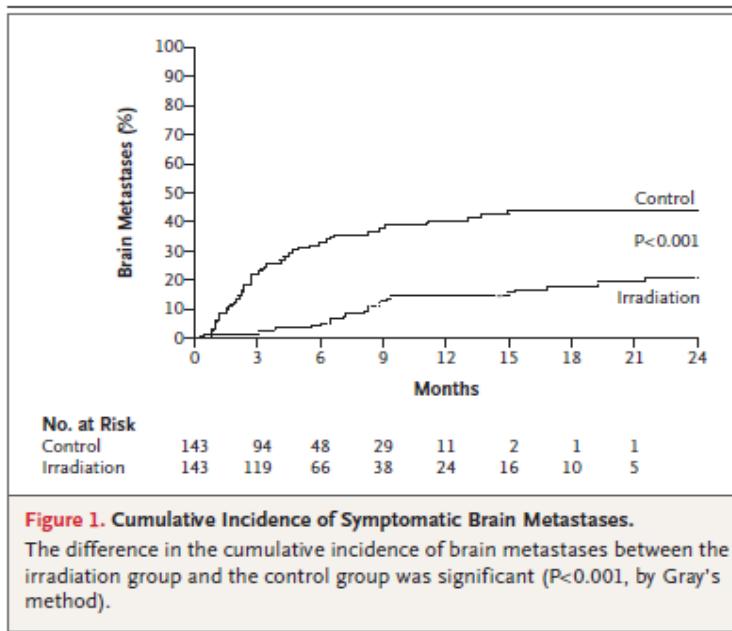


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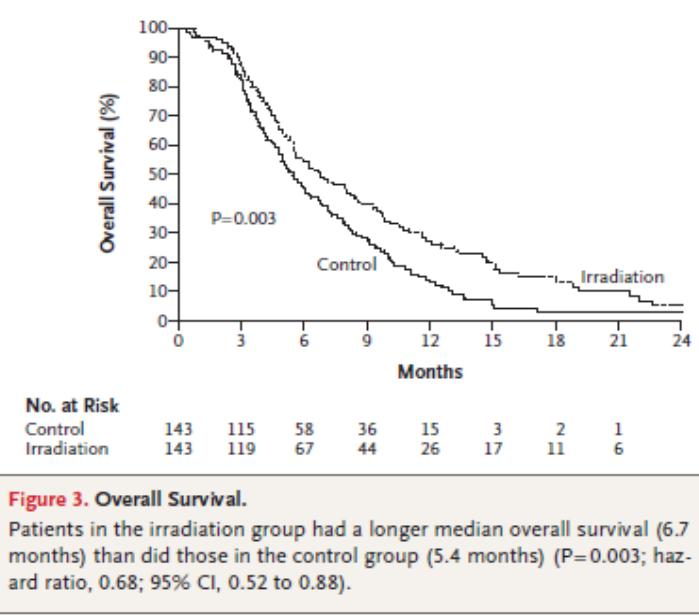
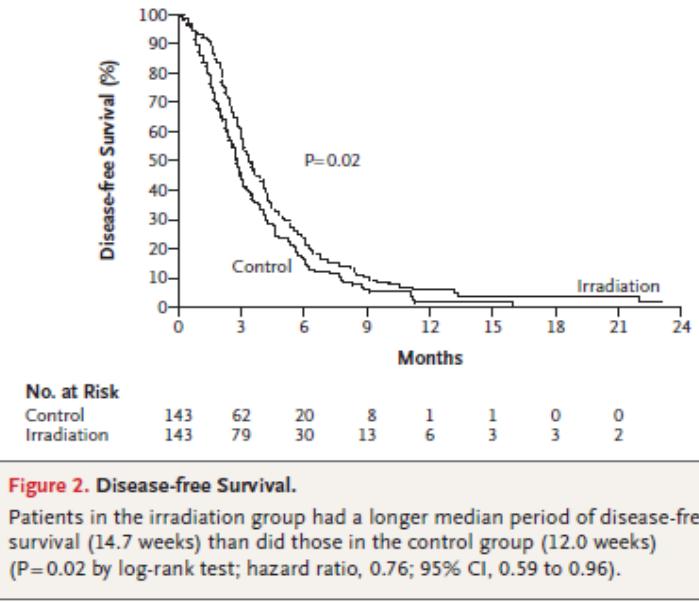
Utbredt sykdom

- Kjemoterapi
- Strålebehandling
 - PCI innen 6 uker etter siste kur
 - For symptomer / plager

PCI-utbredt sykdom

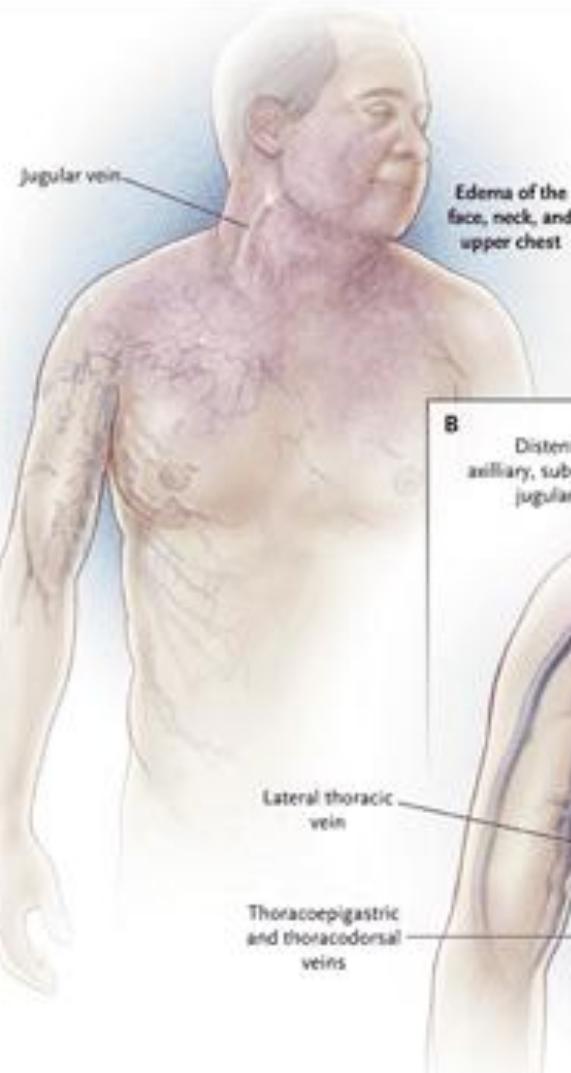
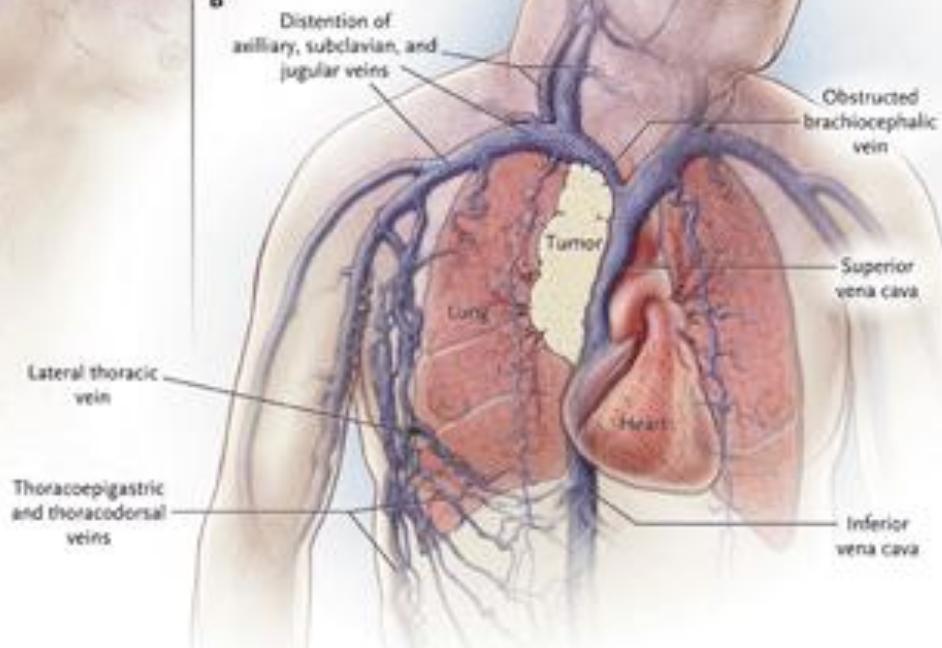


NEJM, 2007



Ø-hjelp onkologi



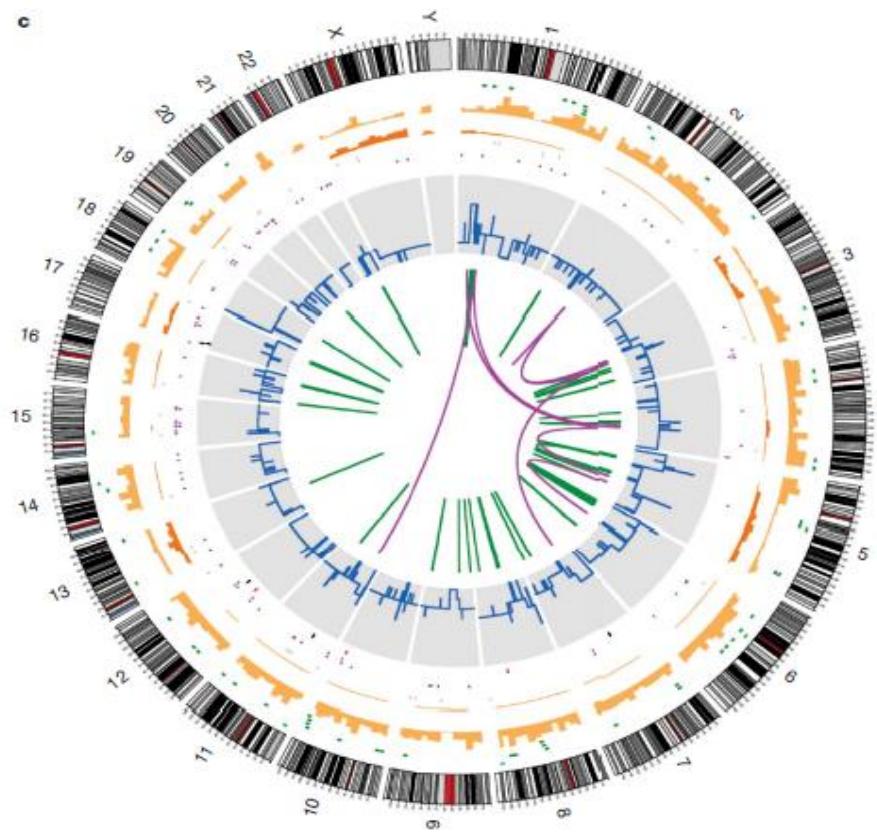
A**B****A****C**

Framtiden

- Genetisk karakterisering av kreftceller
- Identifisering av biomarkører (prediktive / prognostiske)
- Identifisering av mål for terapi (targeted therapy)
- Pasientens eget genom (farmakogenetikk)
- Miljø

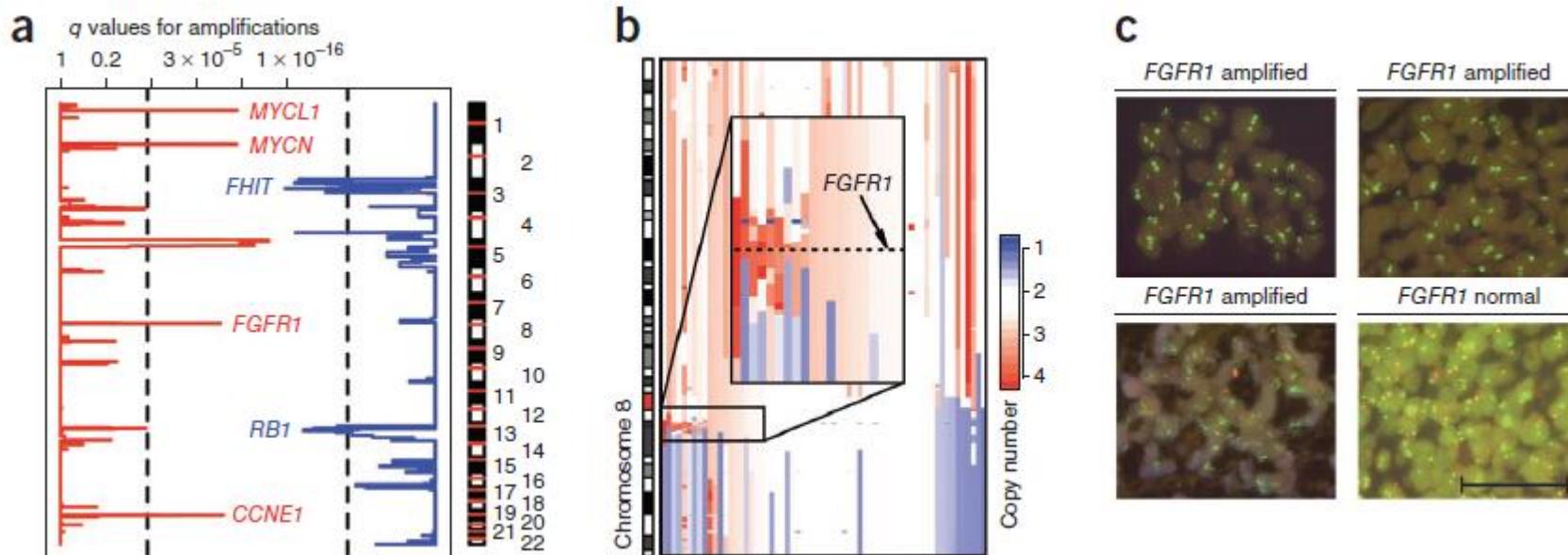
ARTICLES

A small-cell lung cancer genome with complex signatures of tobacco exposure



Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer

Martin Peifer^{1,2,57}, Lynnette Fernández-Cuesta^{1,2,57}, Martin L Sos^{1–4}, Julie George^{1,2}, Danila Seidel^{1,2,5}, Lawryn H Kasper⁶, Dennis Plenker^{1,2}, Frauke Leenders^{1,2,5}, Ruping Sun⁷, Thomas Zander^{1–4}, Roopika Menon⁸, Miriam Koker^{1,2}, Ilona Dahmen^{1,2}, Christian Müller^{1,2}, Vincenzo Di Cerbo⁹, Hans-Ulrich Schildhaus¹⁰.



exomes, 2 genomes and 15 transcriptomes and found an extremely high mutation rate of 7.4 ± 1 protein-changing mutations per million base pairs. Therefore, we conducted

adenocarcinoma^{7–16} and in squamous cell lung carcinoma^{17–19}. By contrast, little is known about the molecular events causing SCLC beyond the high prevalence of mutations in *TP53* and *RBI* (ref. 3).