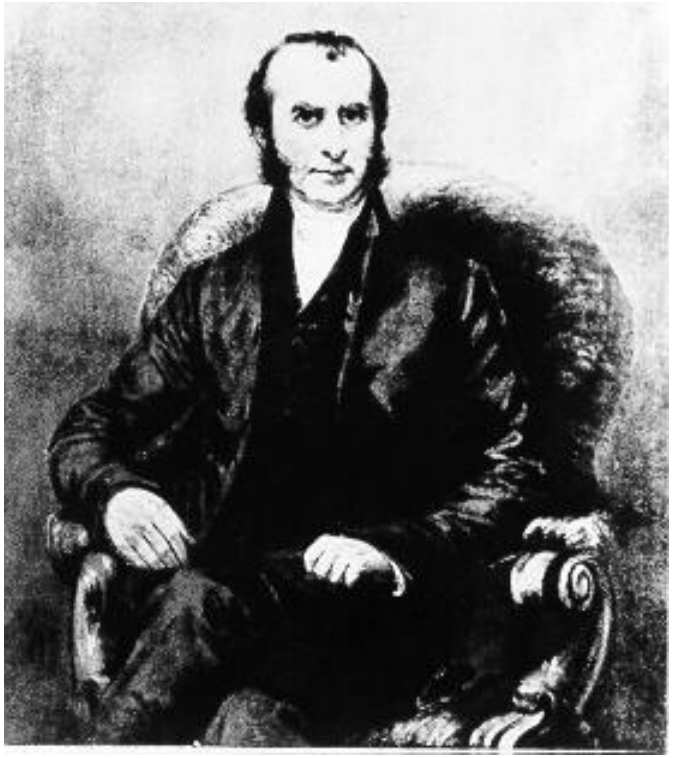
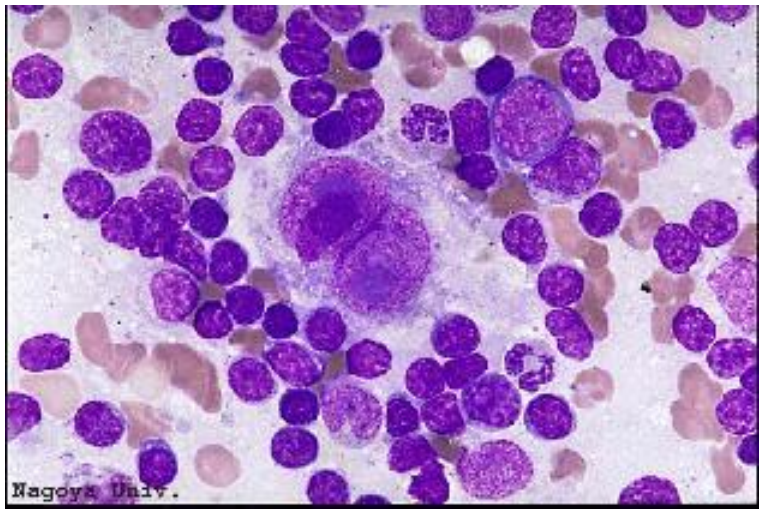
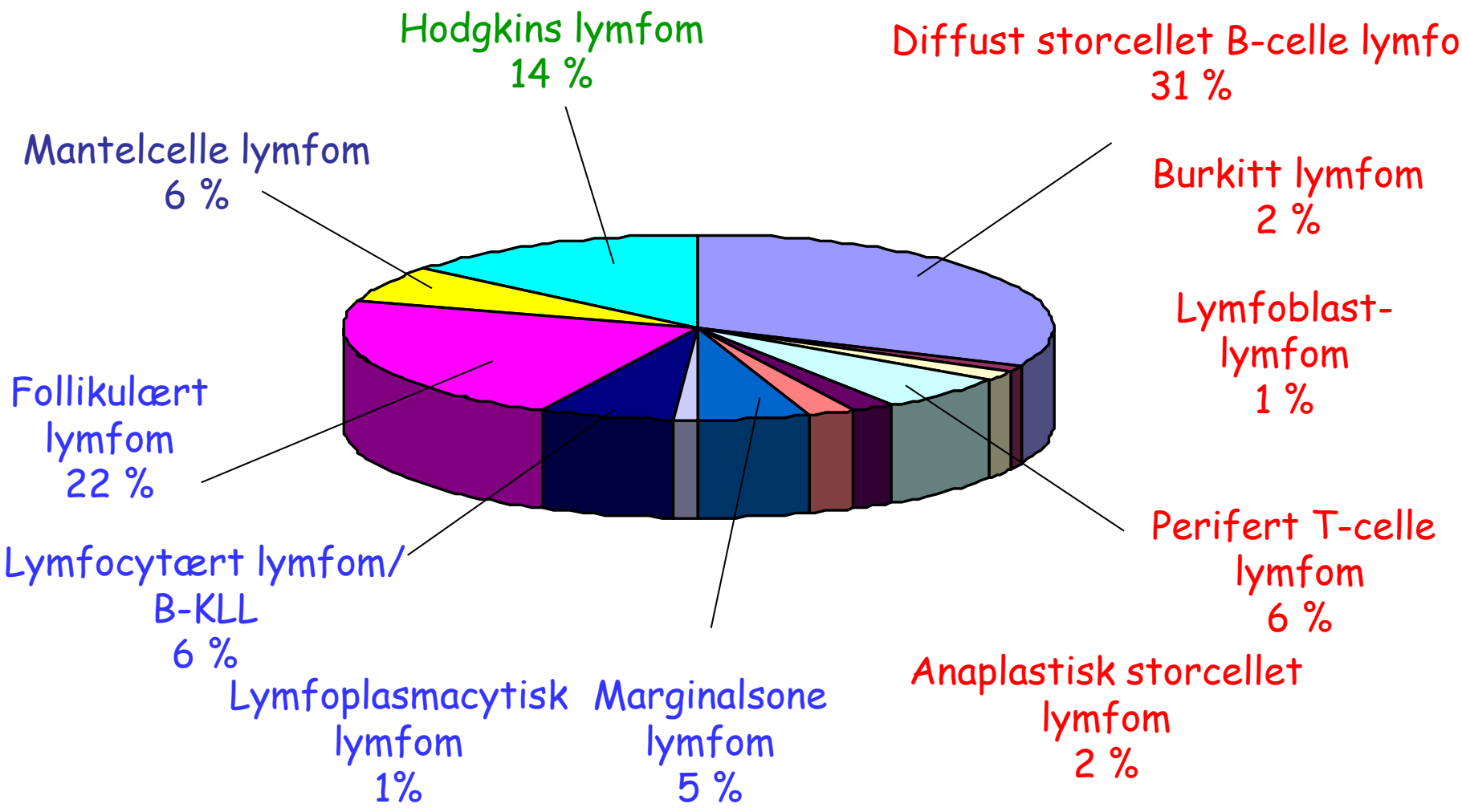
Behandling av Hodgkins lymfom hos voksne

Alexander Fosså
Radiumhospitalet

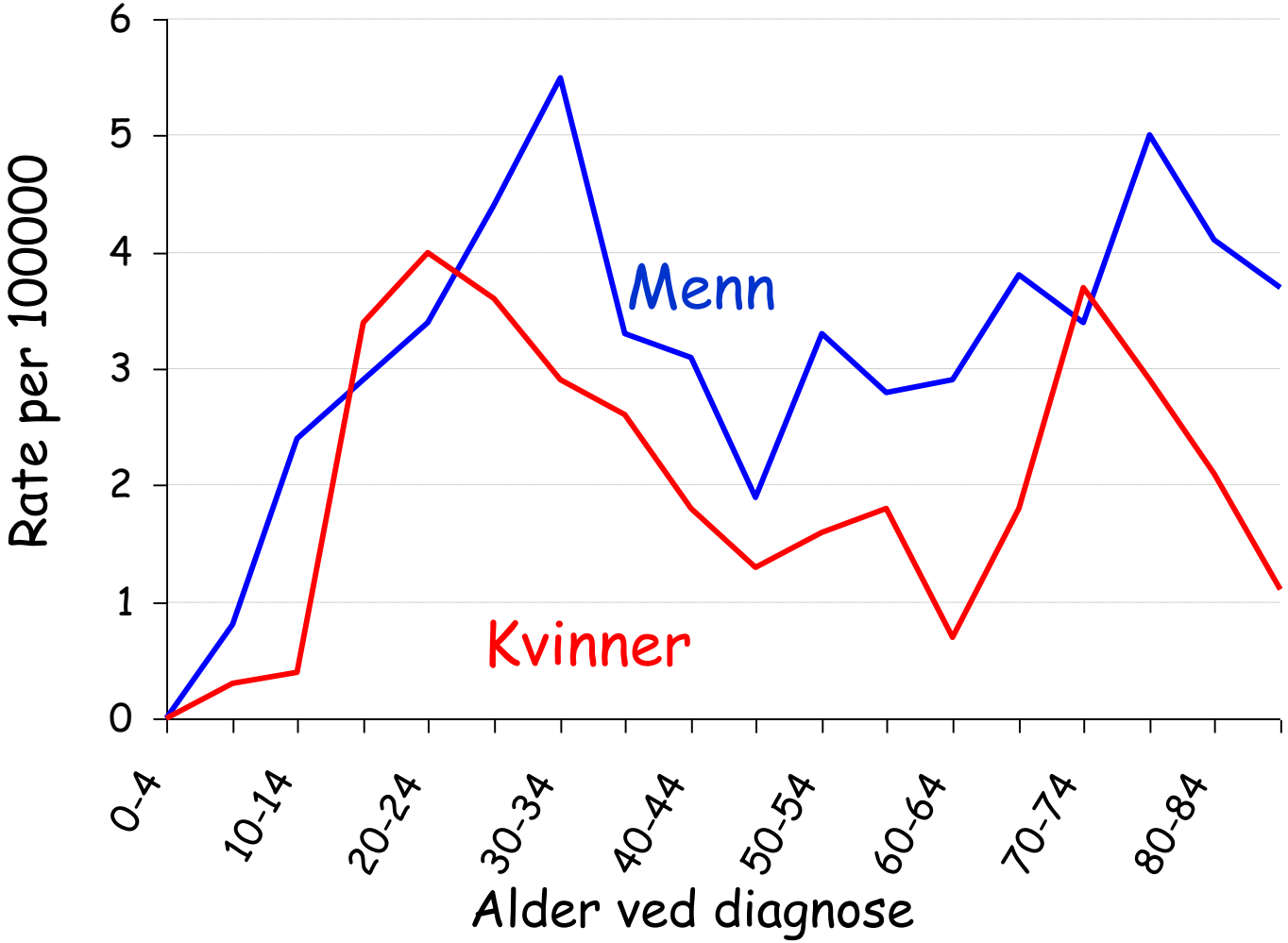




WHO for dummies…

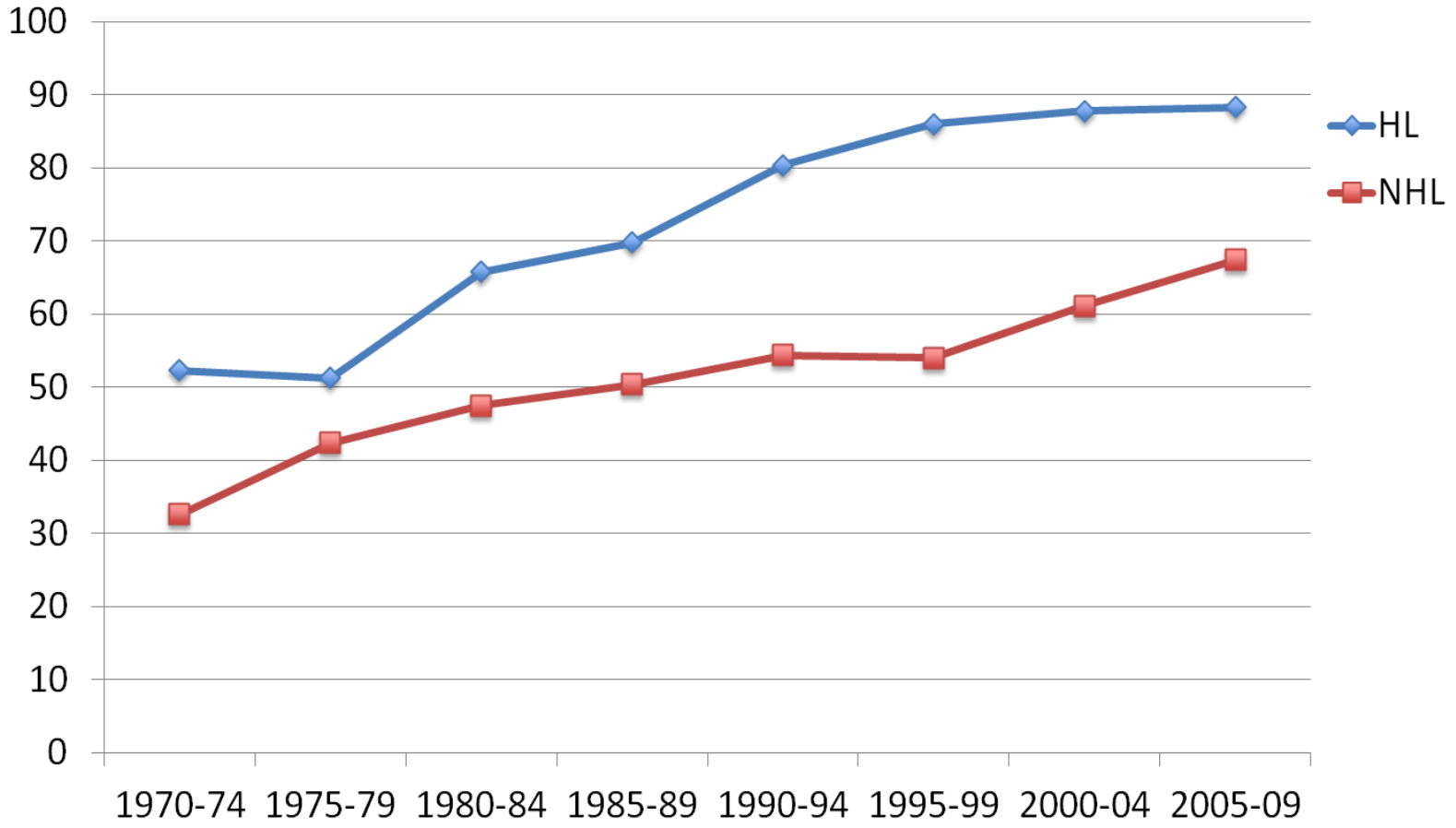


Aldersspesifikk insidensrate 2005-2009
Hodgkins lymfom



Kreftregisteret, 2009

5-års relativ overlevelse lymfom



Cancer in Norway 2009, Norwegian Cancer Registry

Insidens og prevalens av lymfom i Norge (Cancer in Norway 2010)

Hodgkin lymfom

- Insidens: 130
  - Menn: 76
  - Kvinner: 54
- Prevalens: 2216
- 5-års relativ overlevelse (2005-09): 89 %

Non-Hodgkin lymfom

- Insidens: 964
  - Menn: 547
  - Kvinner: 417
- Prevalens: 7079
- 5-års relativ overlevelse (2005-09): 68 %

Cancer in Norway 2010, Norwegian Cancer Registry

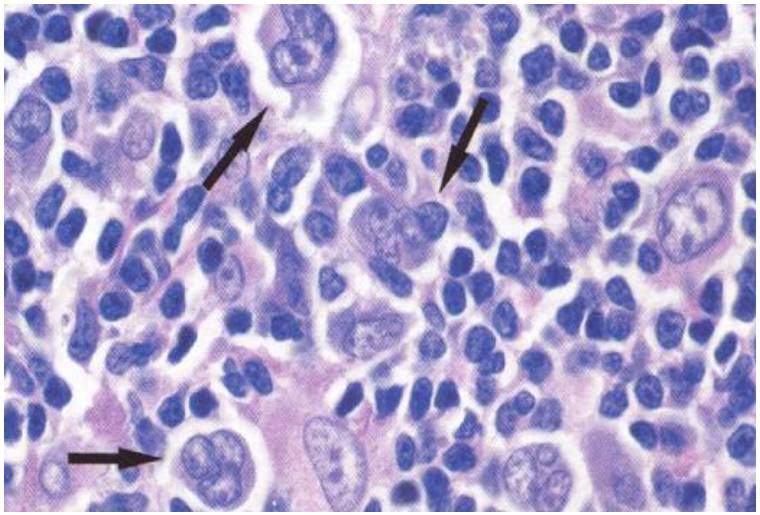
Hodgkins lymfom Histologi

WHO klassifikasjonen

- Klassisk Hodgkins lymfom (95%)
  - nodulær sklerose (45%)
  - blandingstype (40%)
  - lymfocyttfattig (5%)
  - lymfocyttrik (5%)
- Nodulær lymfocyttrik type (NLPHL) (nodulært paragranulom) (5%)

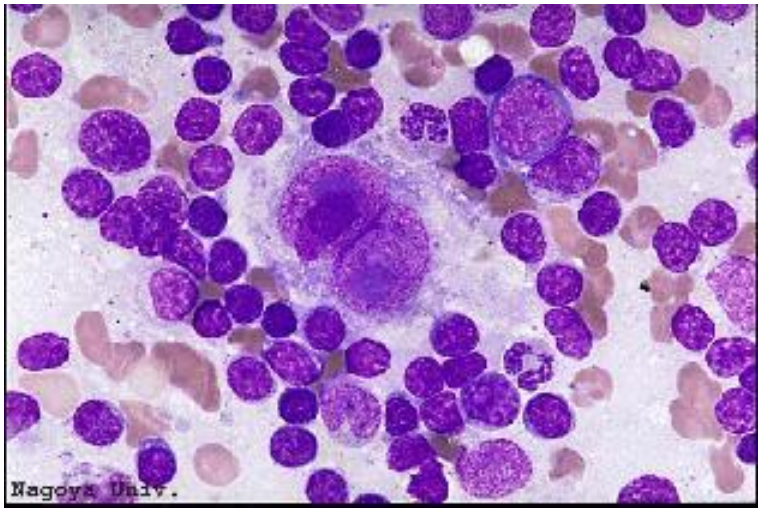
Hodgkins lymfom
-en malign B-celle sykdom

Nodulært lymfocyttrikt HL



Lymphocytic/histiocytic cells (L&H celler; popcorn celler)

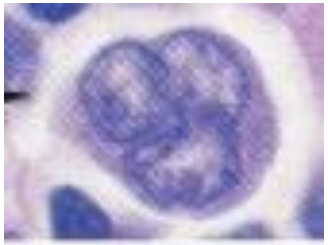
Klassisk HL



Hodgkin celler (HC)
Reed-Sternberg celler (RSC)

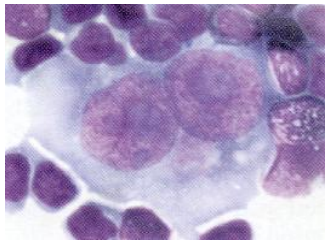
Hodgkins lymfom
-en malign sykdom

L&H celler



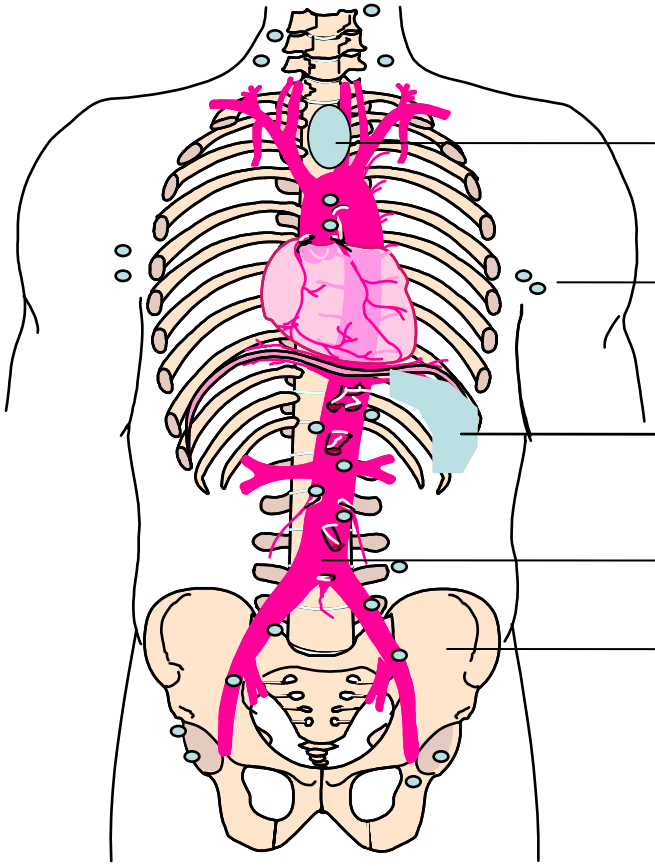
B-celle genotype
Monoklonale
Delvis bevart B-celle fenotype
CD20, CD79a, Pax5
Oct2, BOB.1
Kan være Ig+
Mangler ~~CD~~30 og ~~C~~D15

RS celler



B-celle genotype (>98%)
Monoklonale
Mistet B-celle fenotype
~~CD~~20, ~~CD~~79a, Pax5
~~O~~t2, ~~BO~~B.1
Kan være Ig+
Ekspresjon av **CD30** og CD15 (>85%)
Opphav i germinalcenter celle
Apoptosedefekt? (NFκB, IκB, IκBK, TRAF1, LMP1, EBV)

Lokalisasjon oftest i nodal



thymus

lymfeknuter

milt

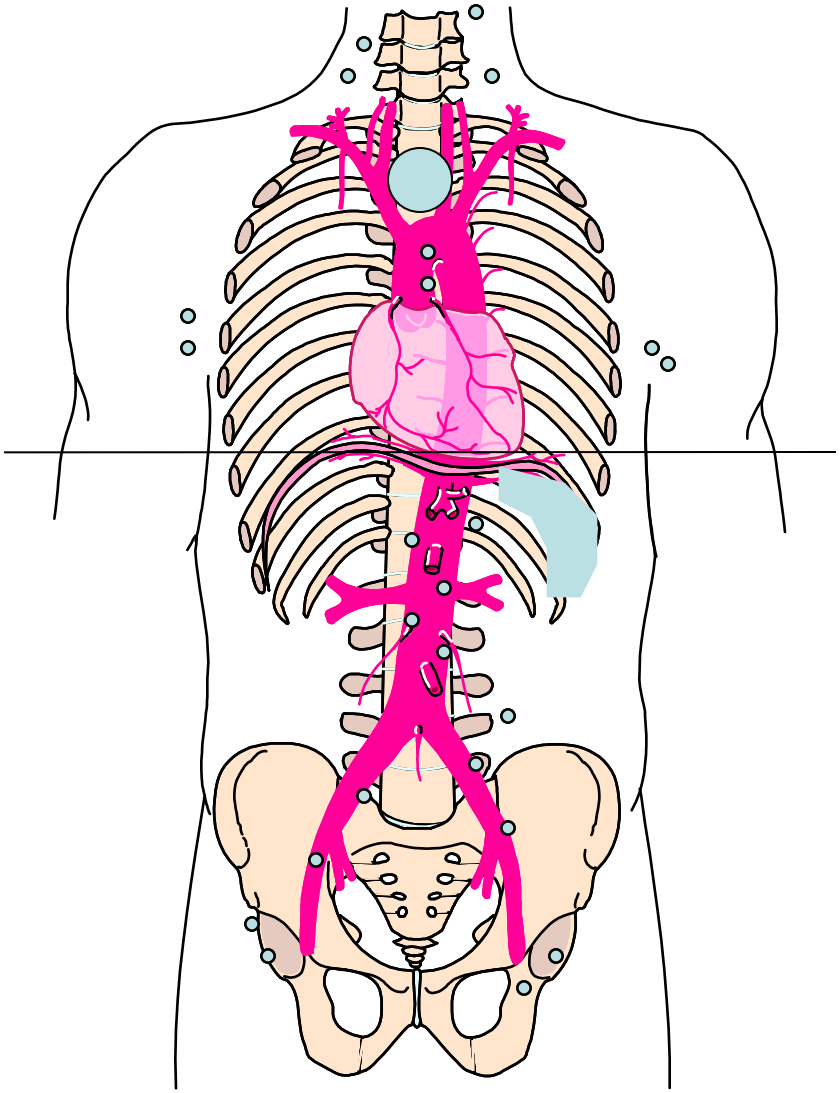
blod

benmarg

men også ekstranodal affeksjon i
andre organer ved generalisering

Modifisert fra G. F. Lauritzsen

Stadieinndeling lymfomer – Ann Arbor



I: Én enkelt lymfeknuteregion

II: To eller flere lymfeknute-regioner på samme side av mellomgulvet

III: Lymfeknuteregioner på begge sider av mellomgulvet

IV: Sykdom i et eller flere andre organer med eller uten lymfeknutesvulst

P_E = Primært ekstranodalt

E = Ekstensjon

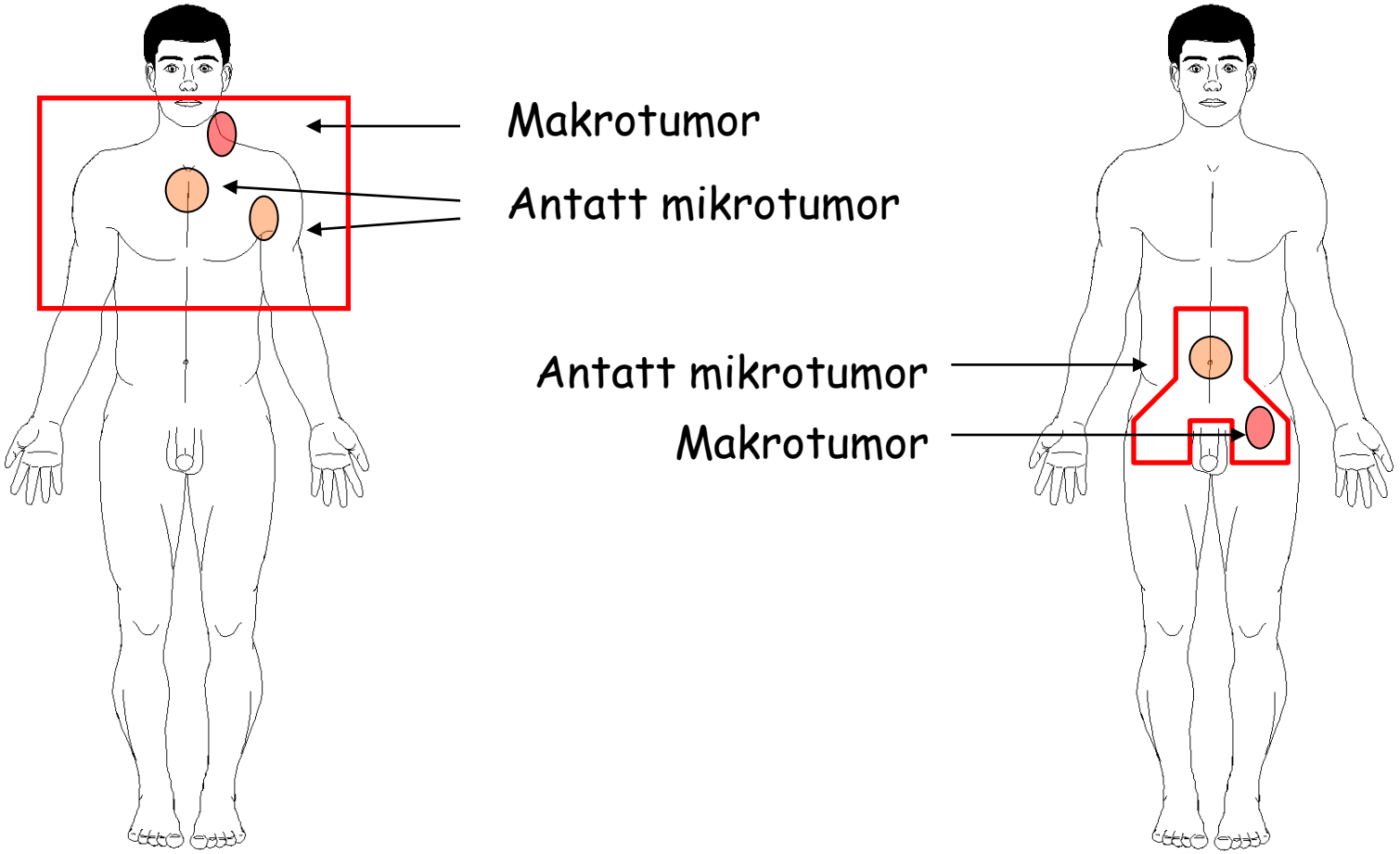
B: Vekttap > 10% på 6 mnd., feber, nattesvette

G. F. Lauritzsen

Hodgkins lymfom strålebehandling

- Henry S. Kaplan var blant de første som benyttet seg av "linacbestråling" og gikk videre med utprøving ved bruk store felt (1956-)
- Study L1: Stadium I og II, randomisering mellom: involved field (40 Gy) og extended field (40 Gy)
- Extended field strålebehandling ble standard for stadium I og II etter disse studiene

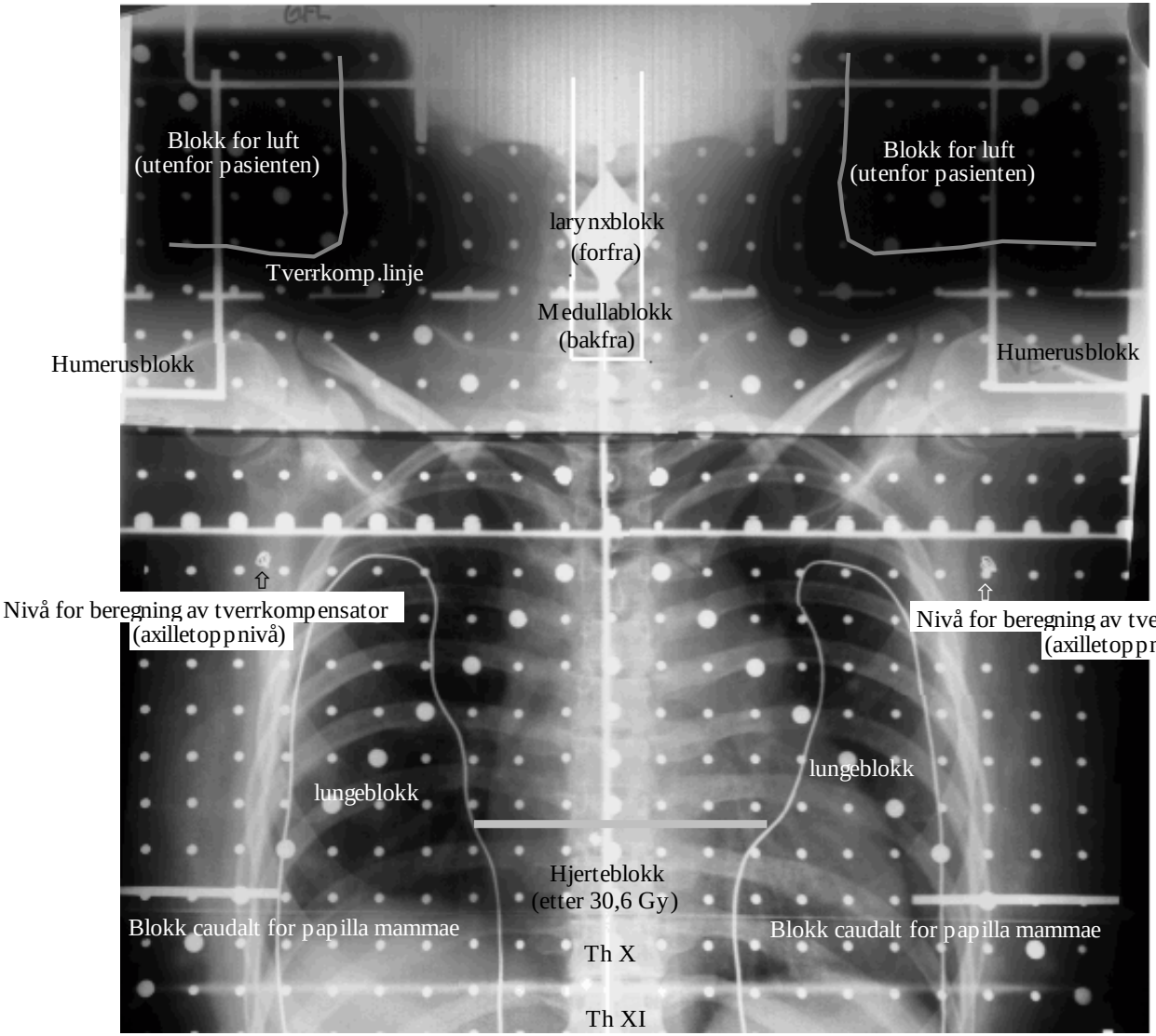
Hodgkin og strålebehandling
Extended field



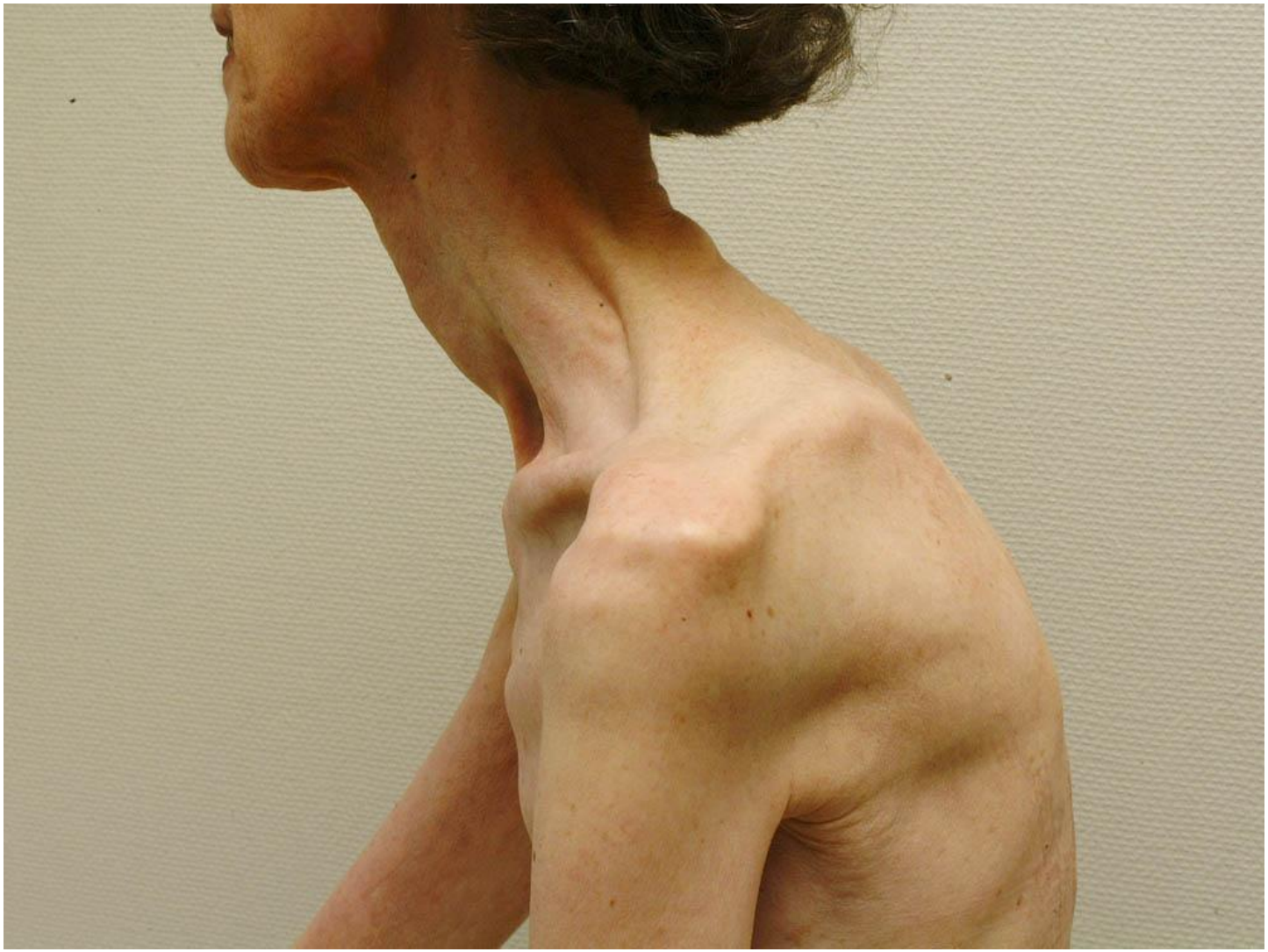
Kappefelt

Omvendt Y-felt

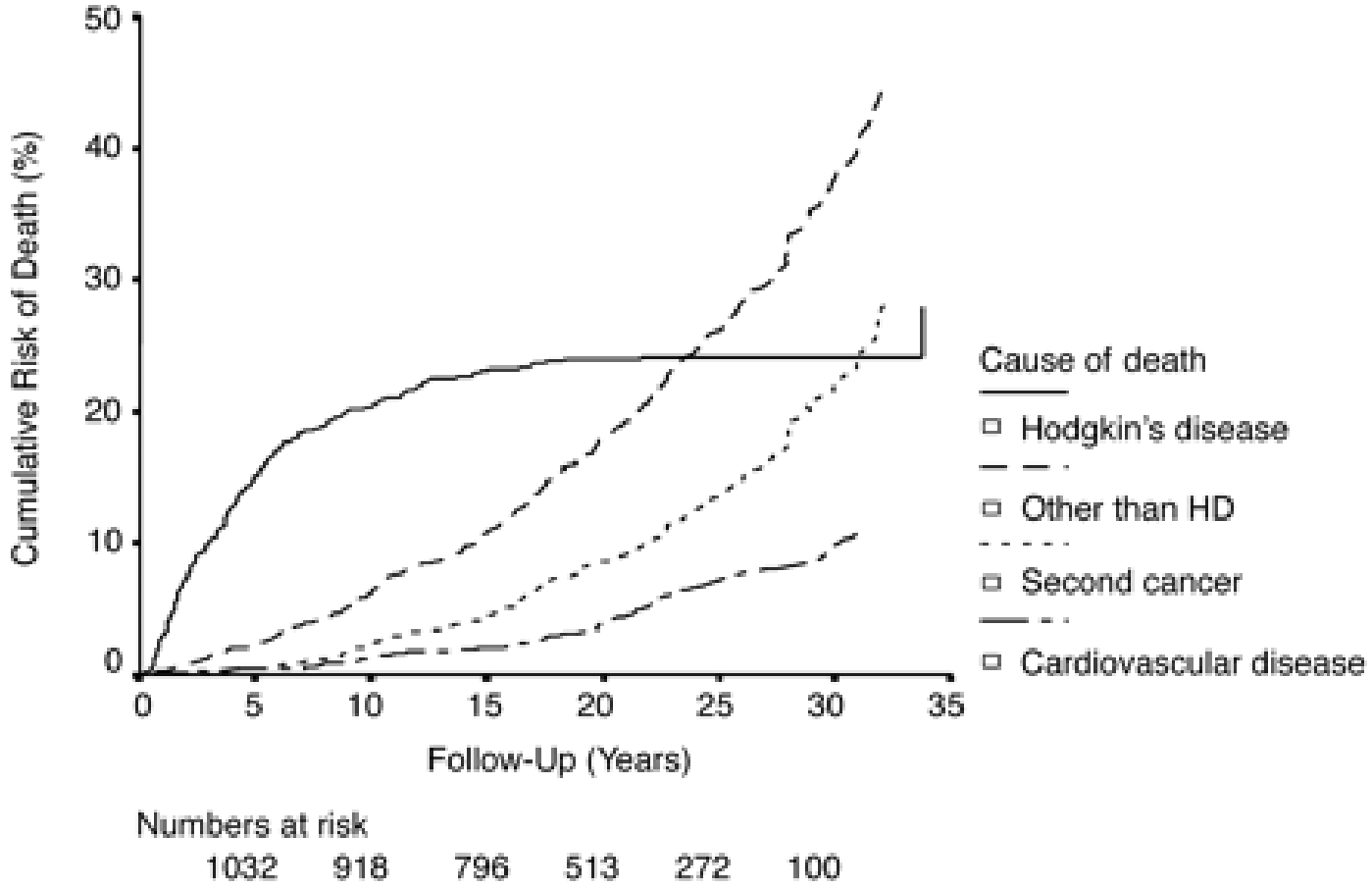
Kappefelt


Blokk for luft
(utenfor pasienten)
Blokk for luft
(utenfor pasienten)
larynxblokk
(forfra)
Tverrkomp.linje
Medullablokk
(bakfra)
Humerusblokk
Humerusblokk
Nivå for beregning av tverrkompensator
(axilletoppnivå)
Nivå for beregning av tverrkompensator
(axilletoppnivå)
lungeblokk
lungeblokk
Hjerteblokk
(etter 30,6 Gy)
Blokk caudalt for papilla mammae
Blokk caudalt for papilla mammae
Th X
Th XI

Muskelatrofi etter kappefelt



Mortalitet etter Hodgkins lymfom



Aleman *et al*, 2003

Behandlingsgrupper (≥ 18år)

Risikogruppe	Stadium	Risikofaktorer
Tidlig	IA-IIA	Ingen *
Intermediær	IA-IIA	Minst én *
Avansert	IIB-IV	<4 &
	IIB-IV	≥4 &

* Nordisk studie fra 1999

& International prognostic score

Stadium IA og IIA
Nordisk protokoll

- Aktivert 1999
- Pasienter uten eller med risikofaktorer
- risikoadaptert kjemoterapi
  - Uten RF: 2 ABVD
  - Med RF: 4 ABVD
- reduksjon av strålebehandlingen
  - Uten RF: modifisert involved field 2 Gy x 10
  - /med RF: modifisert involved field 1,75 Gy x 17

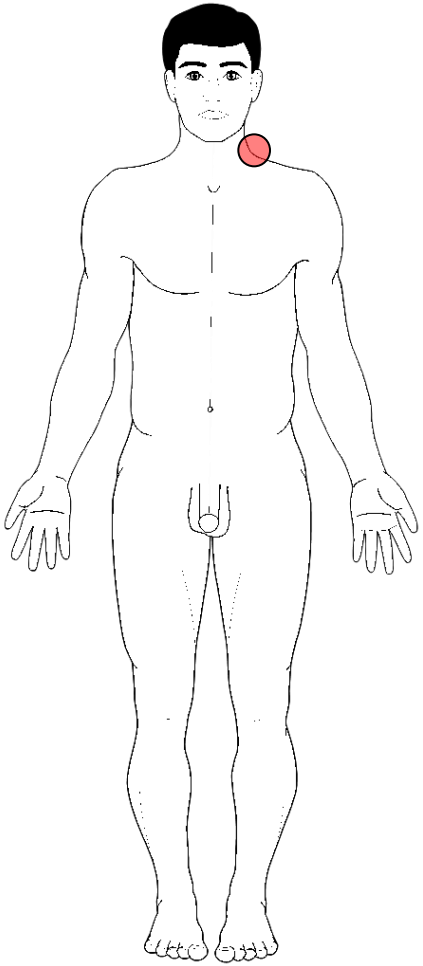
Prognostiske faktorer Hodgkins lymfom I-IIA

Begrenset sykdom (stadium I-IIA)

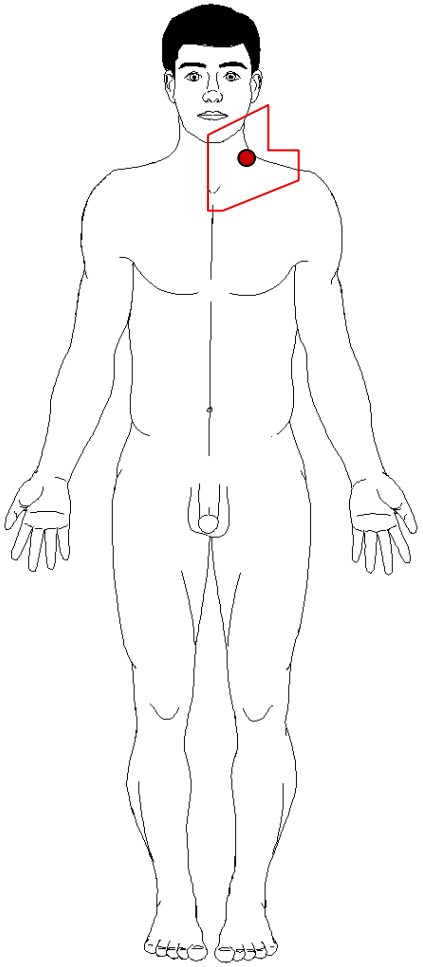
Basert på data fra flere grupper er bl.a. følgende **risikofaktorer** av prognostisk ugunstig betydning

- SR > 50
- > 2 lymfeknutestasjoner involvert
- 2 ikke naboregioner involvert
- Sykdom under diafragma (med unntak av ensidig lyskeaffeksjon)
- Bulky sykdom ≥ 10 cm

Hodgkins lymfom – tidlig og intermediær stadium I-IIA

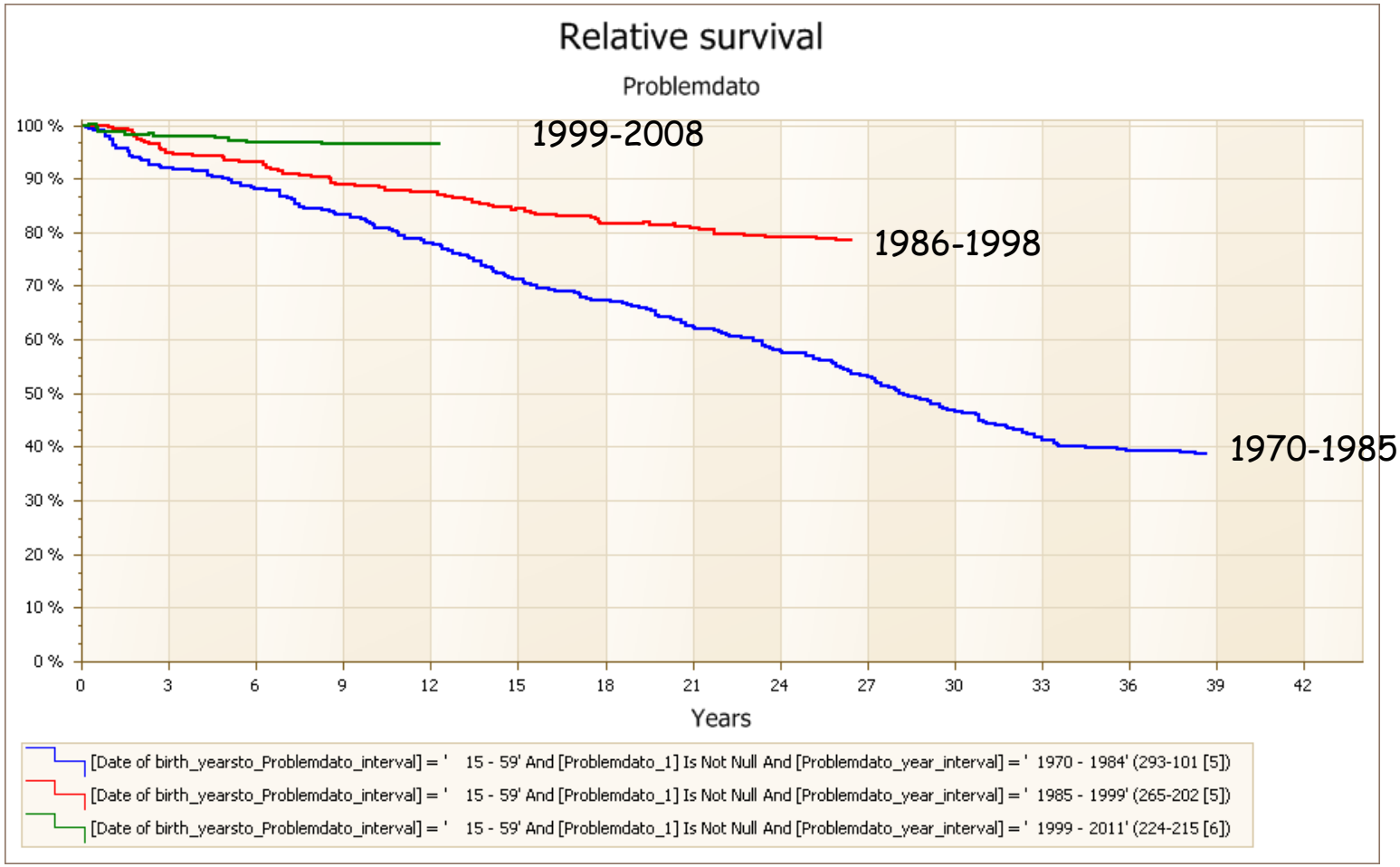


2-4 ABVD mot makro- og mikroskopisk sykdom

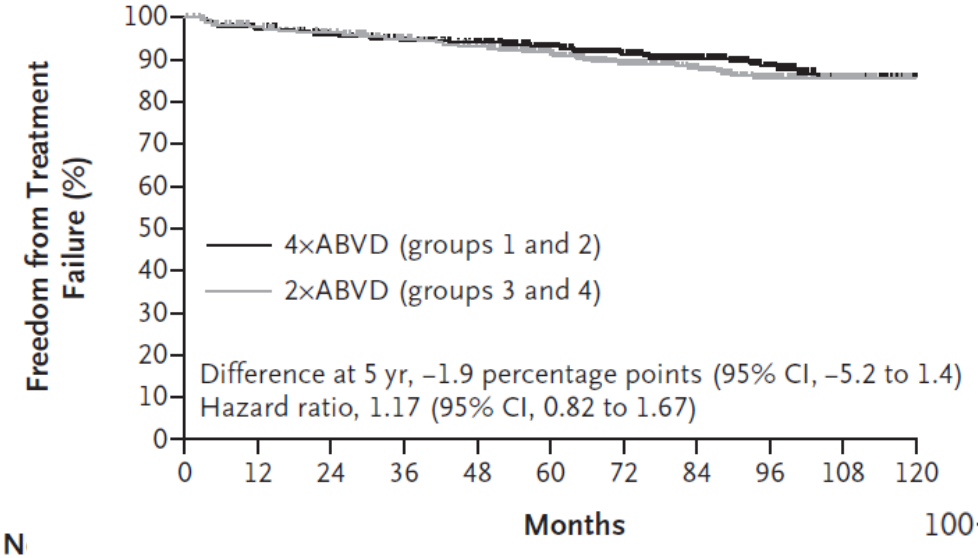


Modifisert IF radioterapi
2 Gy x 10
1,75 Gy x 17
mot makrotumor

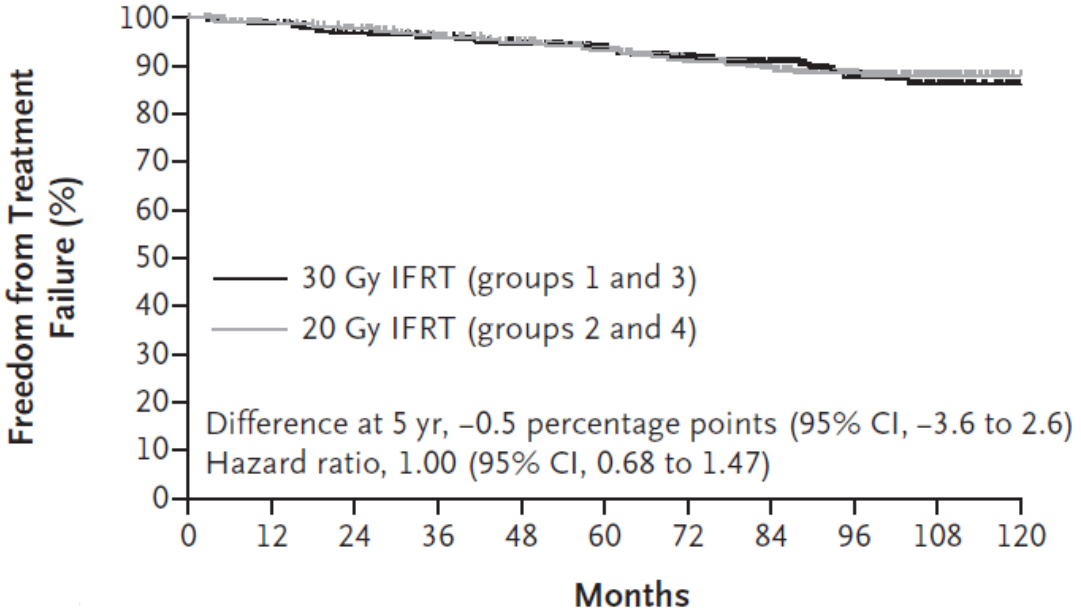
Totaloverlevelse Hodgkin lymfom stadium I-IIA, 18-60 år, gruppert etter diagnoseår



Hodgkins lymfom – stadium I-IIA uten risikofaktorer

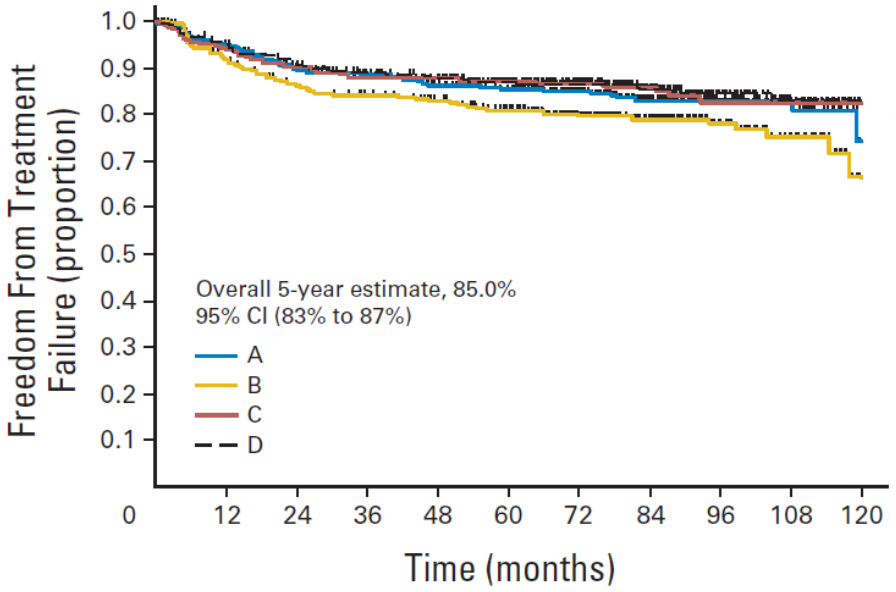


N



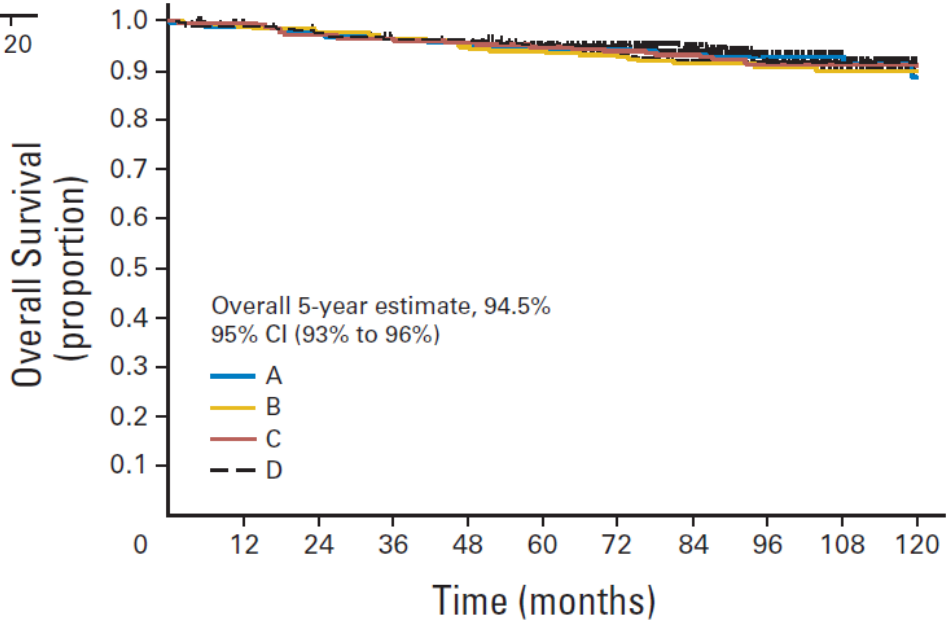
Engert et al, 2010

Hodgkins lymfom – stadium I-IIA med risikofaktorer



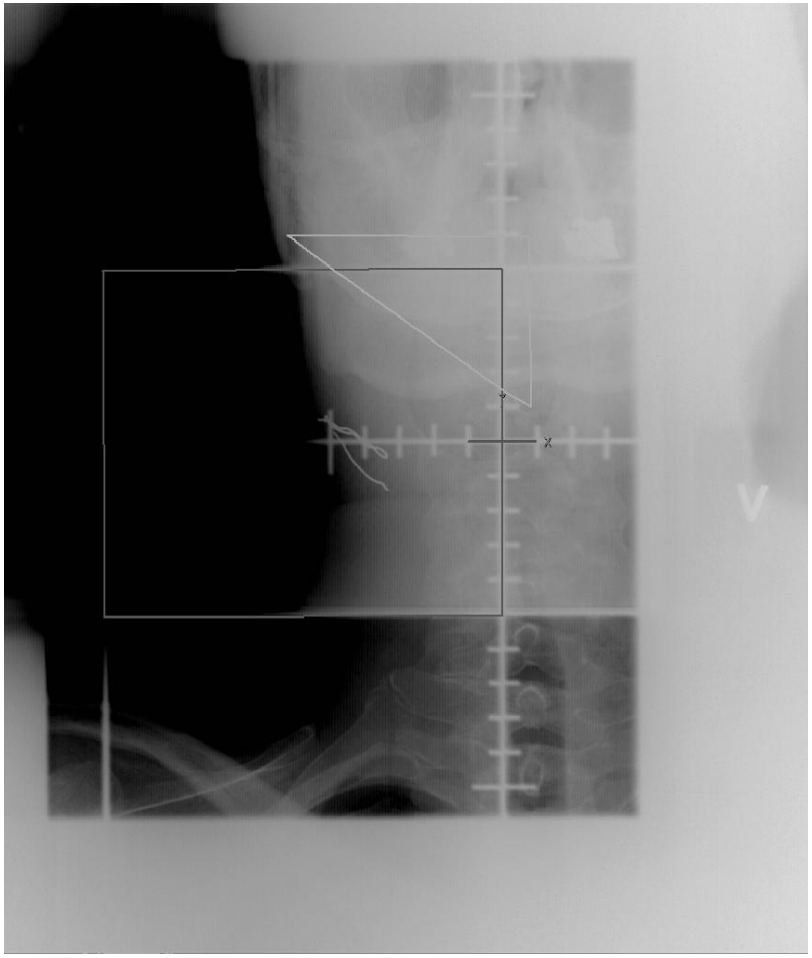
4 ABVD x IF 30 Gy

4 ABVD x IF 20 Gy

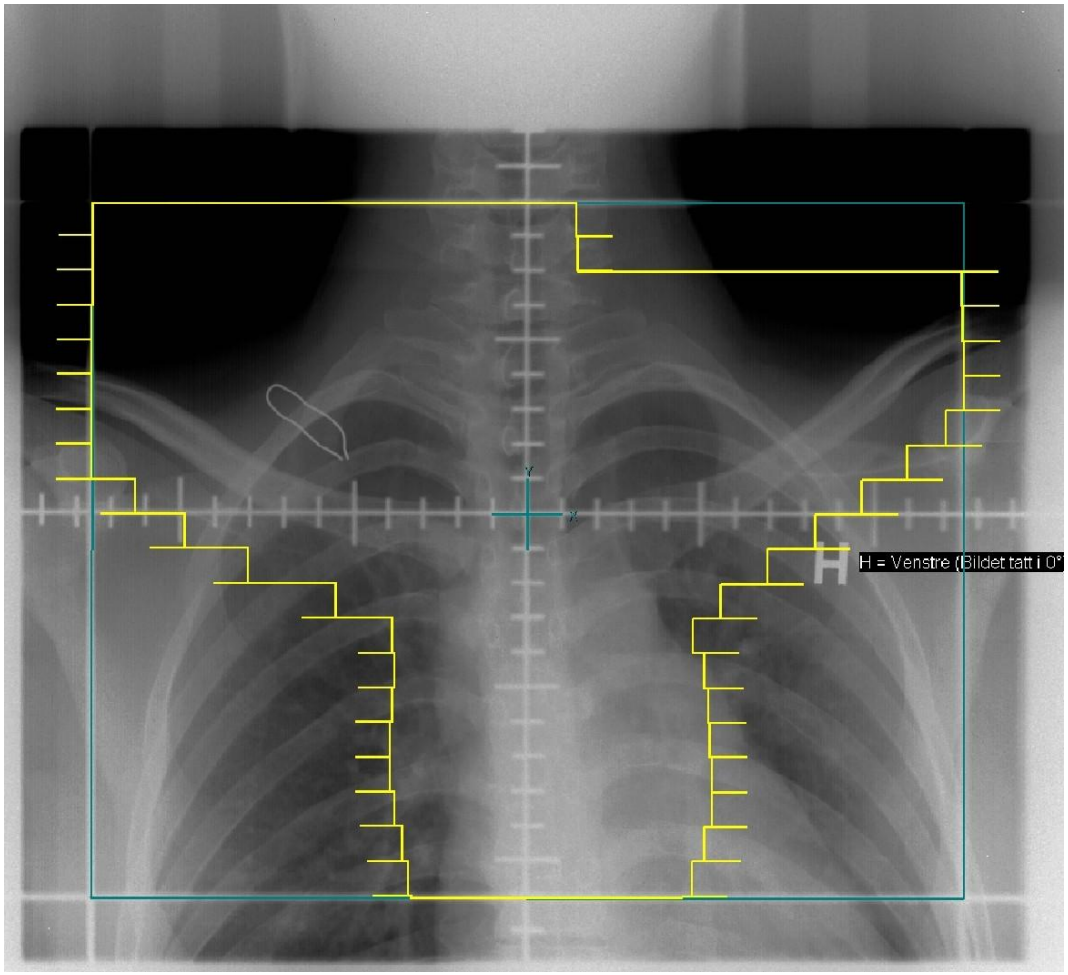


Eich et al, 2010

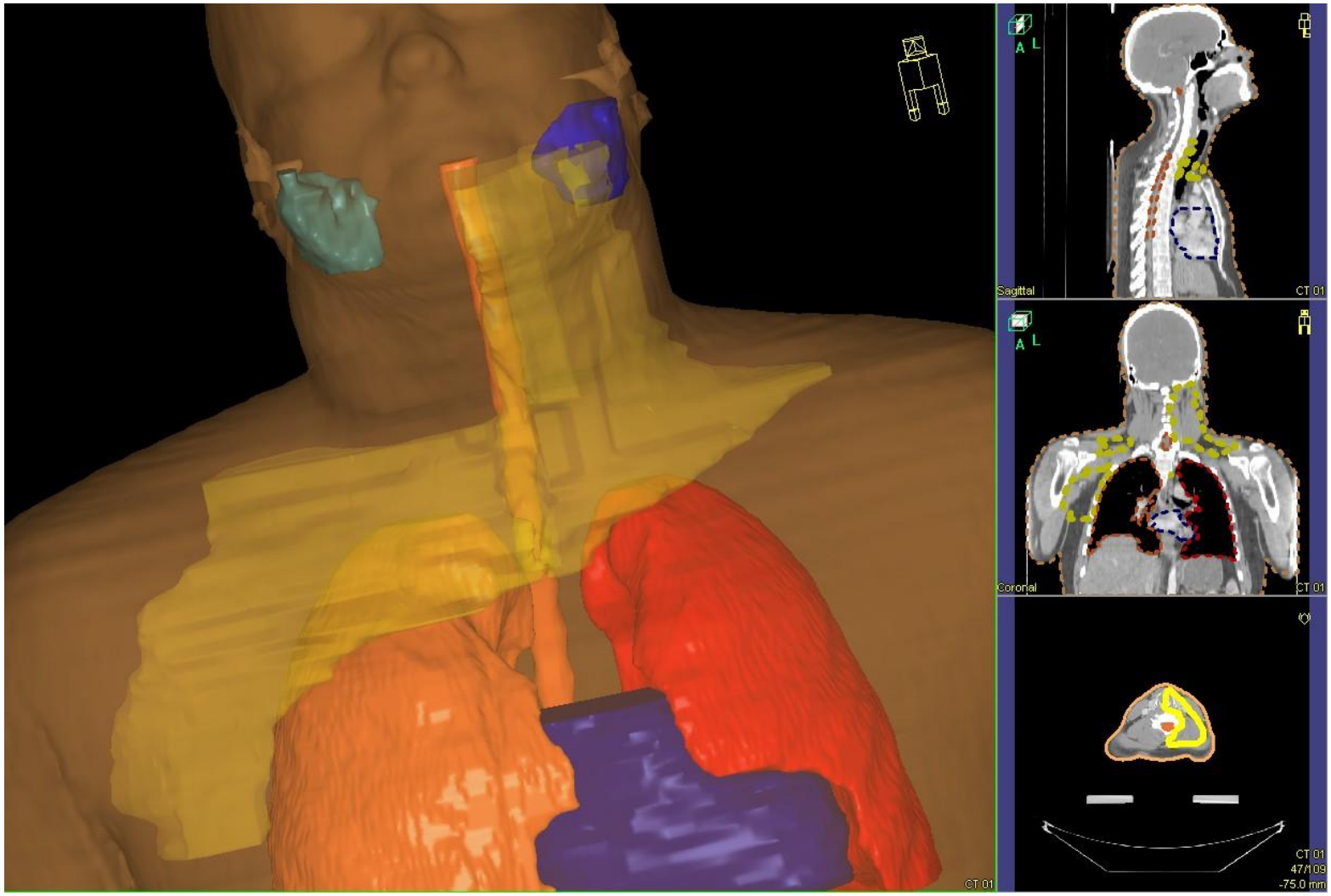
Involved field – modifisert



Involved field – modifisert



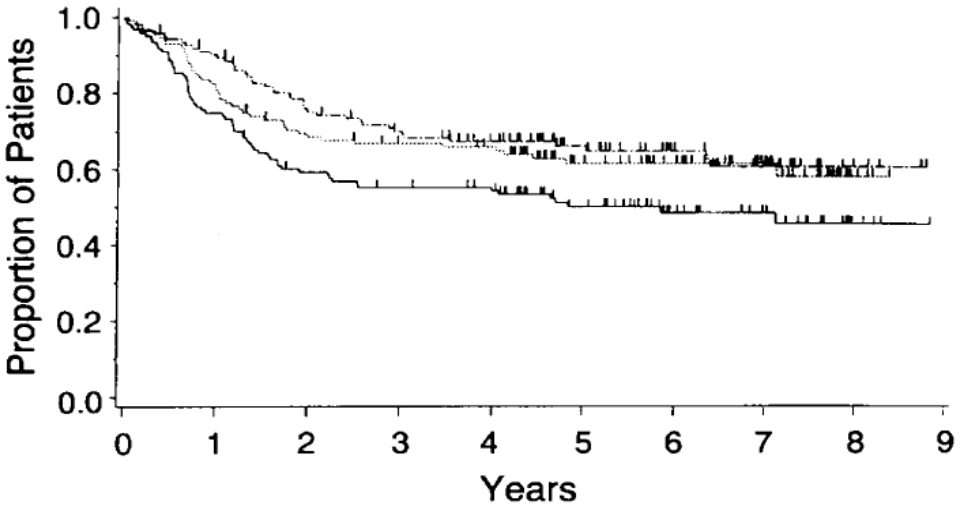
Involved field – CT-doseplanlagt



Veien videre - Hodgkins lymfom I-IIA

- Redusere kjemoterapi – fjerne bleomycin for tidlige stadier?
- Intensivert kjemoterapi for intermediære stadier?
- Involved node RT?
- PET baserte strategier: ingen strålebehandling ved tidlig PET negativ sykdom?

ABVD standard ved avansert Hodgkins lymfom



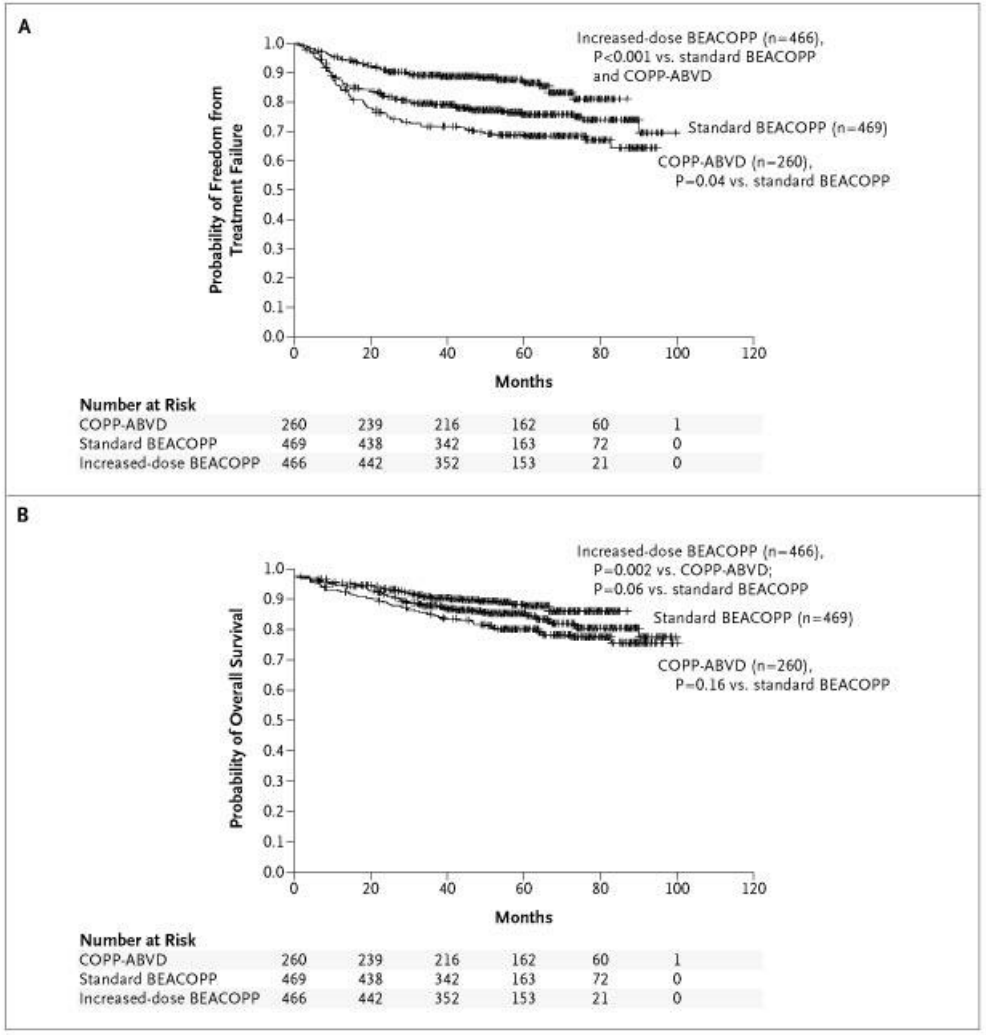
Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
MOPP	123	62 (50)	4.84
ABVD	115	44 (38)	None
MOPP–ABVD	123	43 (35)	None
All	361	149 (41)	—

Figure 1. Failure-free Survival According to Primary Chemotherapeutic Regimen.

P = 0.02 for the difference between MOPP, ABVD, and MOPP–ABVD. In the column for median years of survival, none indicates that the median survival has not yet been reached.

Canellos et al, 1992

Standard and Increased-Dose BEACOPP Chemotherapy Compared with COPP-ABVD for Advanced Hodgkin's Disease



Diehl et al, 2003

Prognostiske faktorer ved avansert Hodgkins lymfom

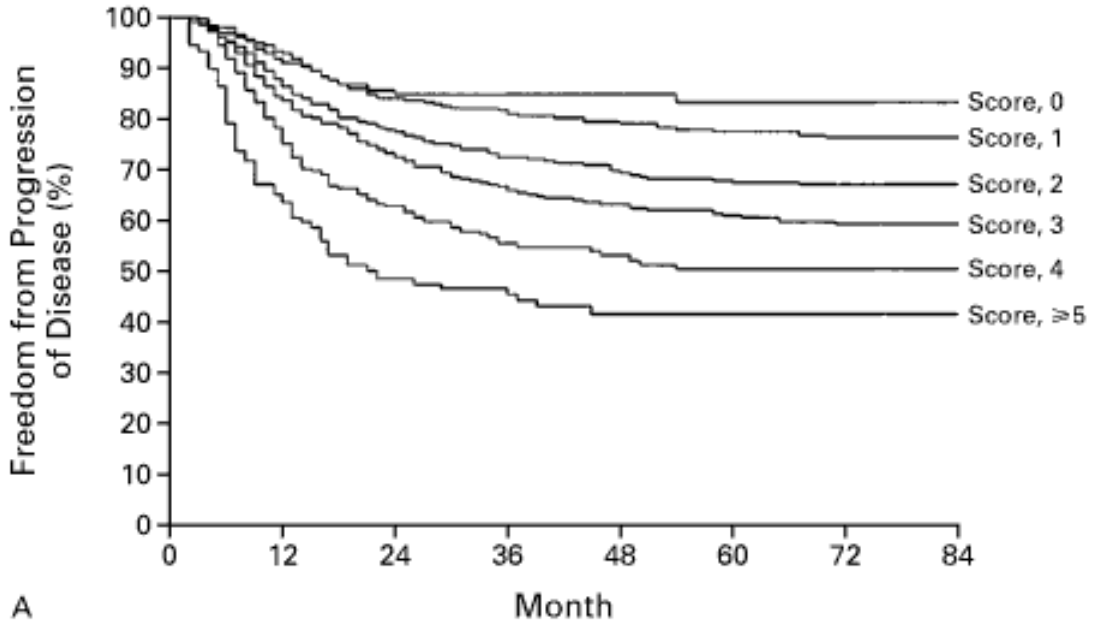
TABLE 2. THE FINAL COX REGRESSION MODEL.*

FACTOR	LOG HAZARD RATIO	P VALUE	RELATIVE RISK
Serum albumin, <4 g/dl	0.40±0.10	<0.001	1.49
Hemoglobin, <10.5 g/dl	0.30±0.11	0.006	1.35
Male sex	0.30±0.09	0.001	1.35
Stage IV disease	0.23±0.09	0.011	1.26
Age, ≥45 yr	0.33±0.10	0.001	1.39
White-cell count, ≥15,000/mm³	0.34±0.11	0.001	1.41
Lymphocyte count, <600/mm³ or <8% of white-cell count	0.31±0.10	0.002	1.38

*Hazard ratios and relative risks are for freedom from progression of disease in patients with the factors as compared with those without the factors. Plus–minus values are rate estimates ±SE (approximate 95 percent confidence intervals can be calculated as the rate estimates ±2 SE).

Hasenclever et al, 1998

Prognostiske faktorer ved avansert Hodgkins lymfom



Hasenclever et al, 1998

Behandlingsgrupper (18-60 år)

Risikogruppe	Stadium	Risikofaktorer
Tidlig	IA-IIA	Ingen
Intermediær	IA-IIA	Minst én
Avansert	IIB-IV	<4
	IIB-IV	≥4

6-8 ABVD

2 eskalerte
+
6 standard
BEACOPP

Overlevelse, avansert HL, IPS ≥ 4

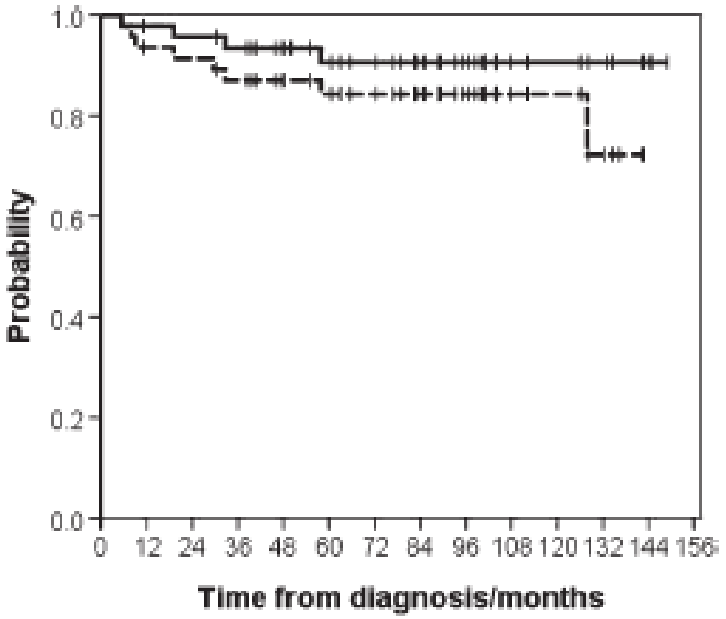
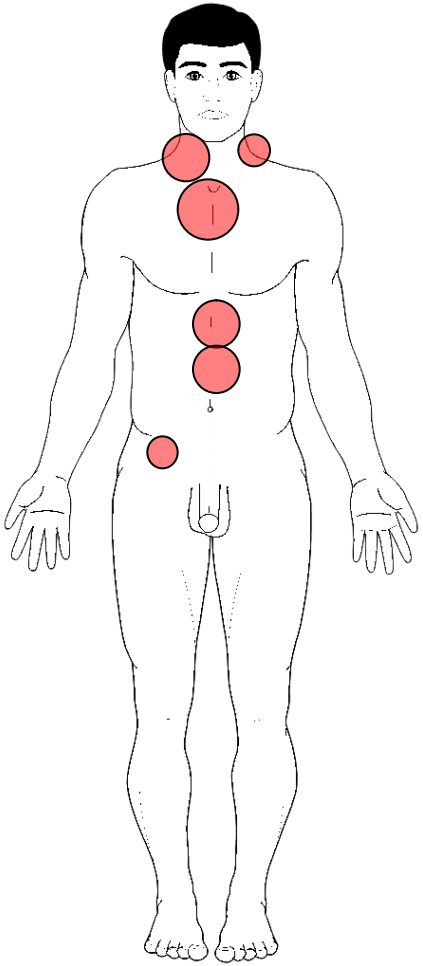


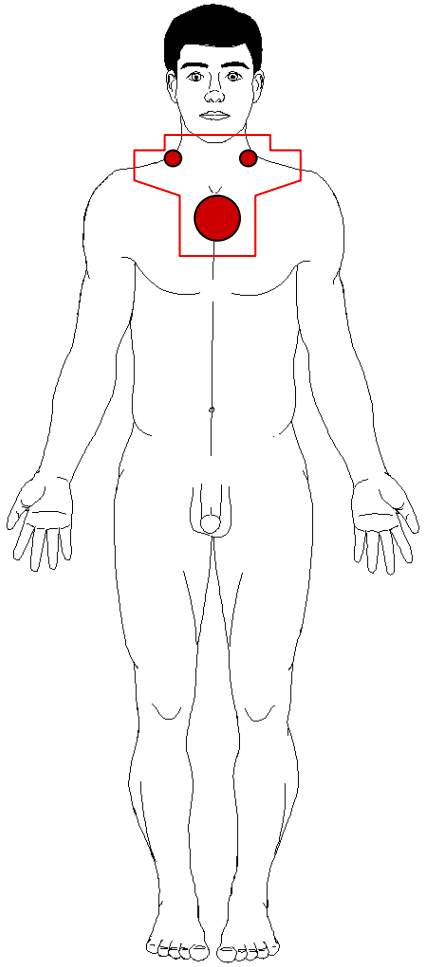
Figure 1. Progression-free (- - - -) and overall (——) survival of 47 patients with intended treatment of two escalated followed by six standard BEACOPP cycles. Median follow-up of surviving patients is 89 months.

Fosså et al, 2011

Hodgkins lymfom – utbredt sykdom IIB-IV - strålebehandling

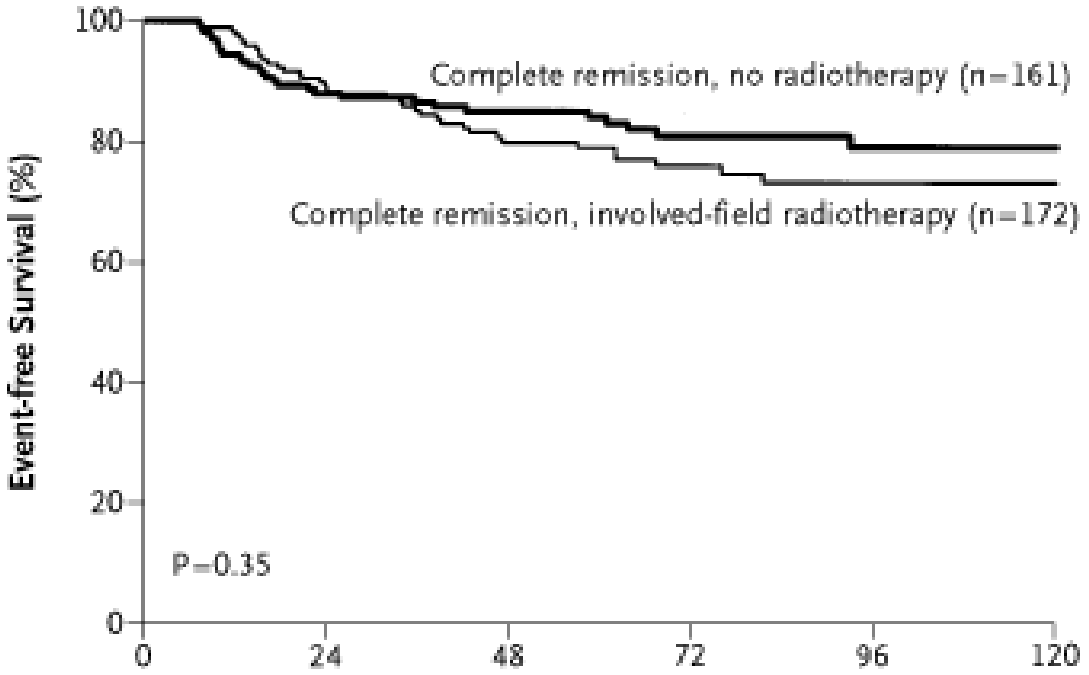


Full kjemoterapi mot makro- og mikroskopisk sykdom



Konsoliderende radioterapi 1,75 Gy x 17 mot begrenset område (Restlymfom, opprinnelig bulky lymfom)

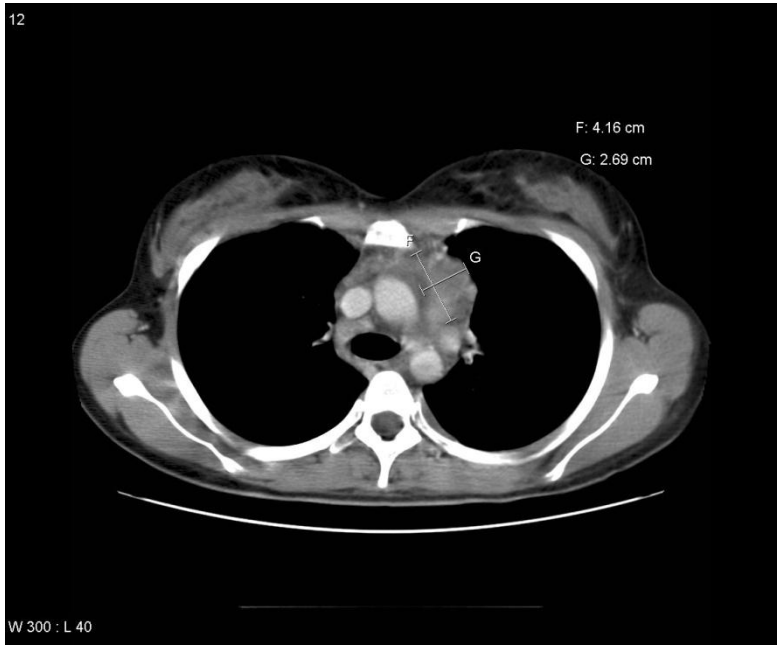
Adjuvant strålebehandling i CR?



No. at Risk						
No radiotherapy	161	135	103	73	40	14
Radiotherapy	172	141	101	68	37	19

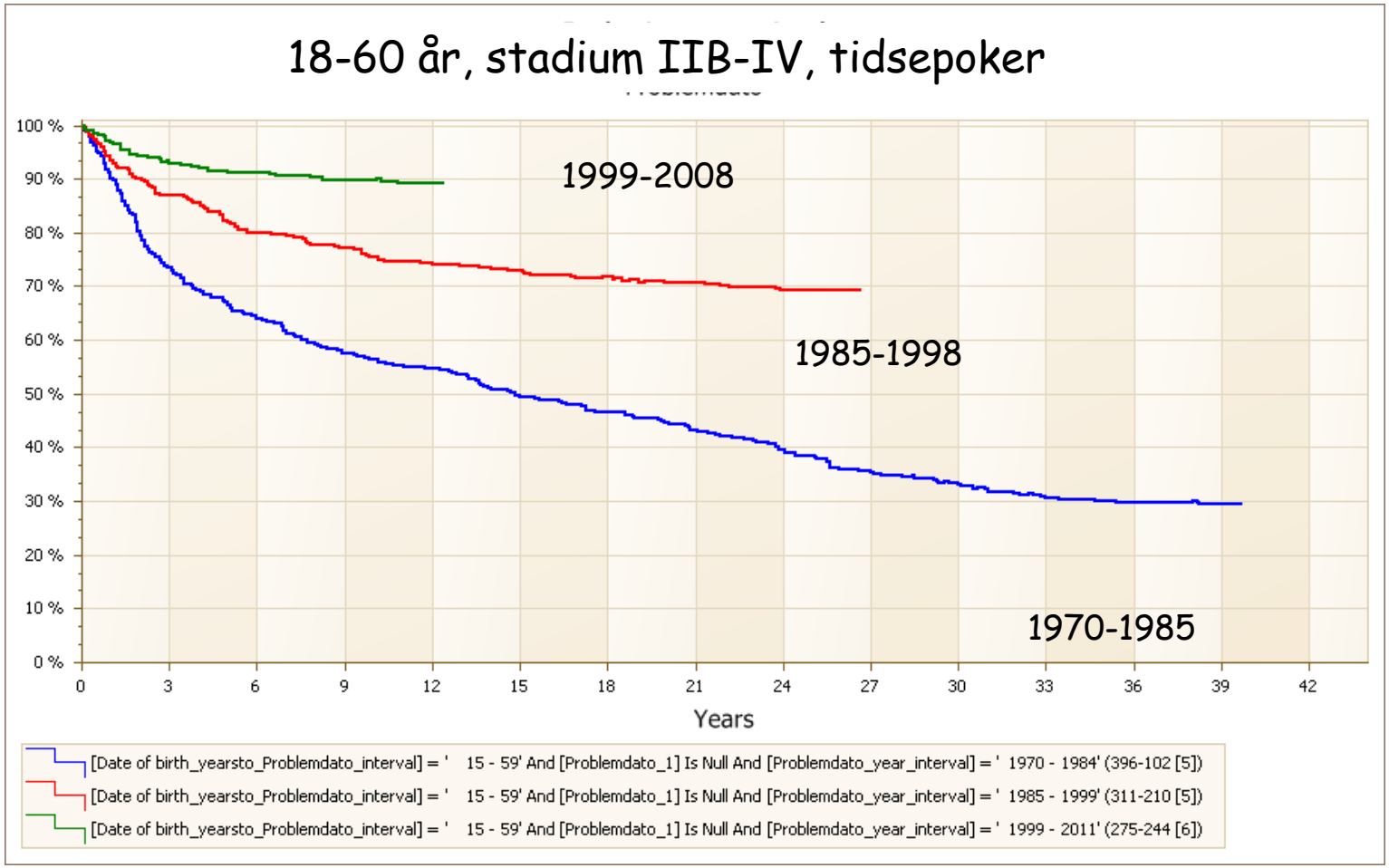
Aleman *et al*, 2003

Strålebehandling ved non CR?



- Responsvurdering i HL vanskelig fibrose/aktiv tumor
- Kinetikk?
- Størrelse av restlesjon?
- PET?
- Rebiopsi?

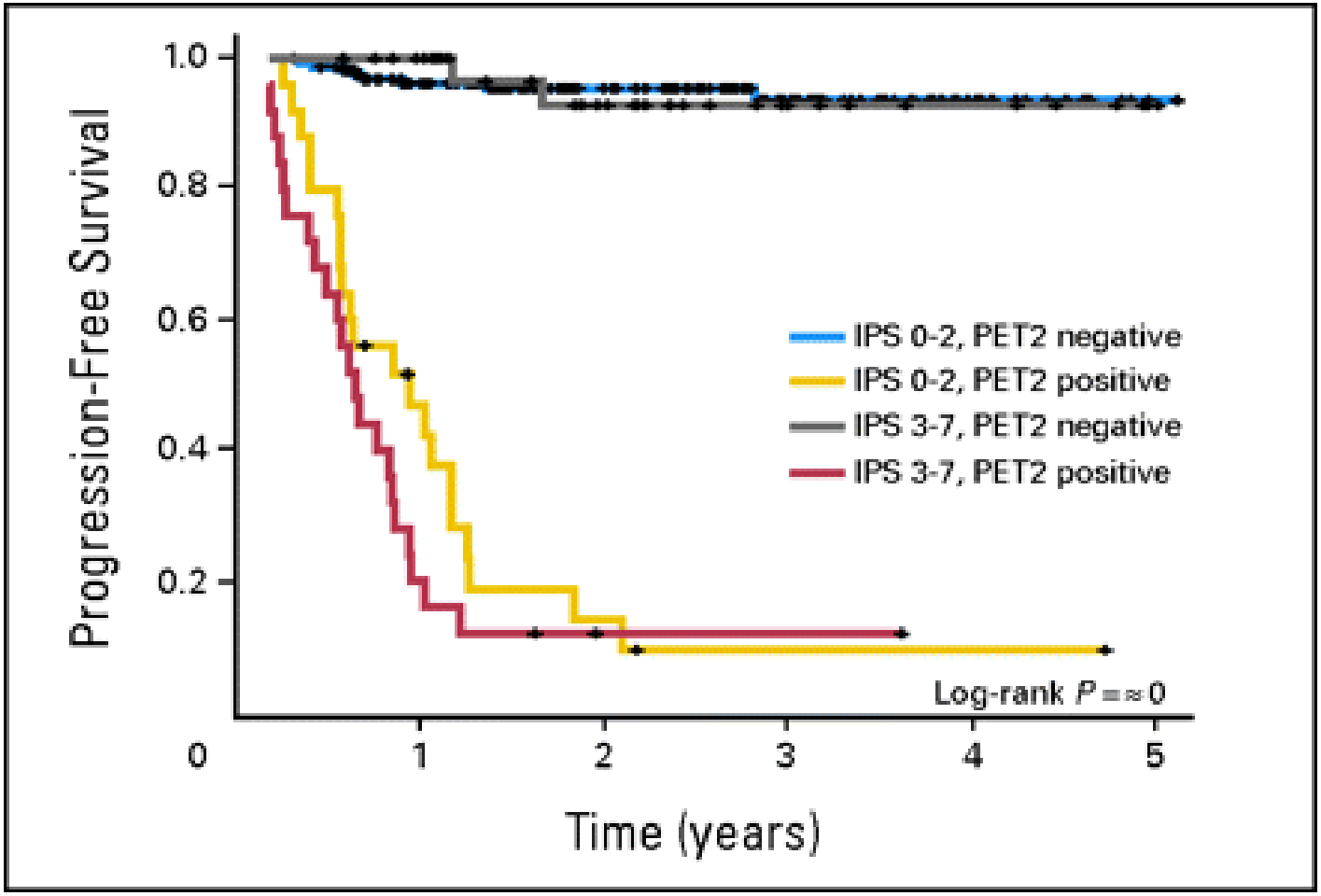
Totaloverlevelse Hodgkin lymfom, stadium IIB-IV i grupper etter diagnoseår



Veien videre
avansert Hodgkins lymfom

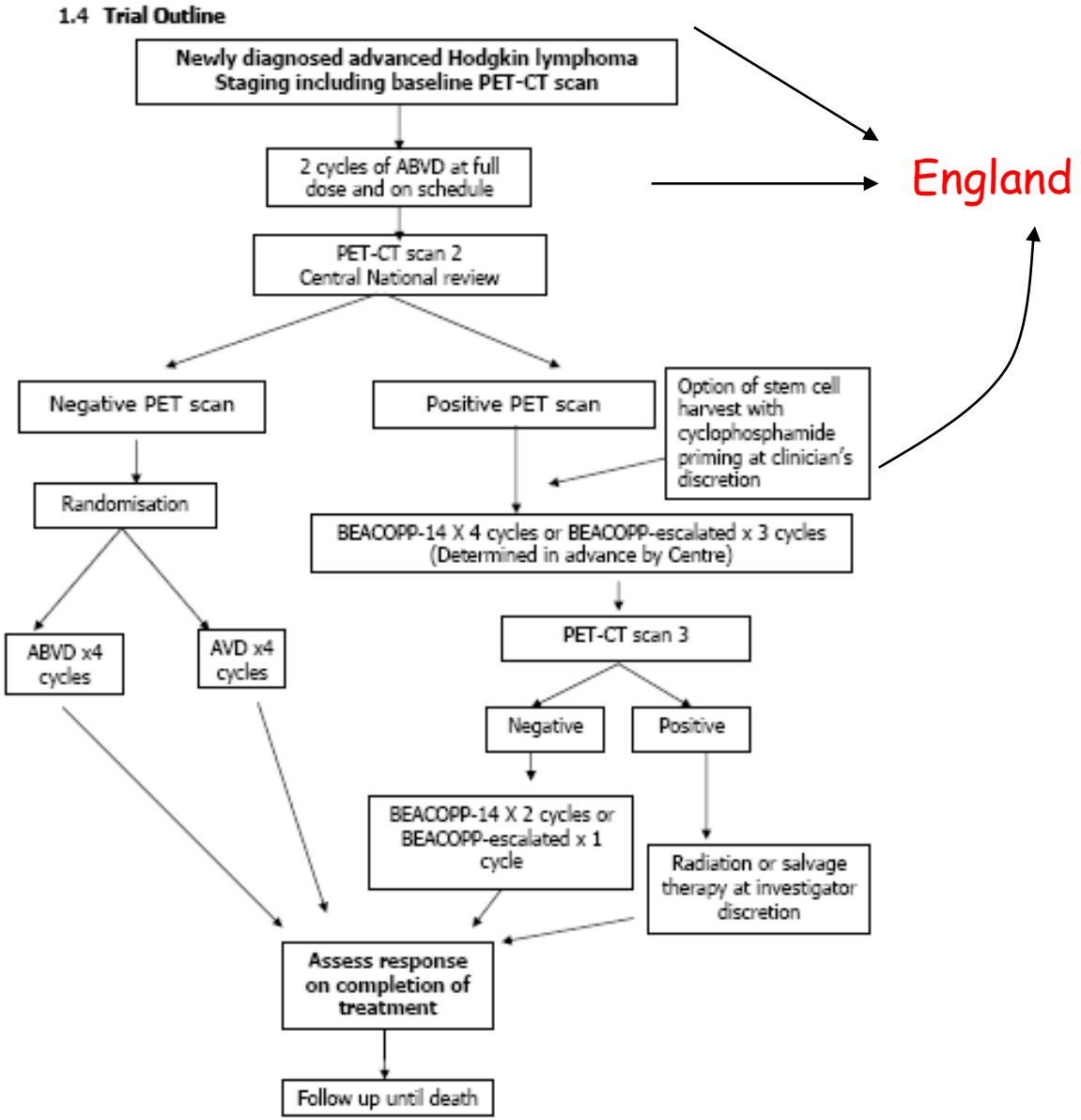
- Definere plass for intensive regimer hos høyrisikopasienter?
- Implementere PET?
- Nye regimer?
- Utvikle medikamenter for targeted therapy?
  - Anti CD 30 antistoff?
  - mTOR inhibitorer?
  - Histondesacetylasehemmere?

Responsadaptert behandling basert på PET



Gallamini *et al*, 2007

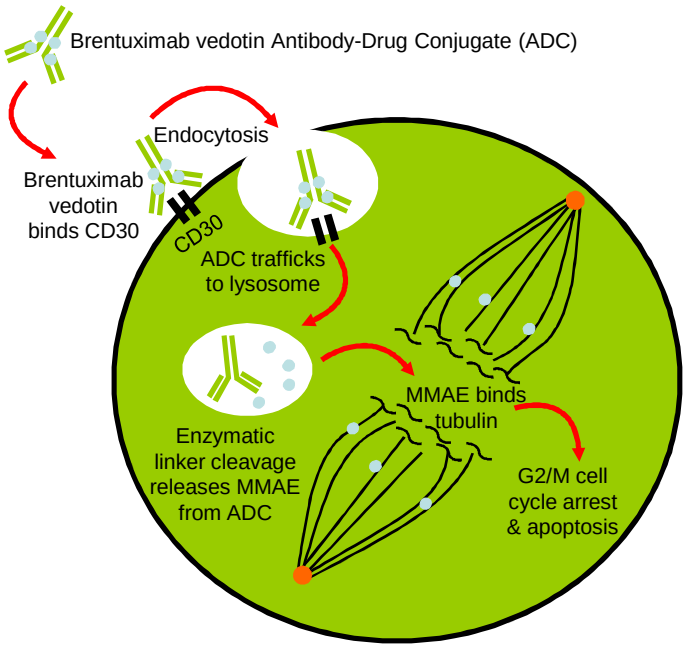
RATHL studien



Forventet 1200 pasienter over 4 år, 80 % PET – og 20 % PET+ etter 2 ABVD

Brentuximab vedotin: overview

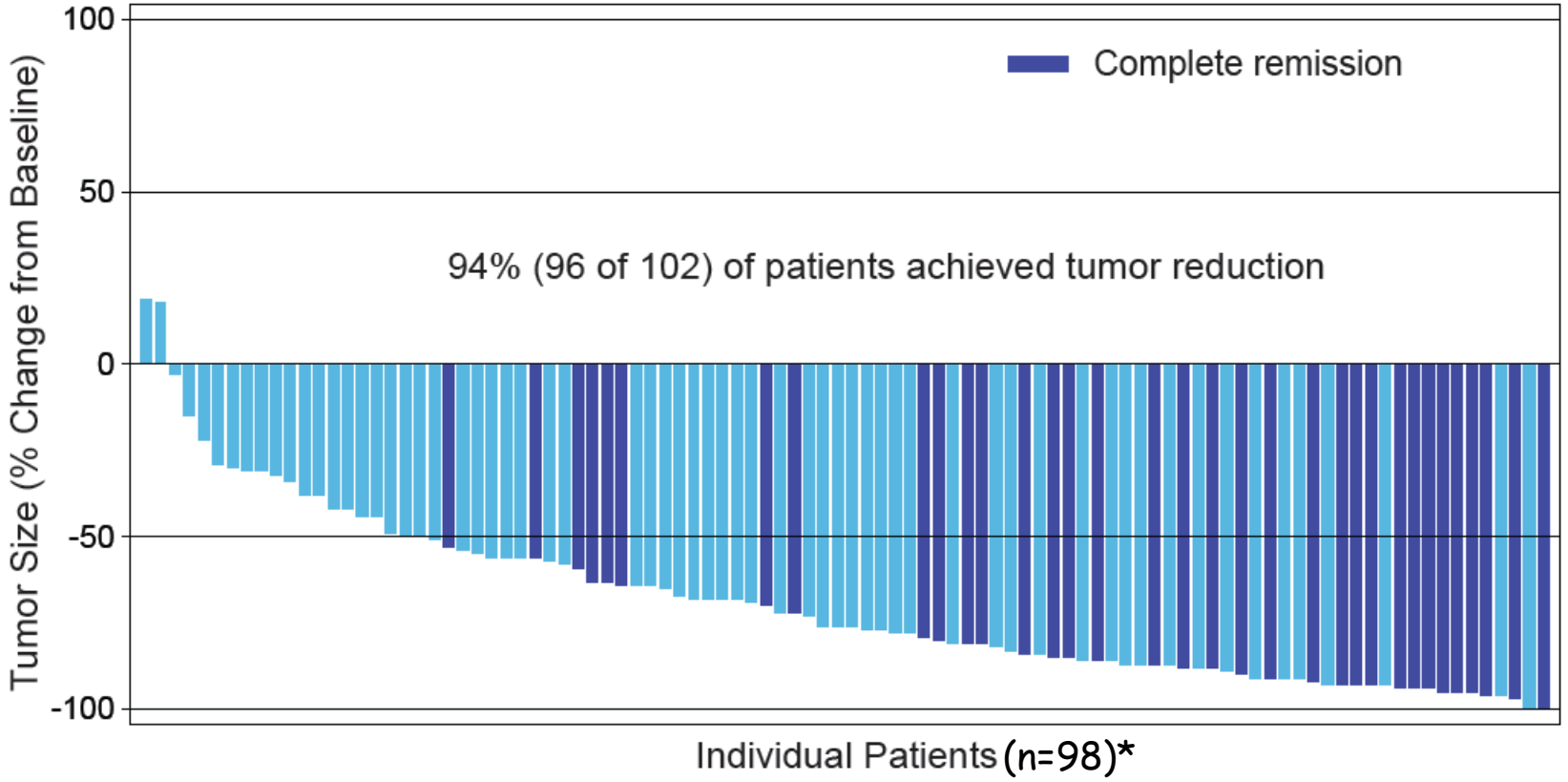
- Three components:
  - Antibody: the antibody cAC10 specific for human CD30
  - Cytotoxic agent: the antimicrotubule agent monomethyl auristatin E (MMAE)
  - Linker: a protease-cleavable linker that covalently attaches MMAE to cAC10
- Biology:
  - CD30 is a cell-surface antigen expressed on Reed-Sternberg cells and some non-Hodgkin lymphomas (NHLs)
  - Antibody delivers drug to target cells by binding to CD30 on cell surface
  - When internalised, the conjugate is trafficked to the lysosomes
  - MMAE is released when the linker is degraded
  - MMAE inhibits tubulin polymerisation resulting in G_2M cell cycle arrest and apoptosis



Bartlett NL, et al., ASCO 2010 Chicago, IL, USA (Abstract #8062).
Senter PD. Curr Opin Chem Biol 2009;13:235–44.
Younes A, et al., ASH 2008, San Francisco, CA, USA (Abstract #1006).

Brentuximab vedotin: Phase II

SGN35-003: Phase 2 pivotal study of brentuximab vedotin in 102 patients with relapsed or refractory HL post ASCT: maximum tumour reduction/IRF



***4 patients were not included in the analysis; 3 patients had no measurable lesions per IRF; 1 patient had no post-baseline scans**

Chen R, et al., ASH 2010 Orlando, FL, USA (Abstract #283).
Chen R, et al., ASCO 2011Chicago, IL, USA (Abstract #8031).

Residivbehandling

- 1. residiv innen to år
  - IGEV+HMAS
- 1. residiv etter to år
  - IGEV+HMAS
  - IGEV, IME, LVPP, BEACOPP
- 2. residiv
  - mange regimer, inklusive brentuximab vedotin
  - allogen TX

Takk for oppmerksomheten