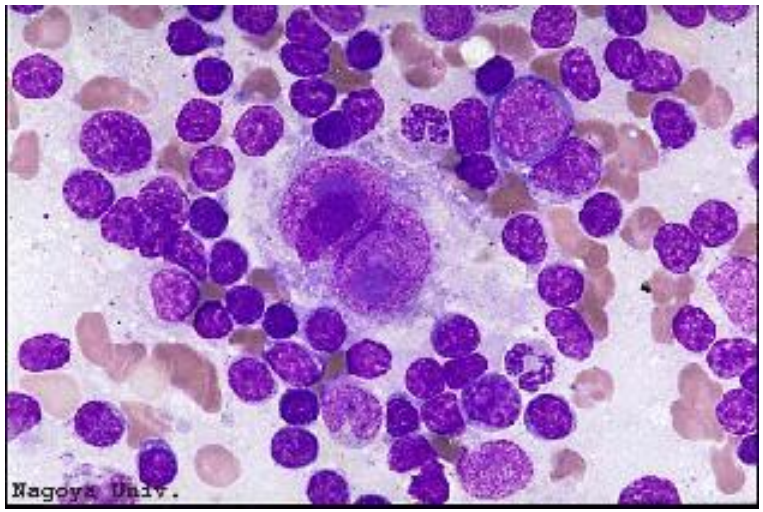
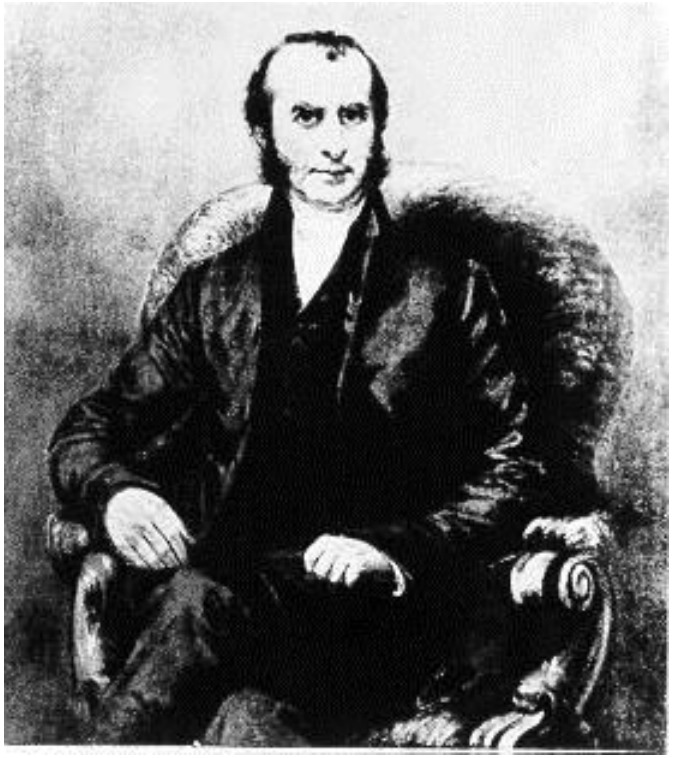
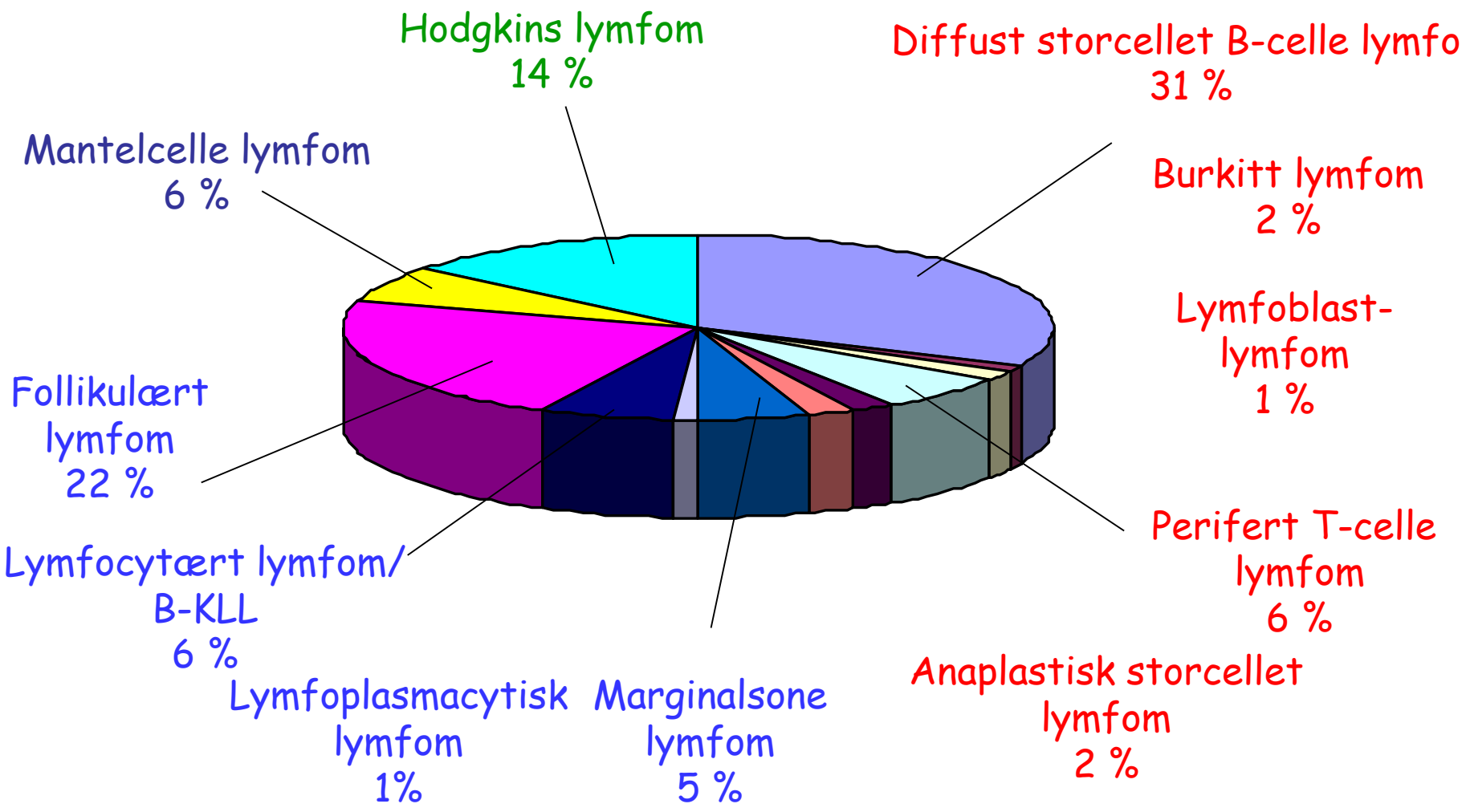
Behandling av Hodgkins lymfom hos voksne

Alexander Fosså
OUS
Radiumhospitalet

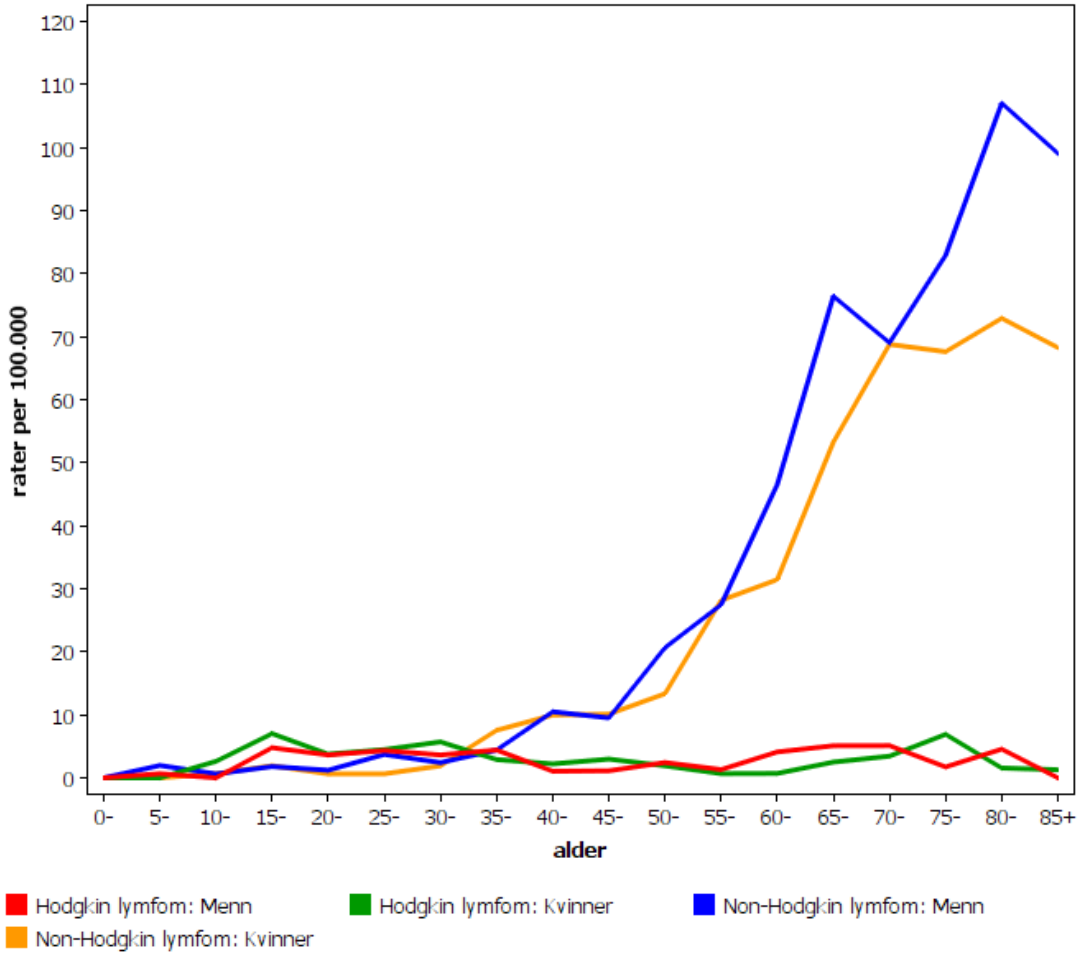




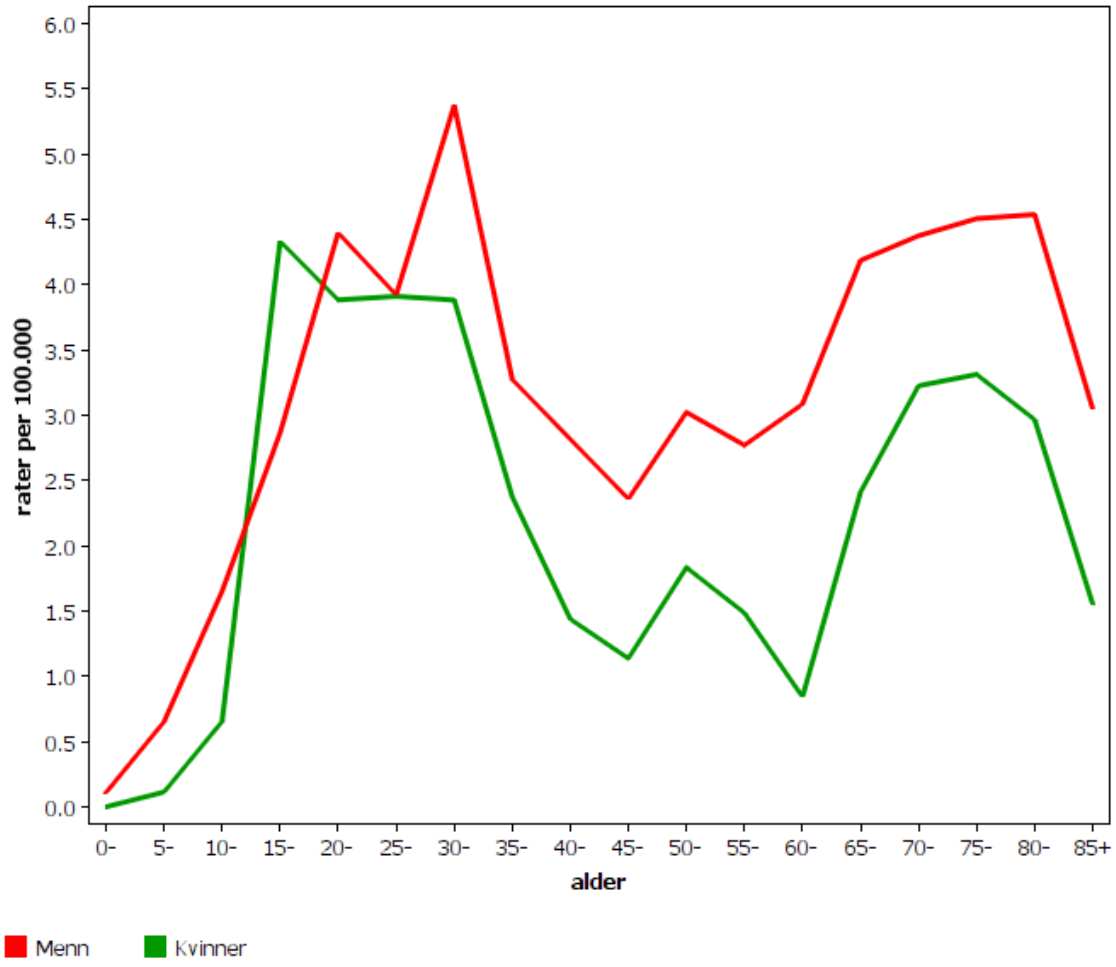
WHO for dummies…



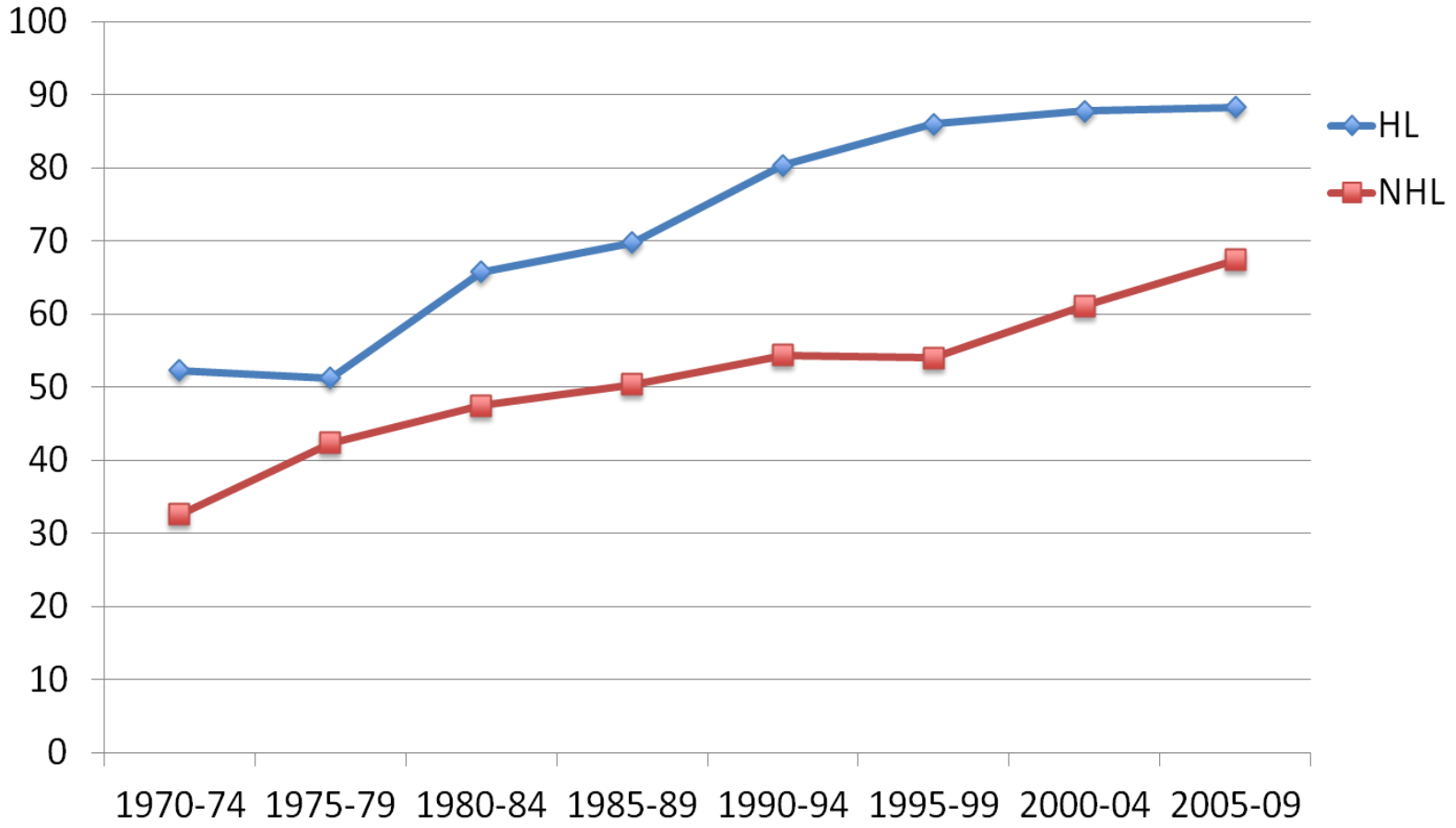
Aldersspesifikk insidensrate 2011
Maligne lymfomer i Norge



Aldersspesifikk insidensrate 2006-2011 Hodgkins lymfom



5-års relativ overlevelse lymfom



Cancer in Norway 2009, Norwegian Cancer Registry

Malignt lymfom (2014)

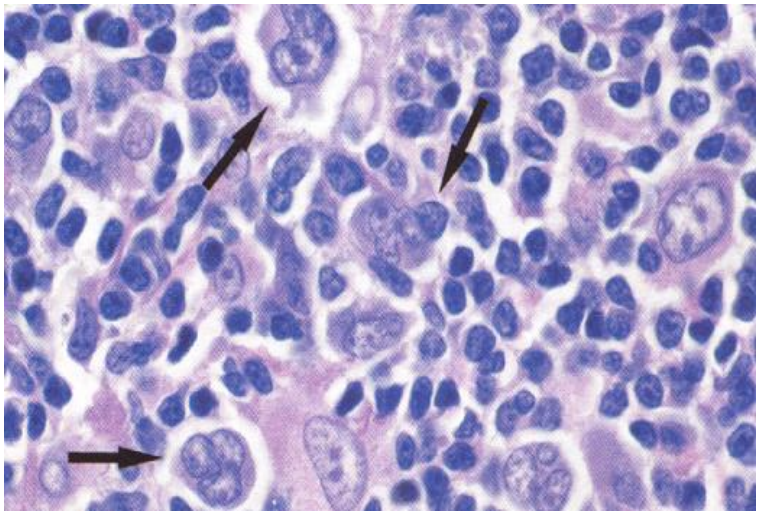
- **Hodgkin lymfom**
- Insidens
  - menn 76
  - kvinner 58
- Prevalens
  - Alle 2547

- **Non-Hodgkin lymfom**
- Insidens
  - menn 539
  - Kvinner 443
- Prevalens
  - Alle 8770

Kreftregisteret, 2014

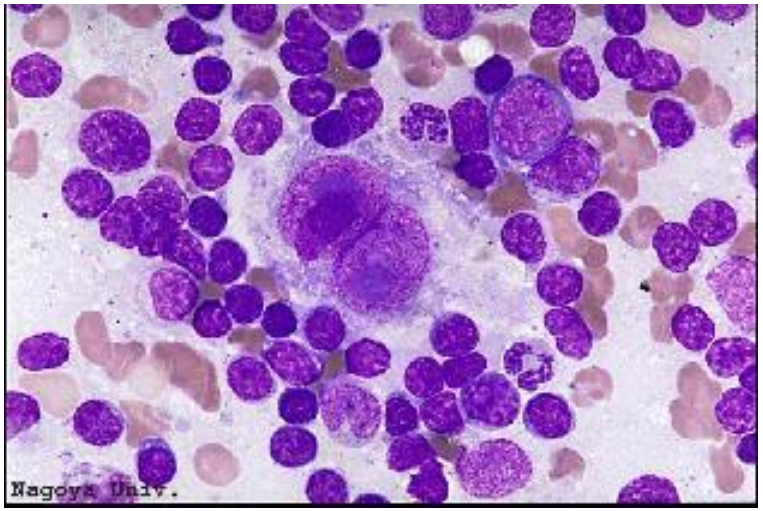
Hodgkins lymfom
-en malign B-celle sykdom

Nodulært lymfocyttrikt HL
5%



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

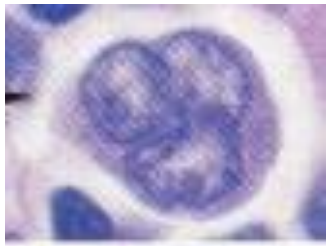
Klassisk HL
95%



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

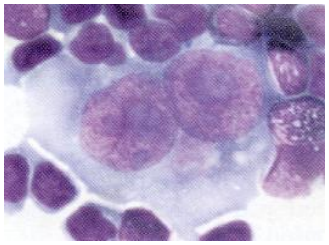
Hodgkins lymfom -en malign sykdom

L&H celler



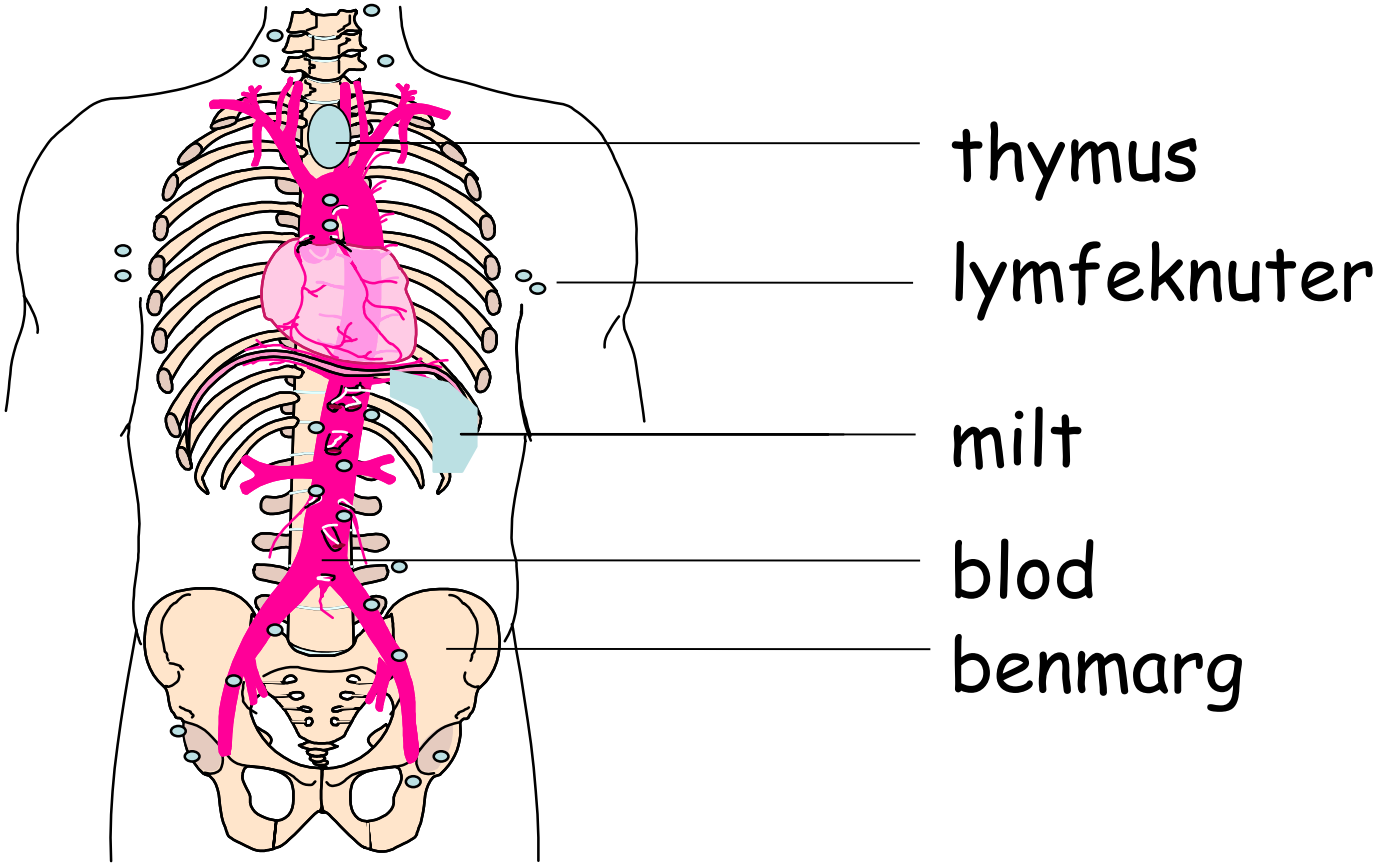
B-celle genotype
Monoklonale
Delvis bevart B-celle fenotype
CD20, CD79a, Pax5
Oct2, BOB.1
Kan være Ig+
Mangler ~~CD~~30 og ~~C~~D15

RS celler



B-celle genotype (>98%)
Monoklonale
Mistet B-celle fenotype
~~CD~~20, ~~CD~~79a, Pax5
~~Oc~~t2, ~~BO~~B.1
Kan være Ig+
Ekspresjon av **CD30** og CD15 (>85%)
Opphav i germinalcenter celle
Apoptosedefekt? (NFκB, IκB, IκBK, TRAF1, LMP1, EBV)
Immune escape (**PDL1/2**)

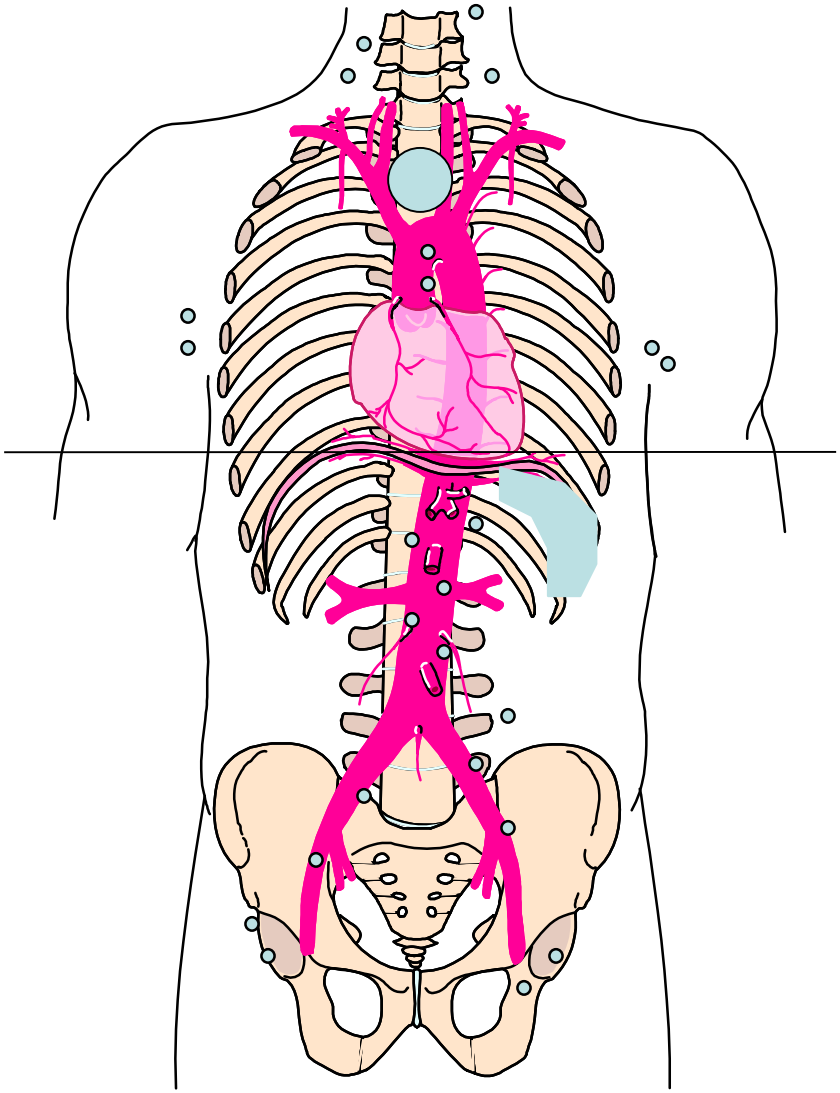
Lokalisasjon oftest nodal = i lymfeknuter



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

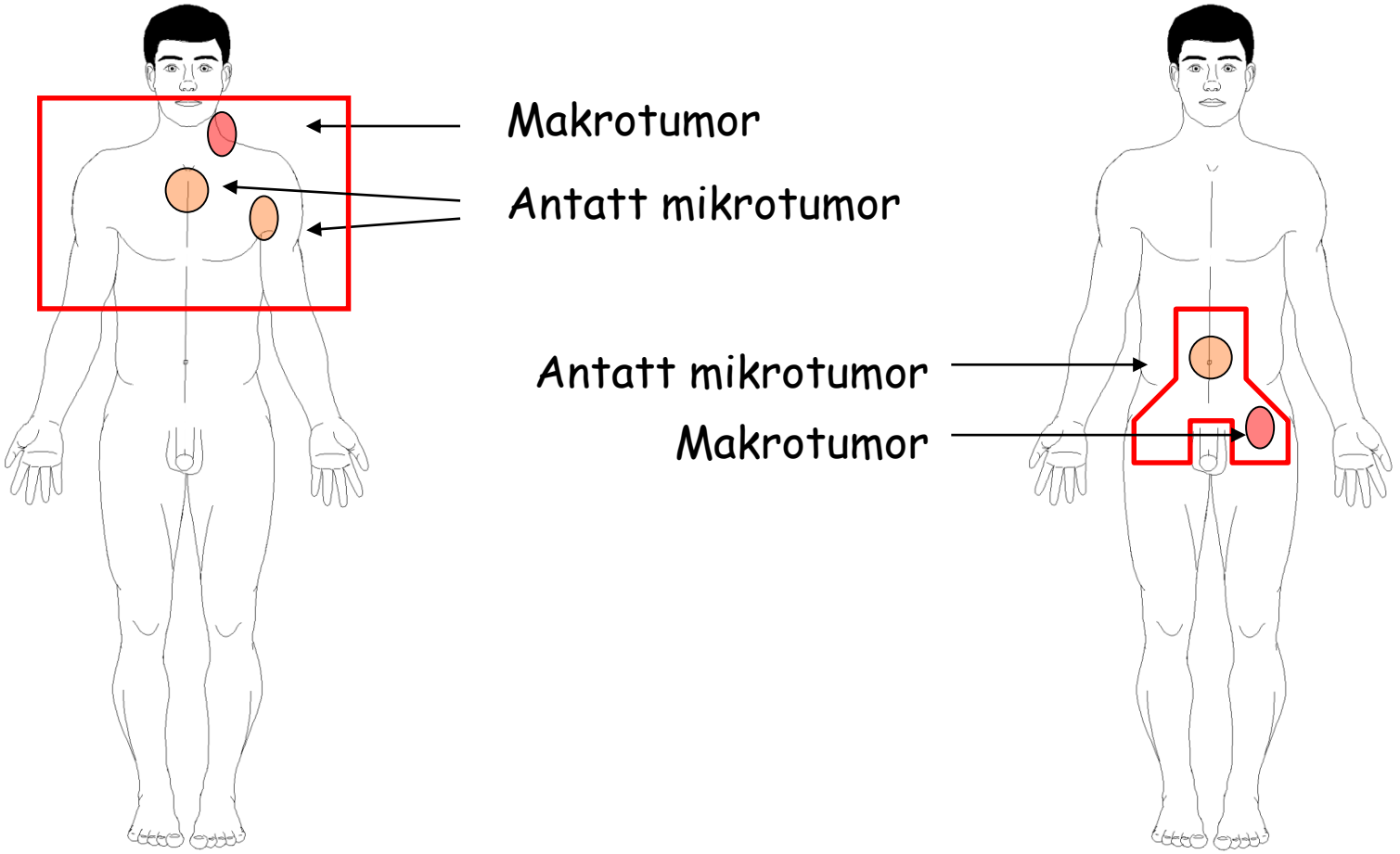
P_E = Primært ekstranodalt

E = Ekstensjon

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

G. F. Lauritzsen

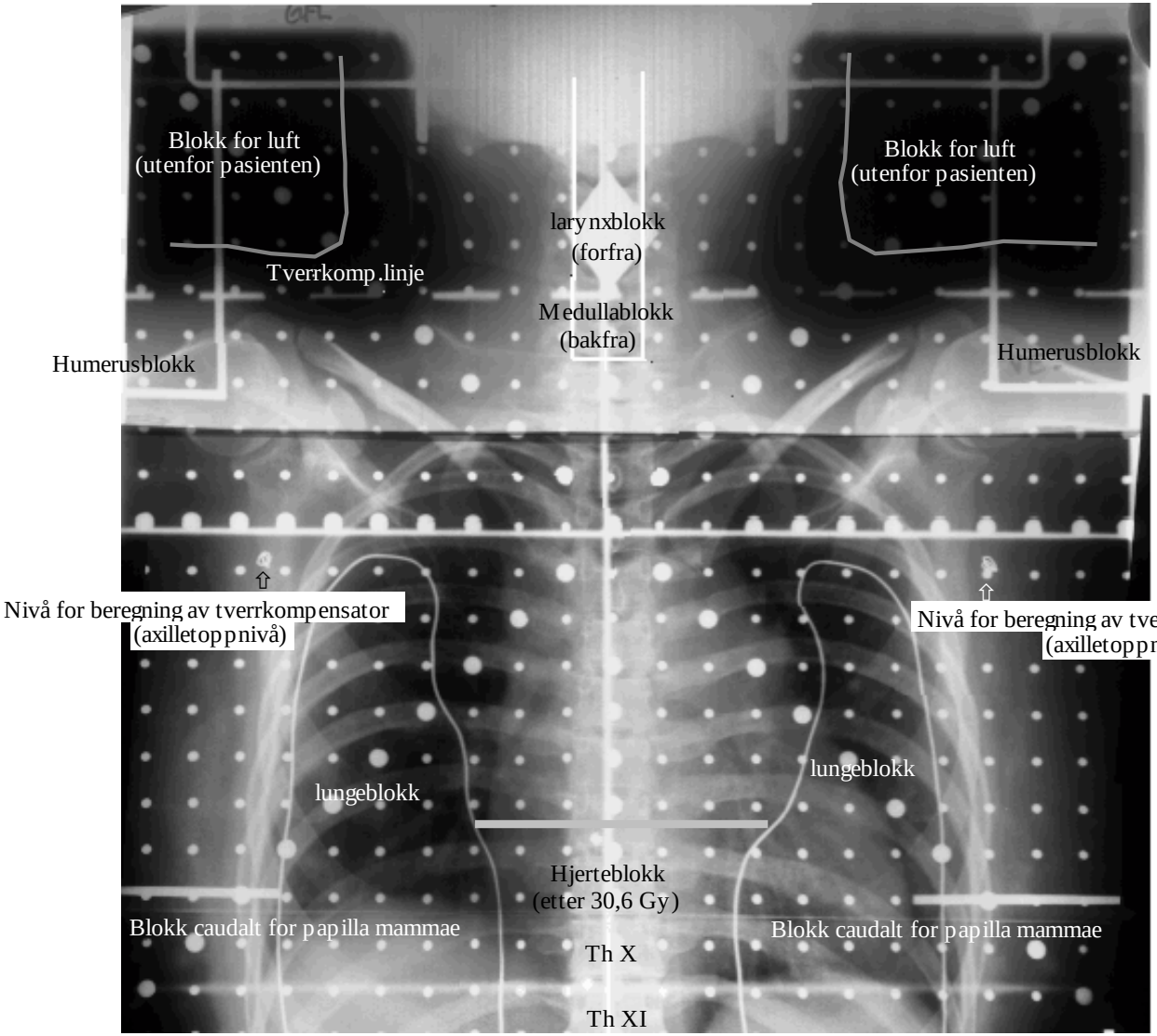
Hodgkin og strålebehandling
Extended field



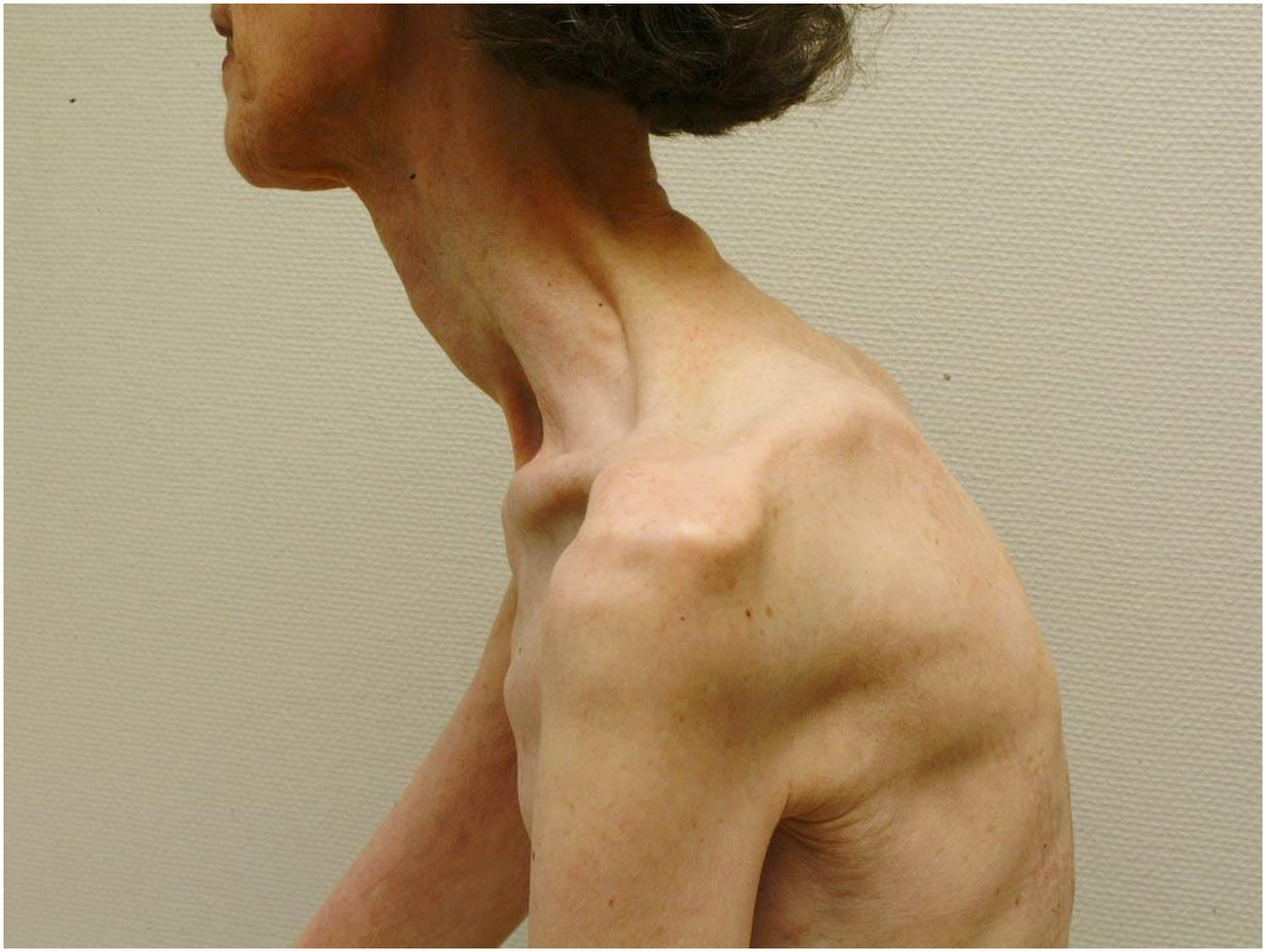
Kappefelt

Omvendt Y-felt

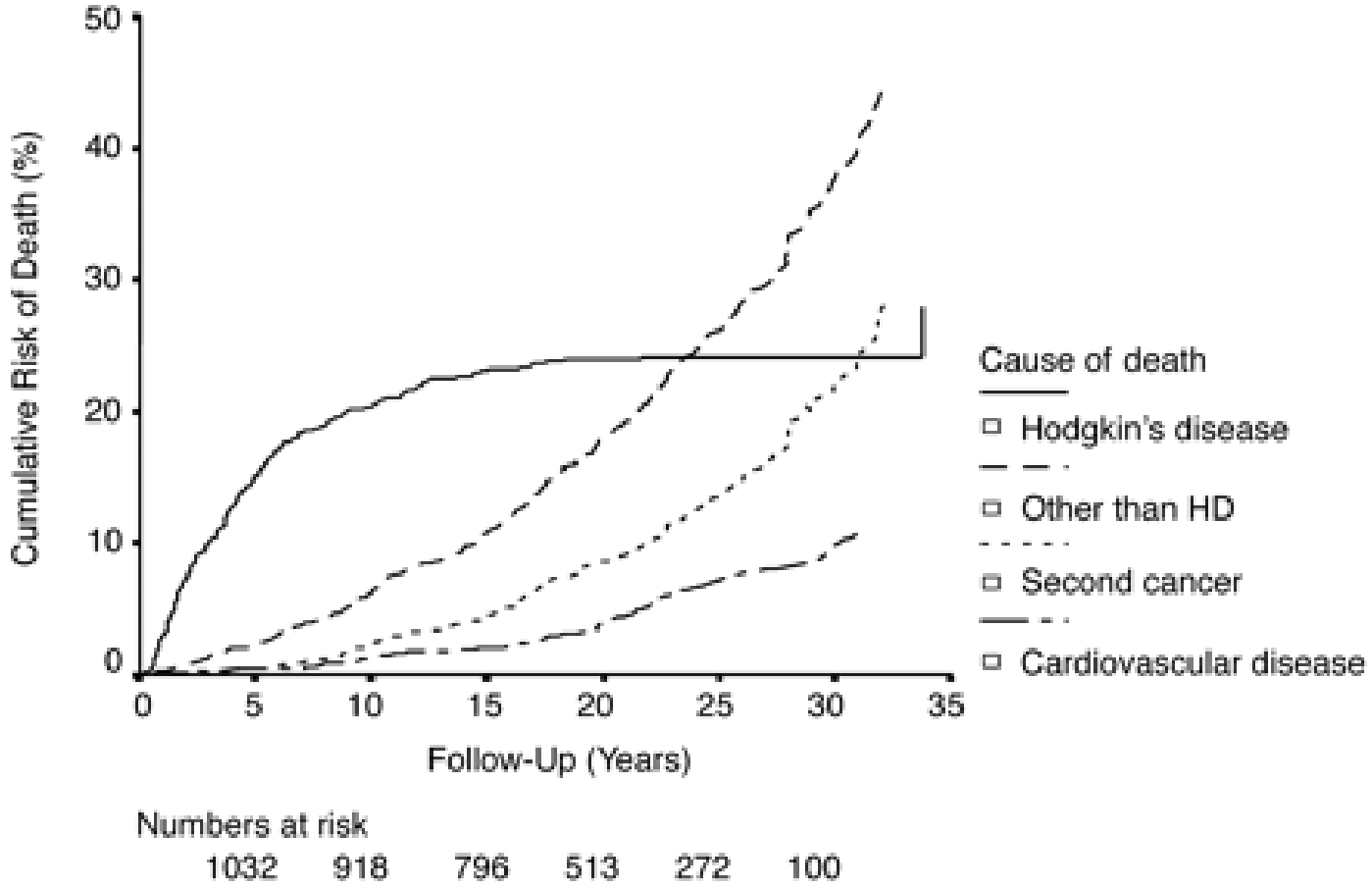
Kappefelt


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

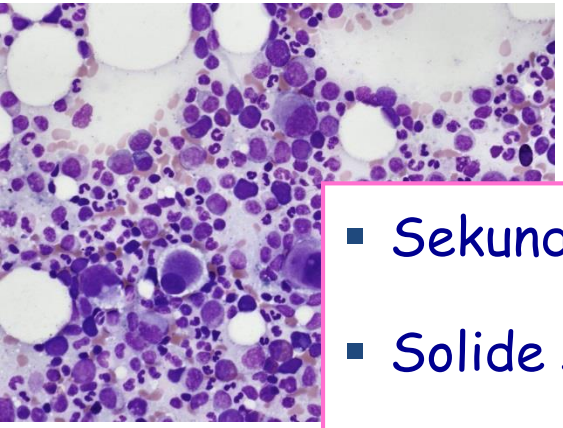


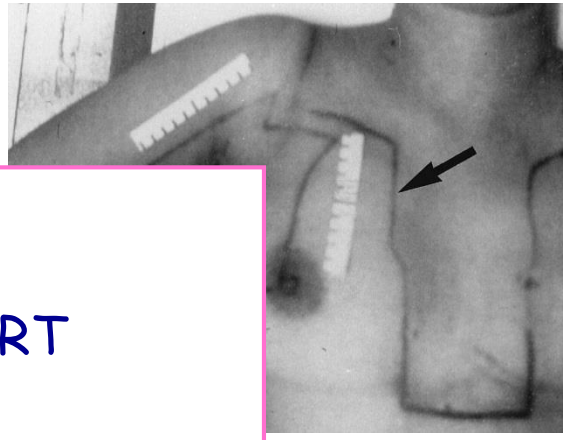
Mortalitet etter Hodgkins lymfom



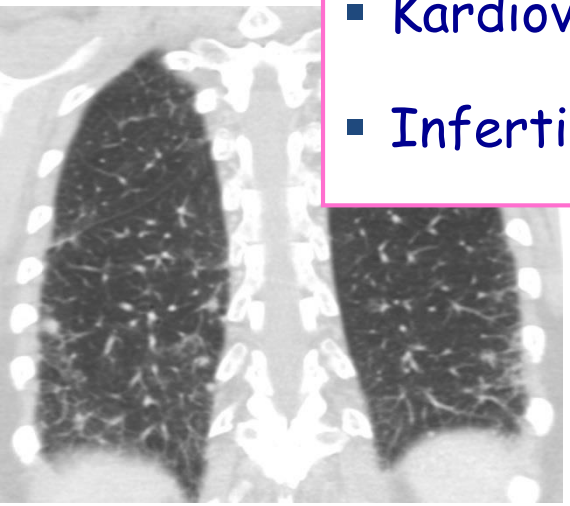
Aleman *et al*, 2003

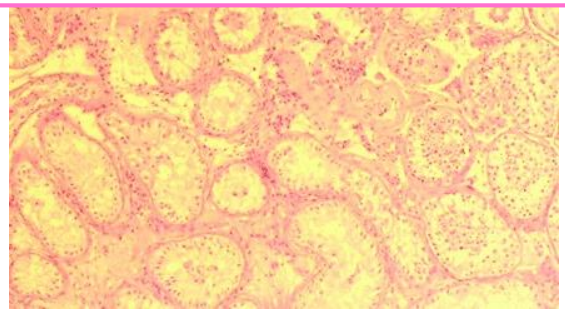
Vesentlige seneffekter etter Hodgkin lymfom

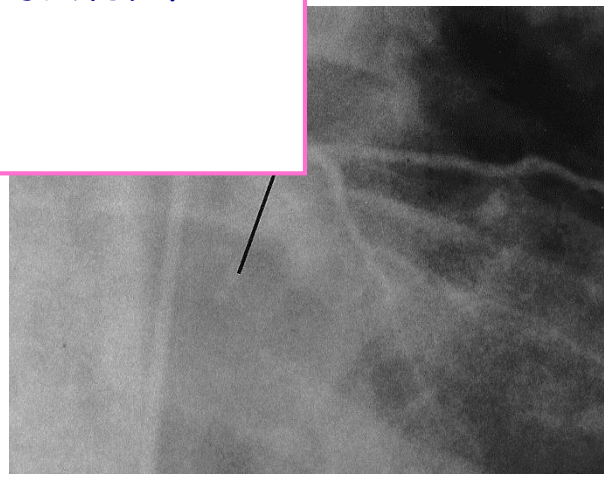




- Sekundær MDS/AML fra alkyansier
- Solide svulster etter "extended field" RT
- Pulmonal fibrose etter bleomycin
- Kardiovaskulær sykdom etter antracycliner / RT
- Infertilitet etter akylansier







MDS; myelodysplastisk syndrom, AML; akutt myelogen leukemi, RT; radioterapi

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

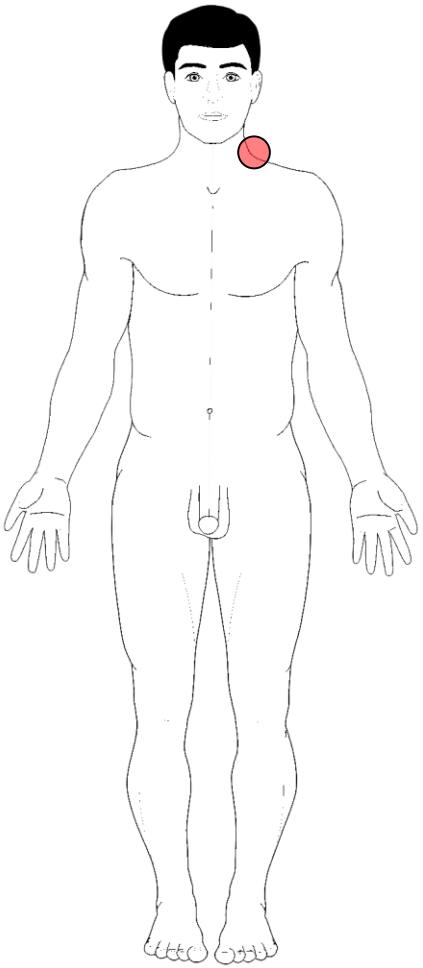
Prognostiske faktorer Hodgkin lymfom I-IIA

Begrenset sykdom (stadium I-IIA)

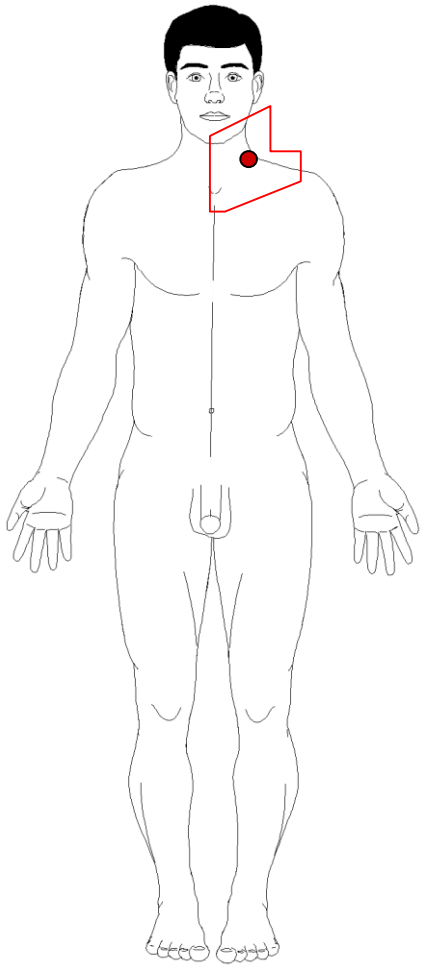
Basert på data fra flere grupper er bl.a. følgende **risikofaktorer** av prognostisk ugunstig betydning

- 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

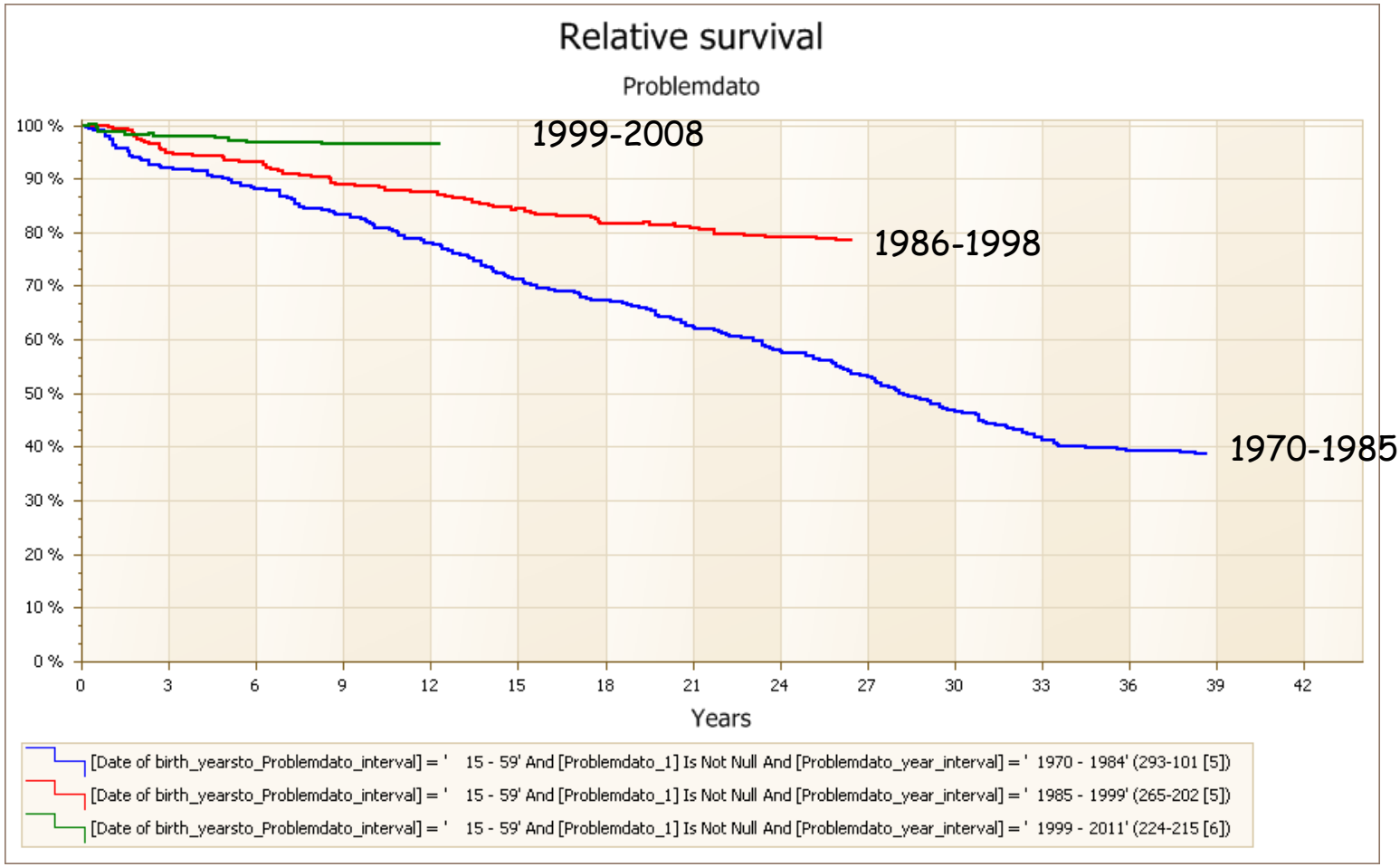


2-4 ABVD mot makro- og mikroskopisk sykdom



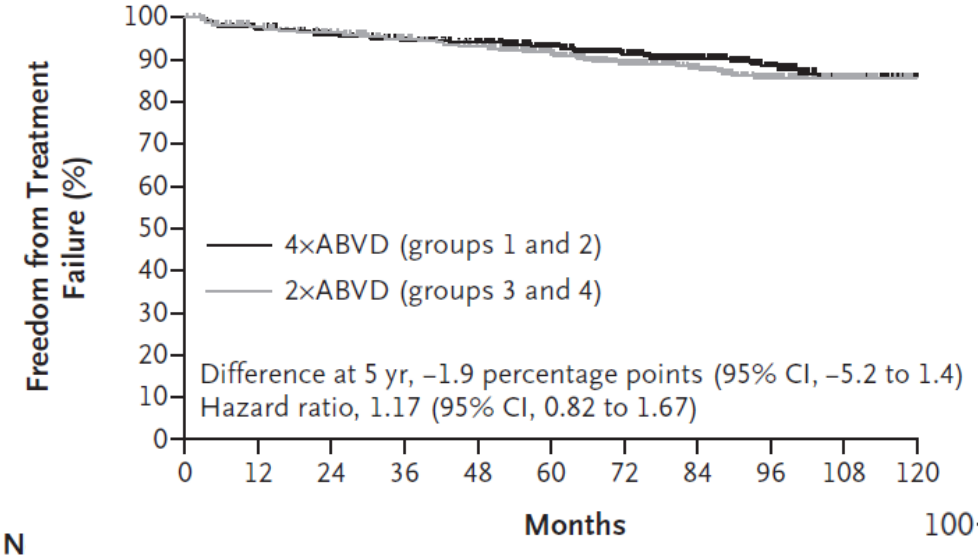
Modifisert IF radioterapi
2 Gy x 10
1,75 Gy x 17
mot makrotumor

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

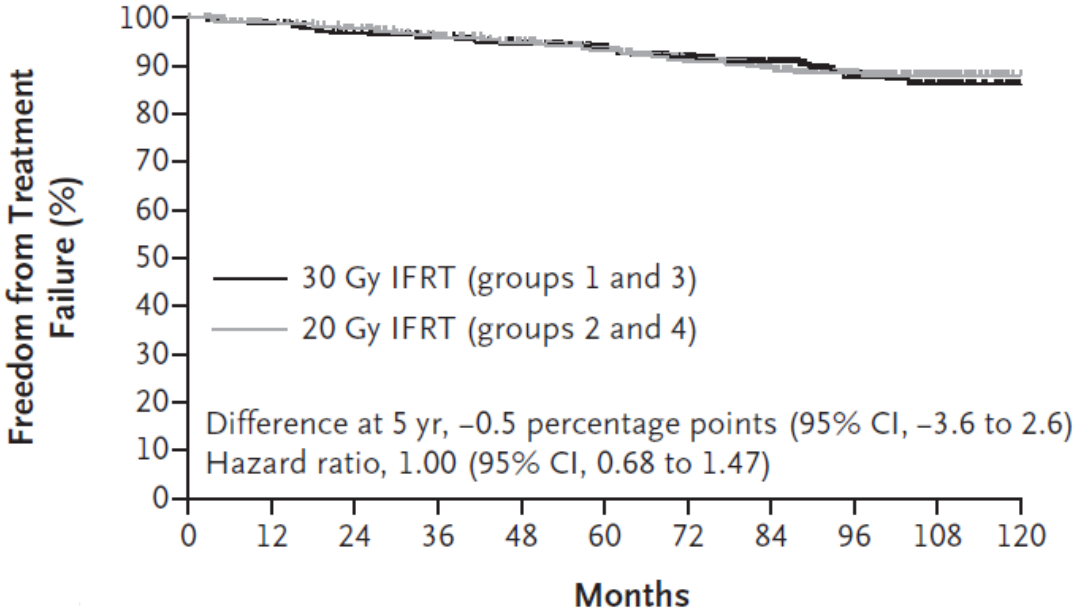


Holte unpublished, 2009

Hodgkins lymfom – stadium I-IIA uten risikofaktorer

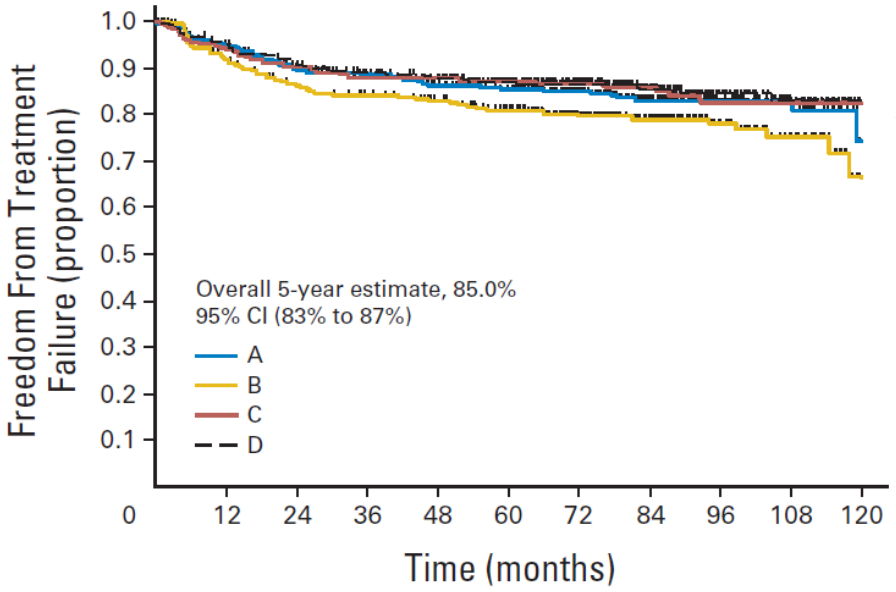


N



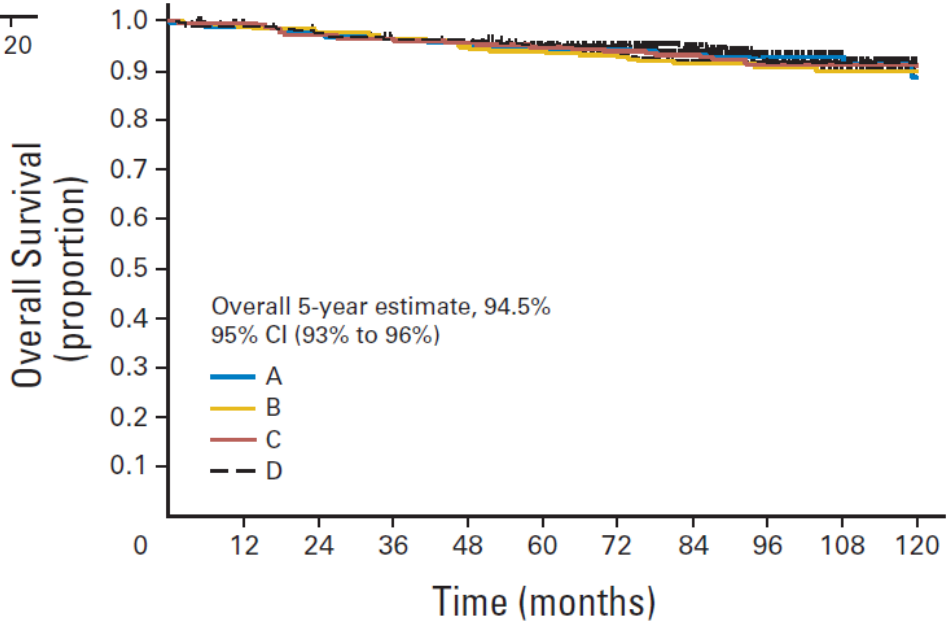
Engert et al, 2010

Hodgkins lymfom – stadium I-IIA med risikofaktorer



4 ABVD x IF 30 Gy

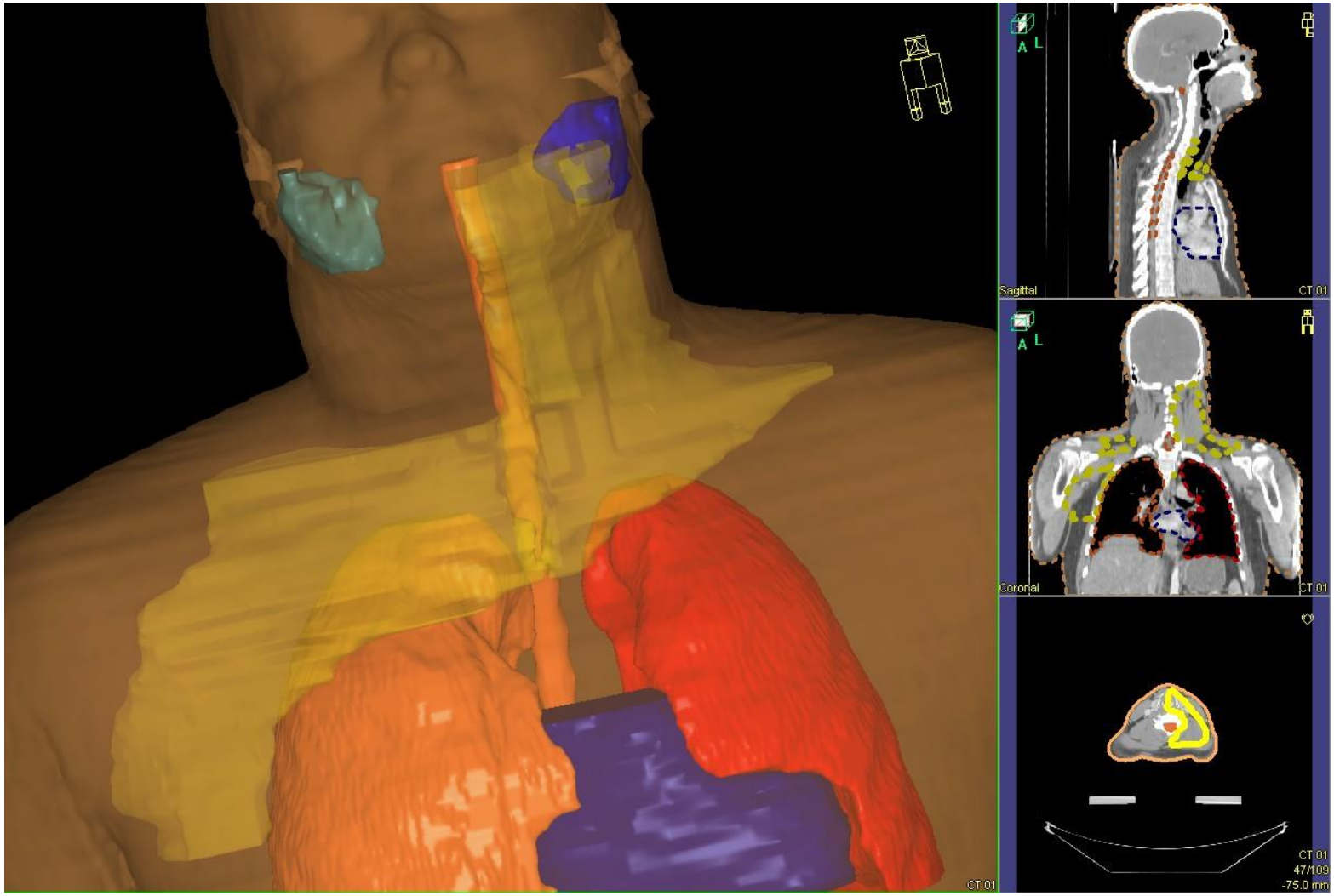
4 ABVD x IF 20 Gy



Eich et al, 2010

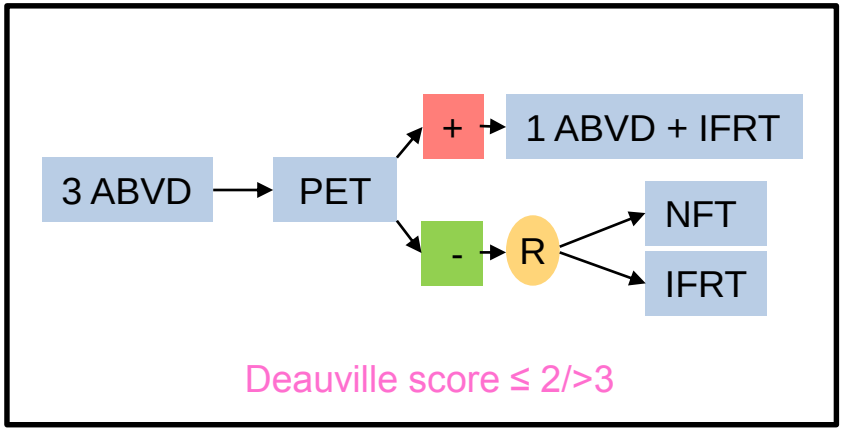
Involved field – modifisert - 3D plan

Involved site



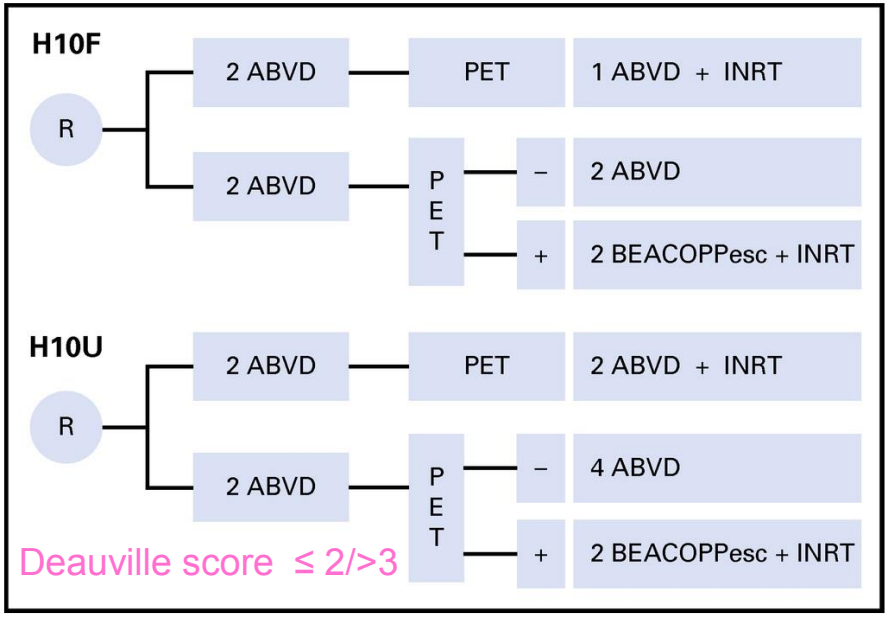
Randomised trials to test the role of interim PET Early stage disease

RAPID*



*Stage I-IIA, no bulky disease or B symptoms

EORTC H10#



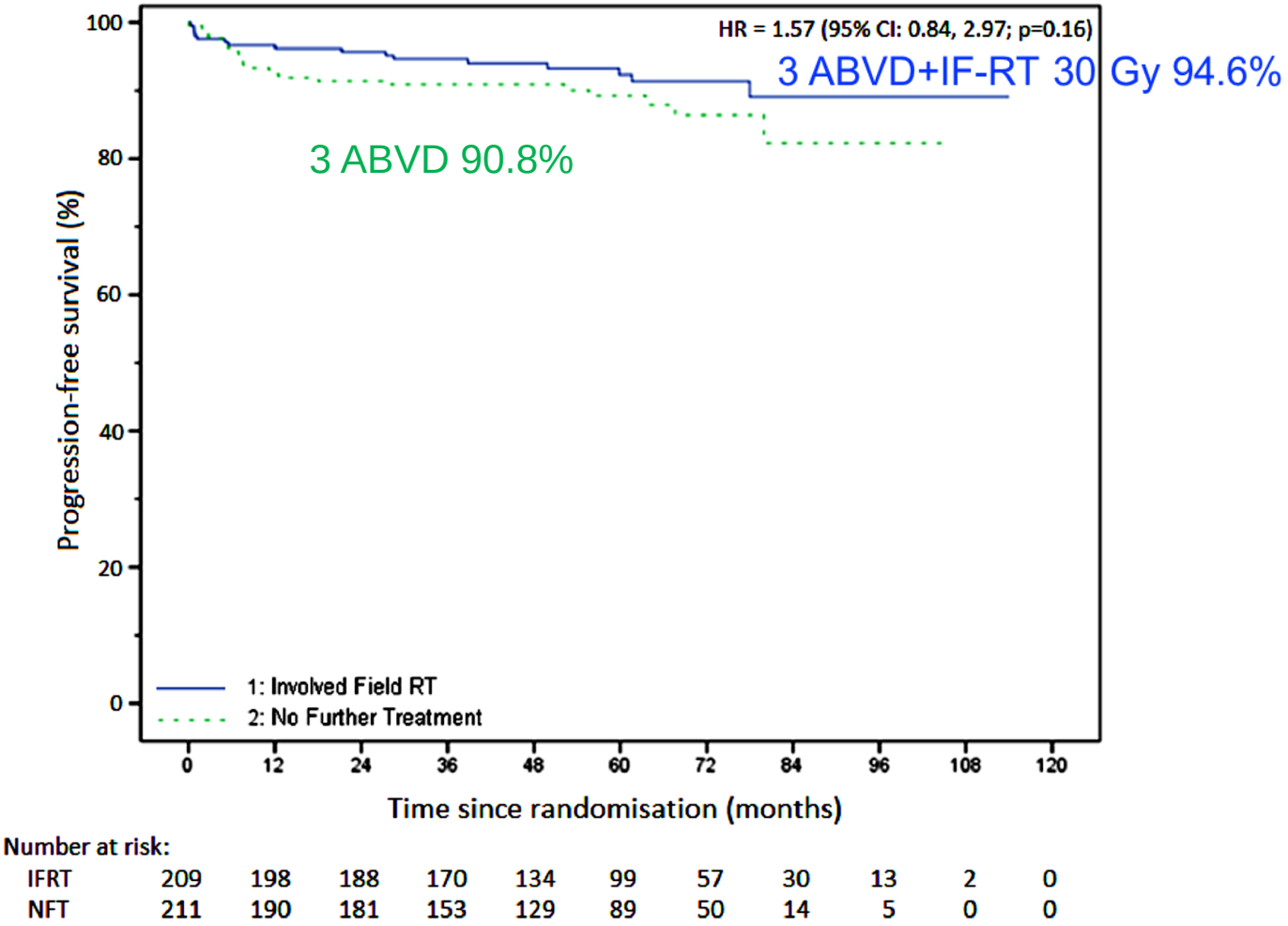
#Stage I-II, bulky tumor and/or B symptoms allowed

ABVD; Adriamycin, Bleomycin, Vinblastin, Dacarbazine, IFRT; involved field radiotherapy, INRT; involved node radiotherapy; NFT; no further treatment, PET; positron emission tomography, BEACOPPesc; Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisolone

RAPID: Progression-free survival at 3 years

Interim PET negative

Intention to treat analysis

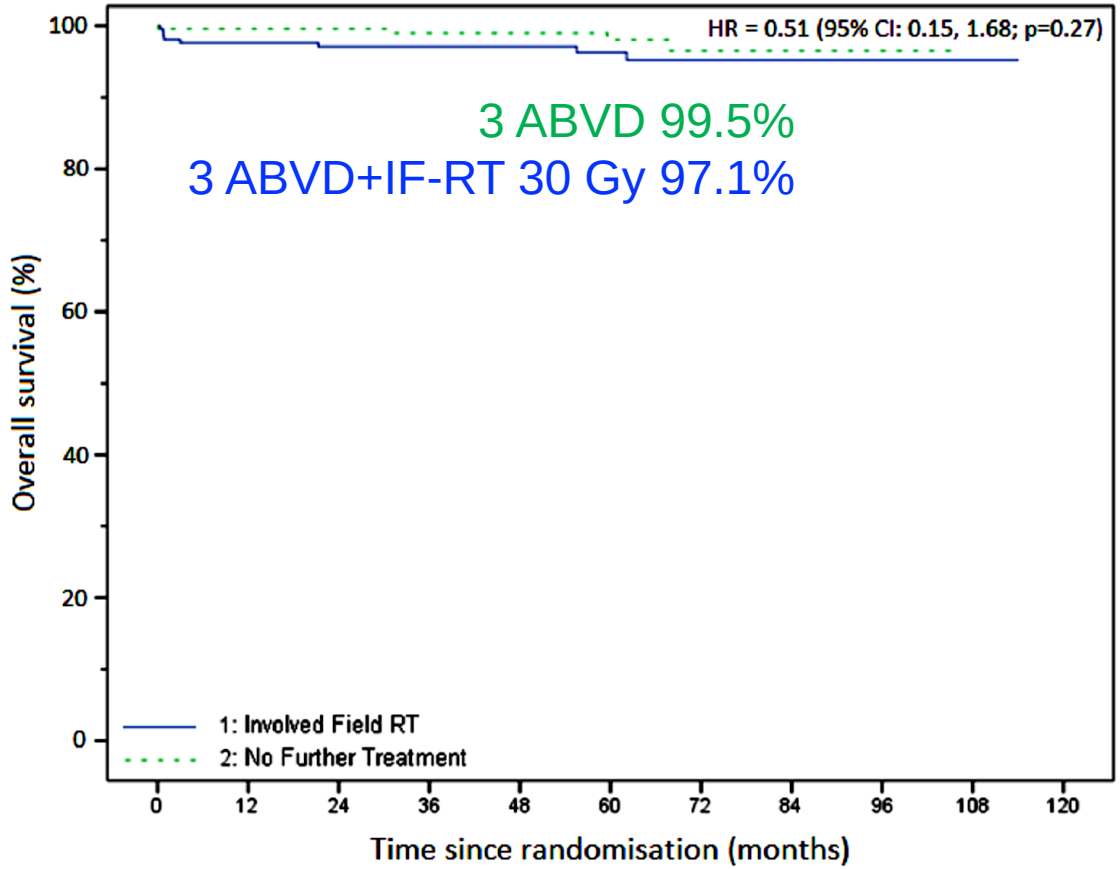


Radford J et al. N Engl J Med 2015;372:1598-1607.

RAPID: Overall survival at 3 years

Interim PET negative

Intention to treat analysis



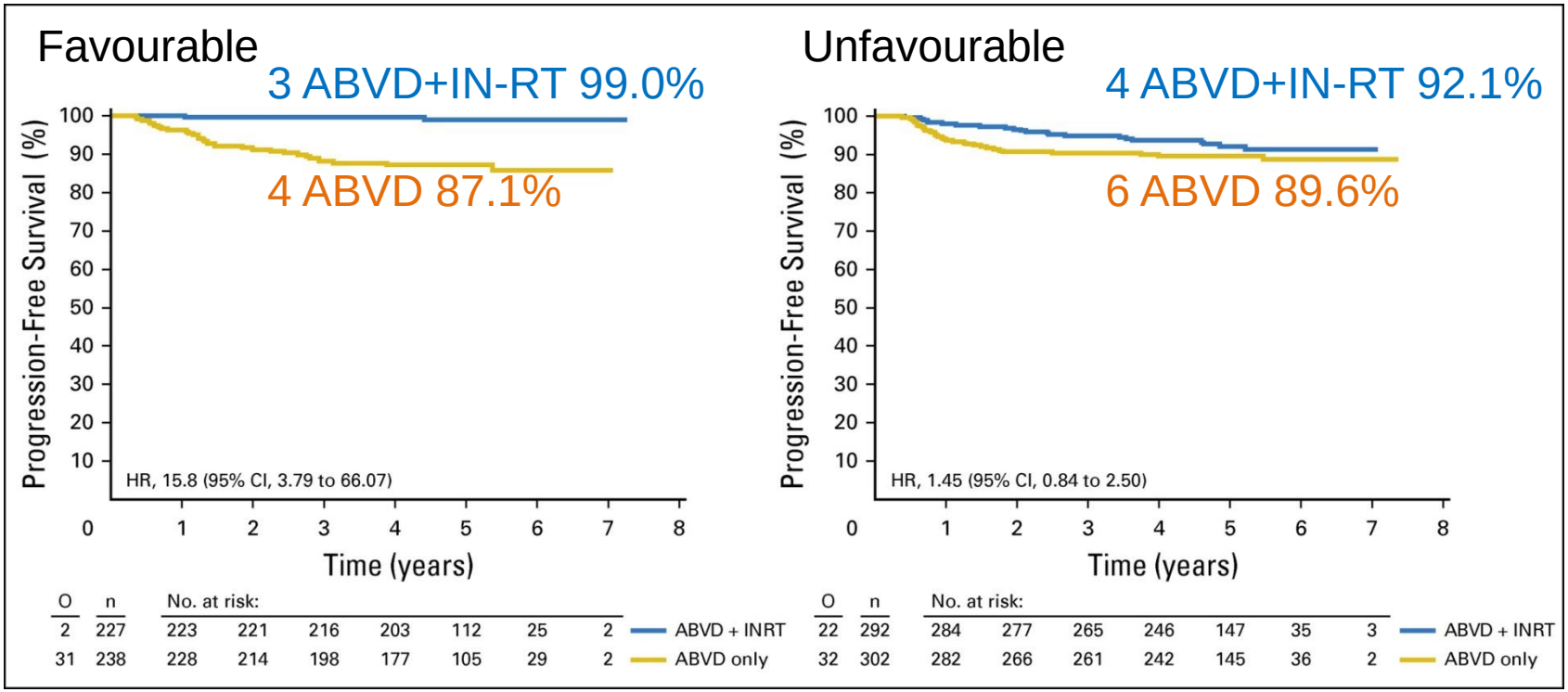
Number at risk:

IFRT	209	200	191	175	139	103	60	34	13	2	0
NFT	211	204	196	167	140	97	56	18	6	0	0

Radford J et al. N Engl J Med 2015;372:1598-1607.

H10: Progression-free survival at 5 years: Interim PET negative

Intention-to-treat analysis



Marc Andre et al. J Clin Oncol 2017;35:1786-1794

H10 PET negative: sites of relapse

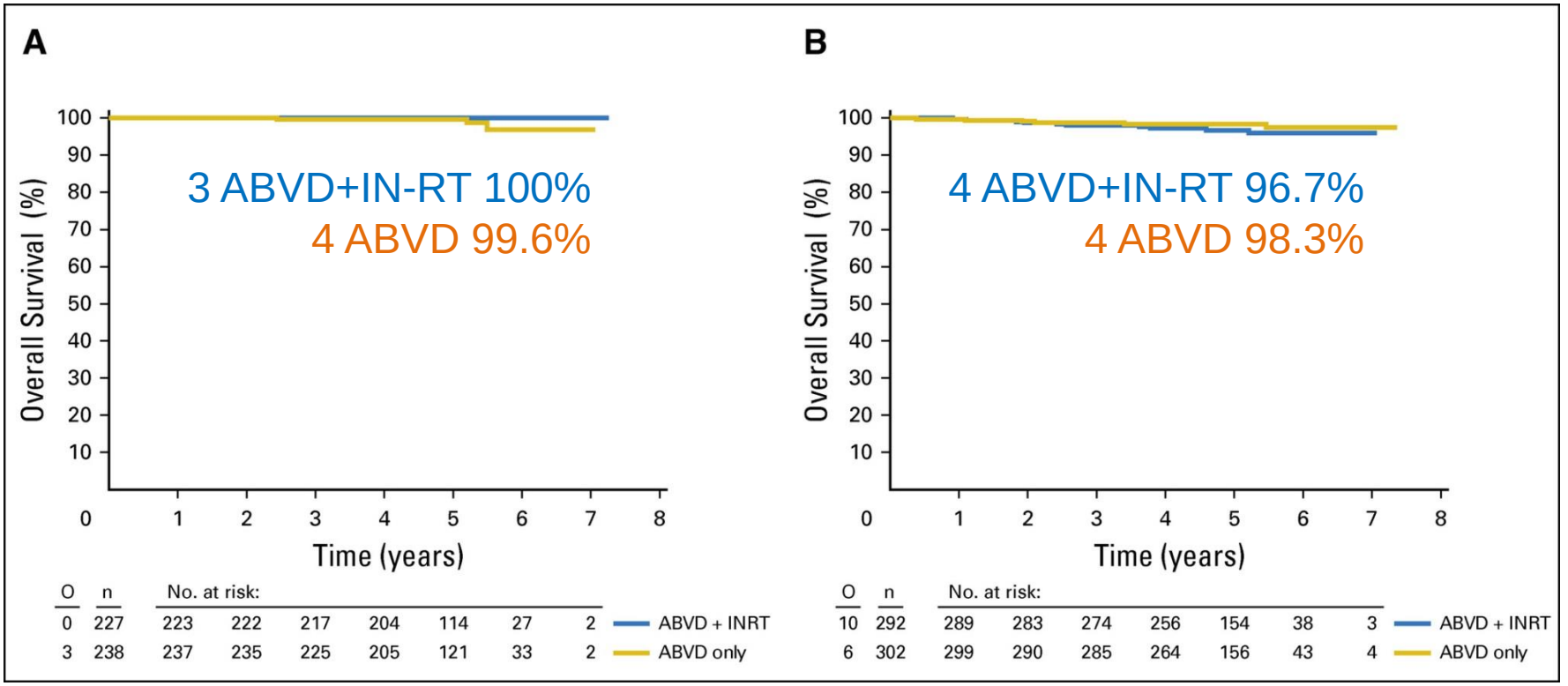
Site of progression/relapse	Favourable		Unfavourable	
	Std. ABVD+INRT N=2/238	Exp. ABVD, no RT N=30/227	Std. ABVD+INRT N=16/292	Exp. ABVD, no RT N=30/302
	N	N	N	N
Initially involved	0	22	5	20
Initially uninvolved	1	5	4	4
Both	1	3	6	6

Median time to relapse	36 months	12 months
N(%) relapses <= 24 months	7/16 (44%)	27/30 (90%)

Marc Andre et al., J Clin Oncol 2017: 35(16):1786-1794

H10: Overall survival at 5 years: Interim PET negative

Intention-to-treat analysis

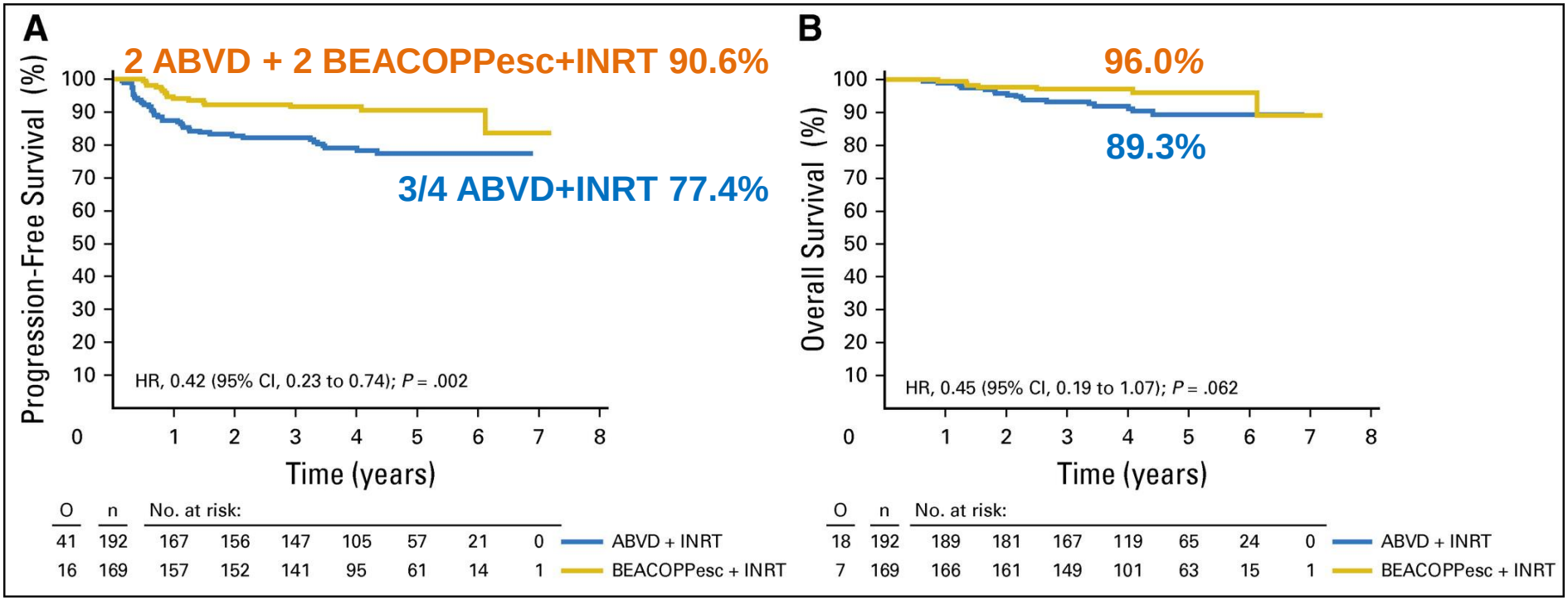


Marc Andre et al. J Clin Oncol 2017;35:1786-1794

H10: Interim PET+: Progression-free and overall survival at 5 years

Intention-to-treat analysis

Deauville score ≥ 3, ~ 20 % of patients



Marc Andre et al. J Clin Oncol 2017: 35(16):1786-1794

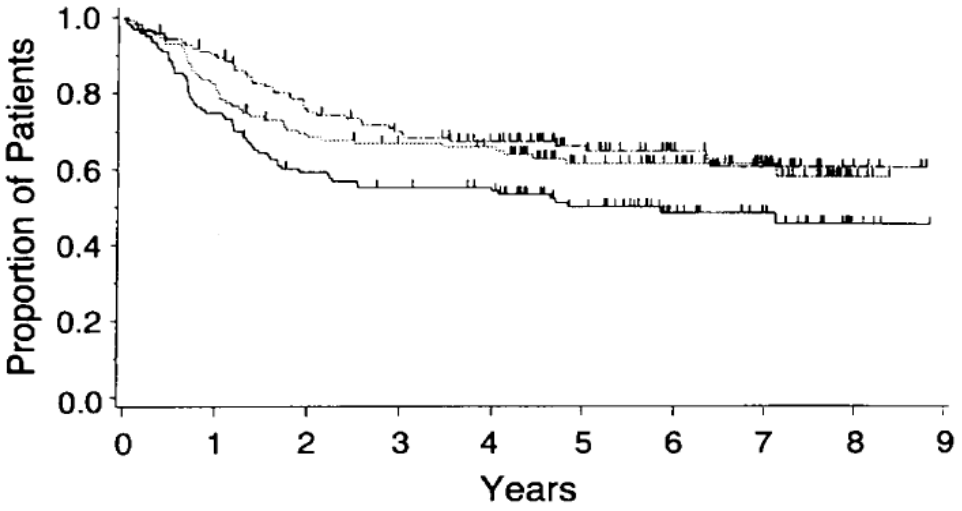
Behandlingsgrupper (≥ 18år)

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

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

Prognostiske faktorer ved avansert Hodgkins lymfom

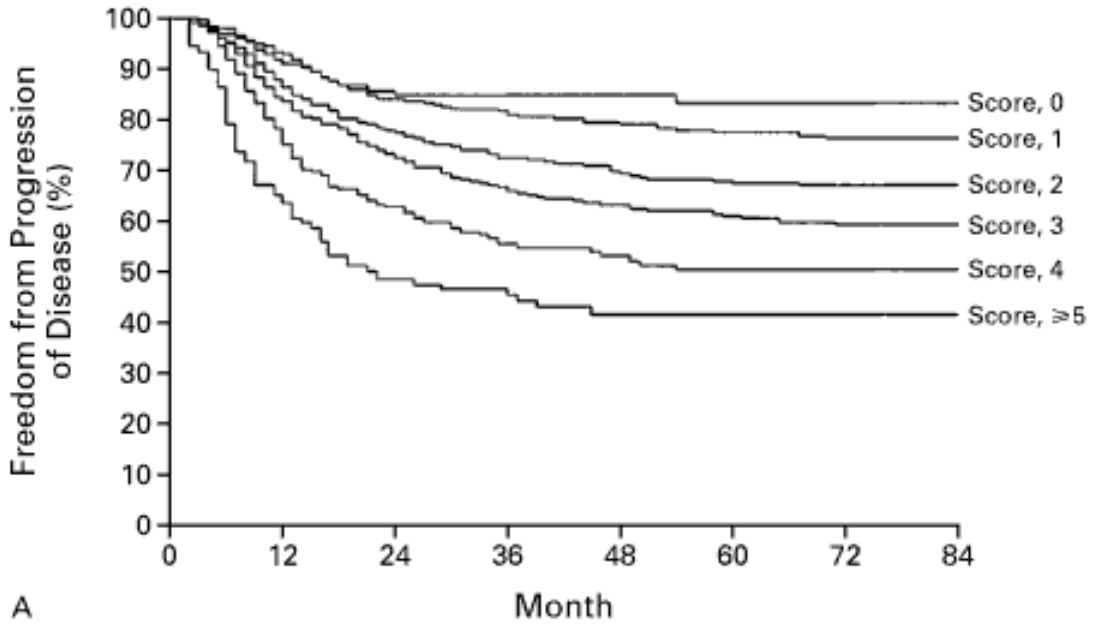
TABLE 2. THE FINAL COX REGRESSION MODEL.*

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).

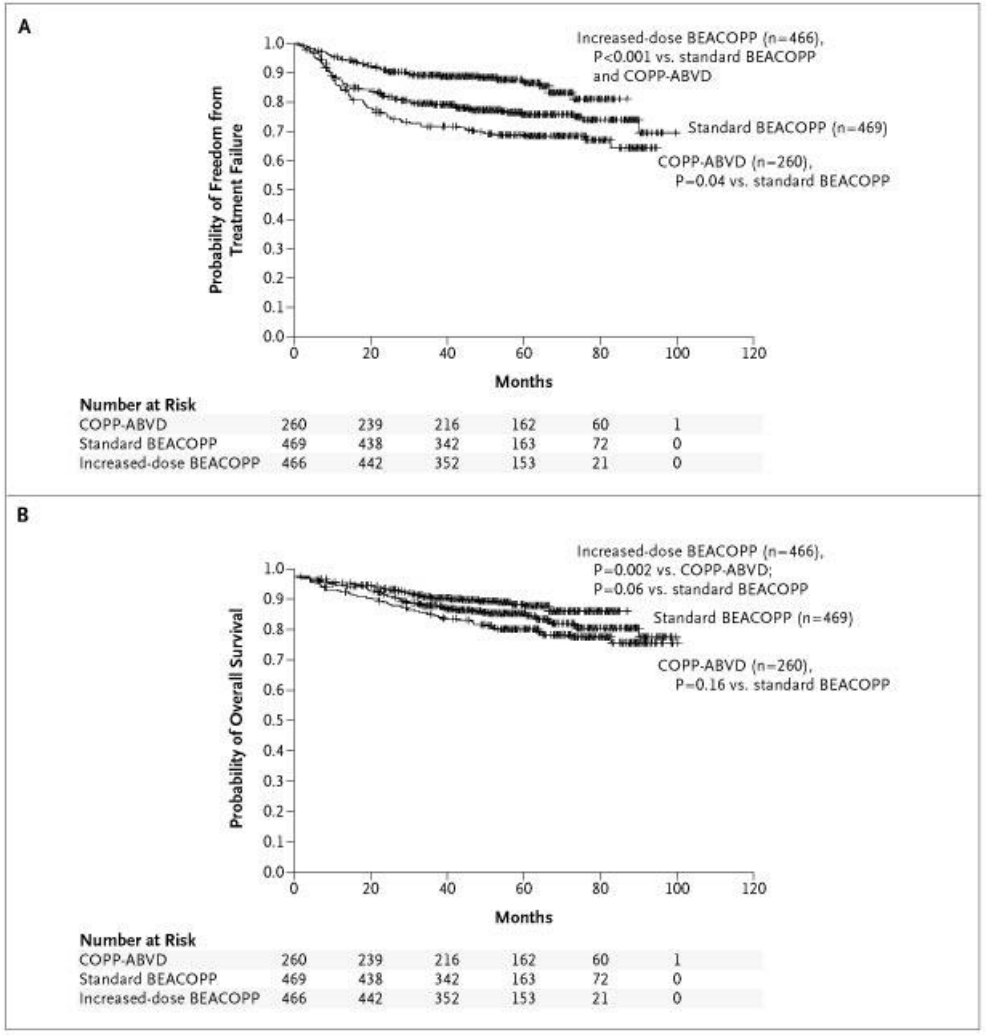
Hasenclever et al, 1998

Prognostiske faktorer ved avansert Hodgkins lymfom



Hasenclever et al, 1998

Doseeskalert BEACOPP sammenliknet med COPP-ABVD for avansert Hodgkin lymfom



Diehl et al, 2003

Behandlingsgrupper (18-60 år)

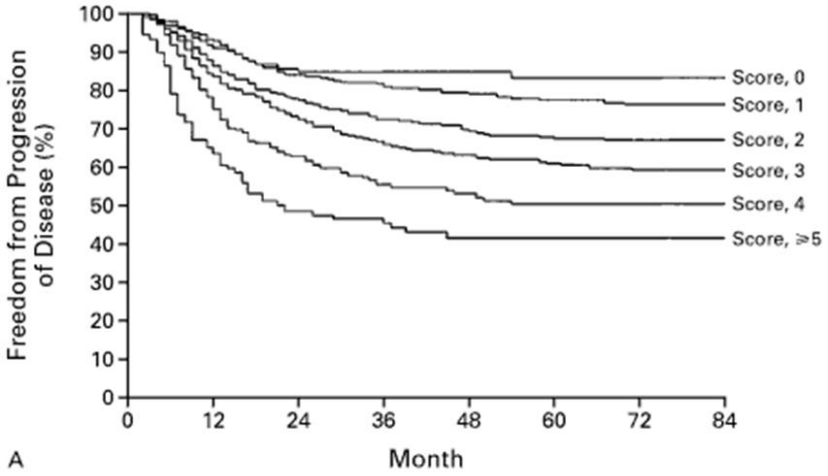
Risikogruppe	Stadium	Risikofaktorer
Tidlig	IA-IIA	Ingen
Intermediær	IA-IIA	Minst én
Avansert	IIB-IV	<4
	IIB-IV	≥4

6-8 ABVD

2 eskalerte
+
6 standard
BEACOPP

Prognose ved avansert Hodgkin lymfom

ABVD type behandling



Hasenclever et al, 1998

Eskalert BEACOPP type behandling

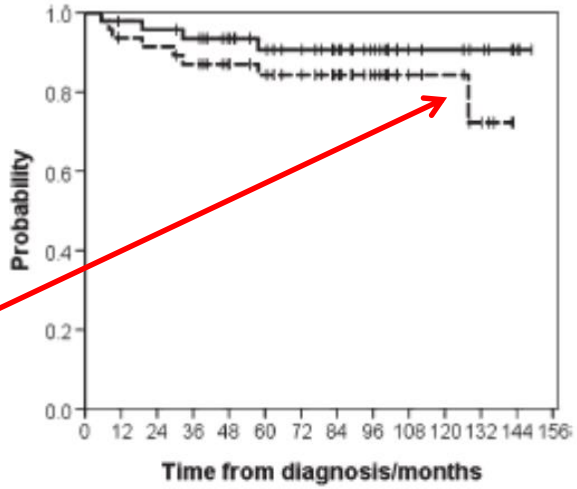
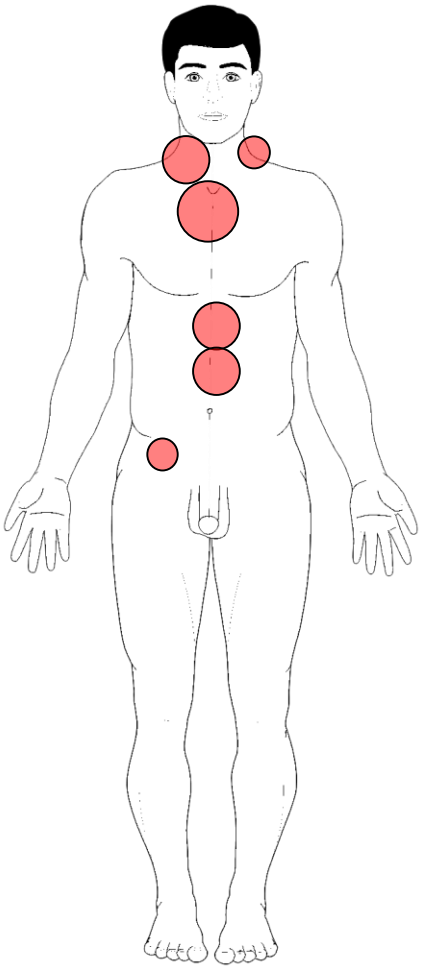


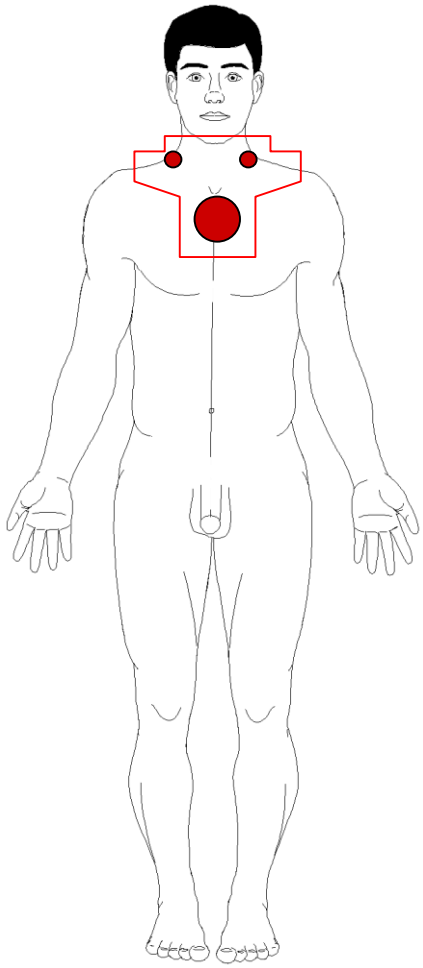
Figure 1. Progression-free (- - - -) and overall (——) survival of 47 patients with intended treatment of two escalated followed by six standard BEACOPP cycles. Median follow-up of surviving patients is 89 months.

Fosså et al, 2011

Hodgkins lymfom – utbredt sykdom IIB-IV - strålebehandling

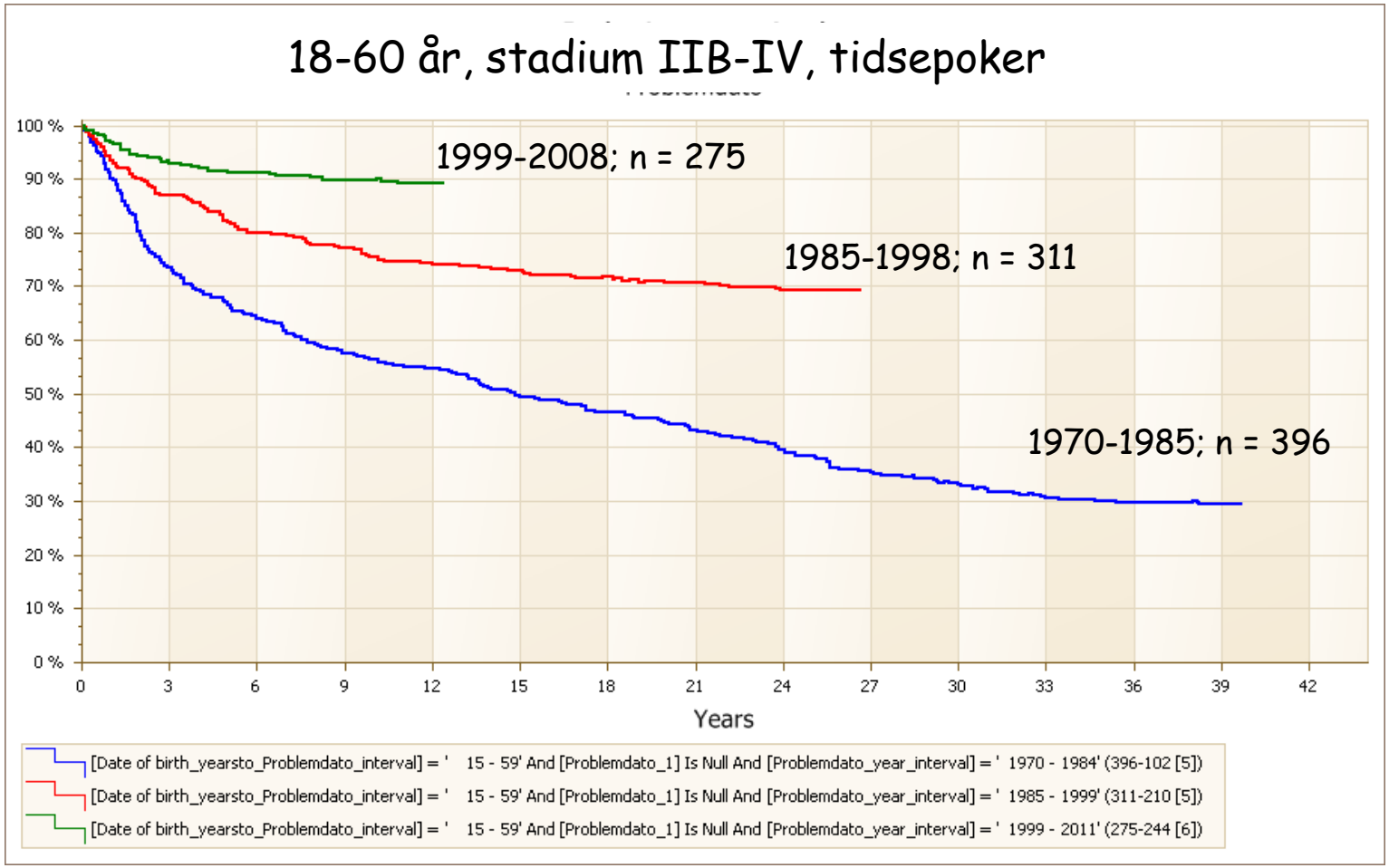


Full kjemoterapi mot makro- og mikroskopisk sykdom



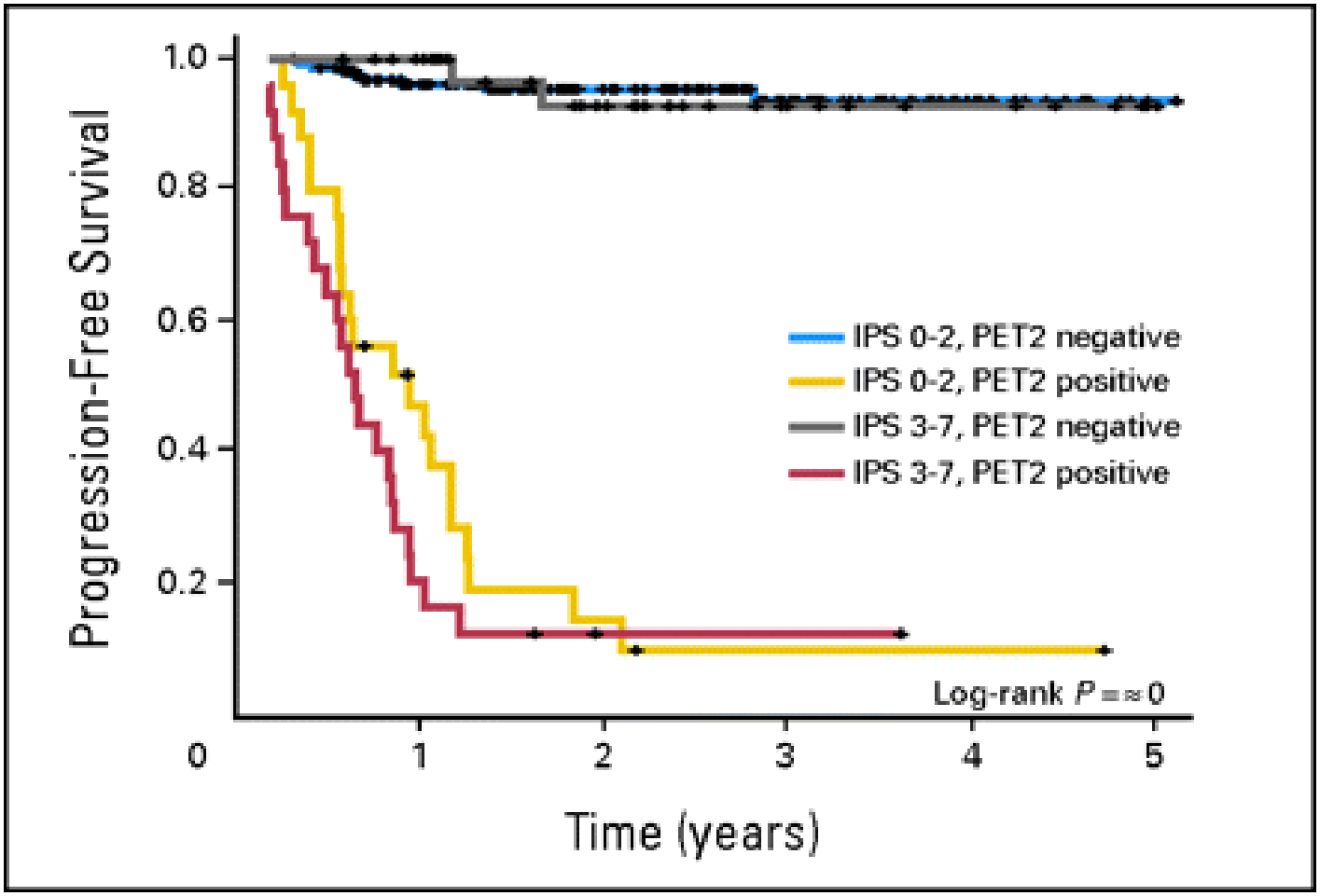
Konsoliderende radioterapi 1,75 Gy x 17 mot begrenset område (Restlymfom, opprinnelig bulky lymfom)

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



Holte unpublished, 2011

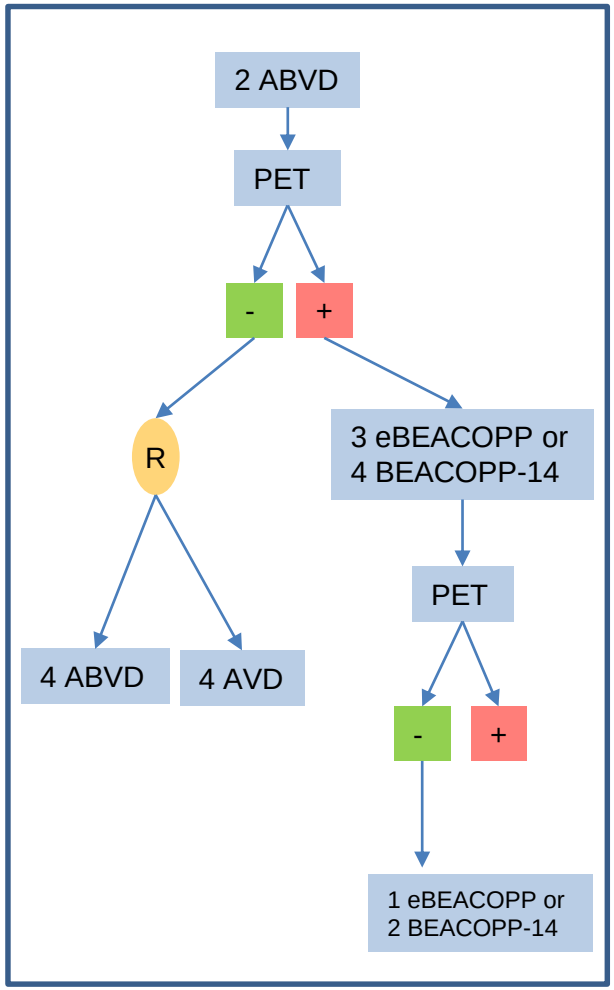
PET-CT og behandling av avansert Hodgkin lymfom



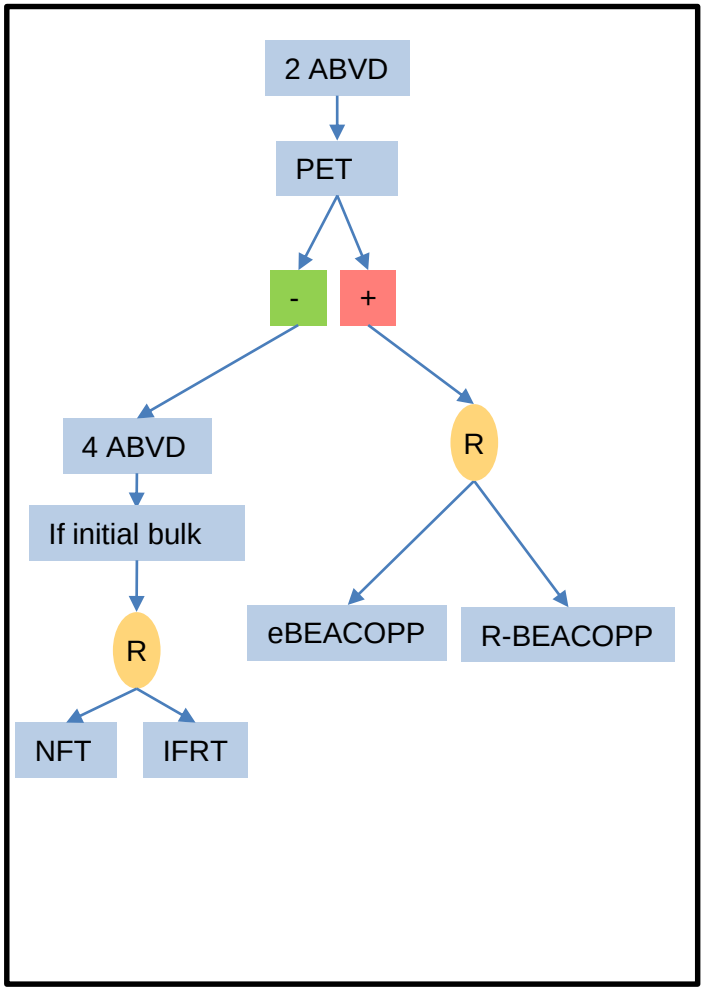
Gallamini *et al*, 2007

Randomised trials to test the role of interim PET in advanced stage disease

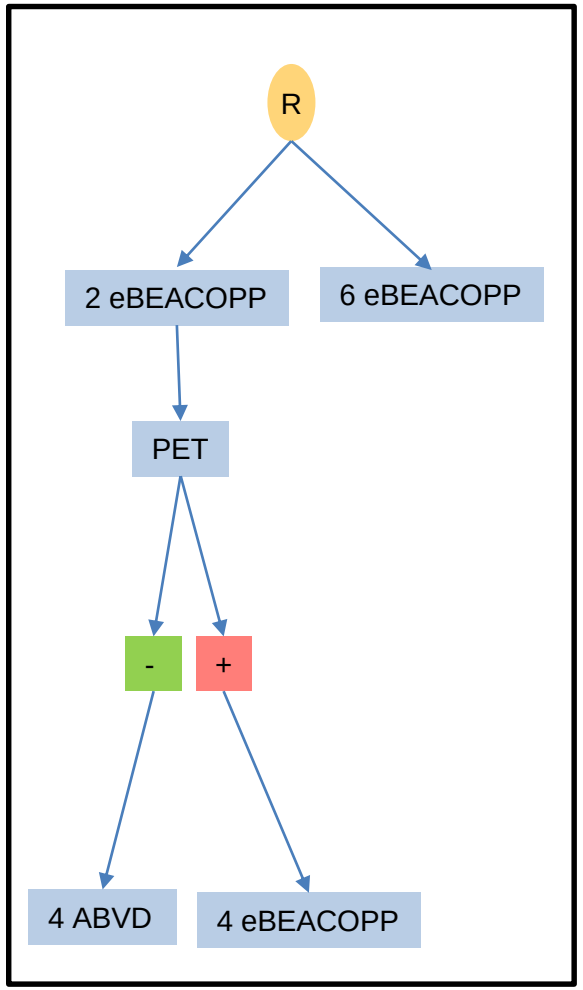
RATHL



GITIL 0607

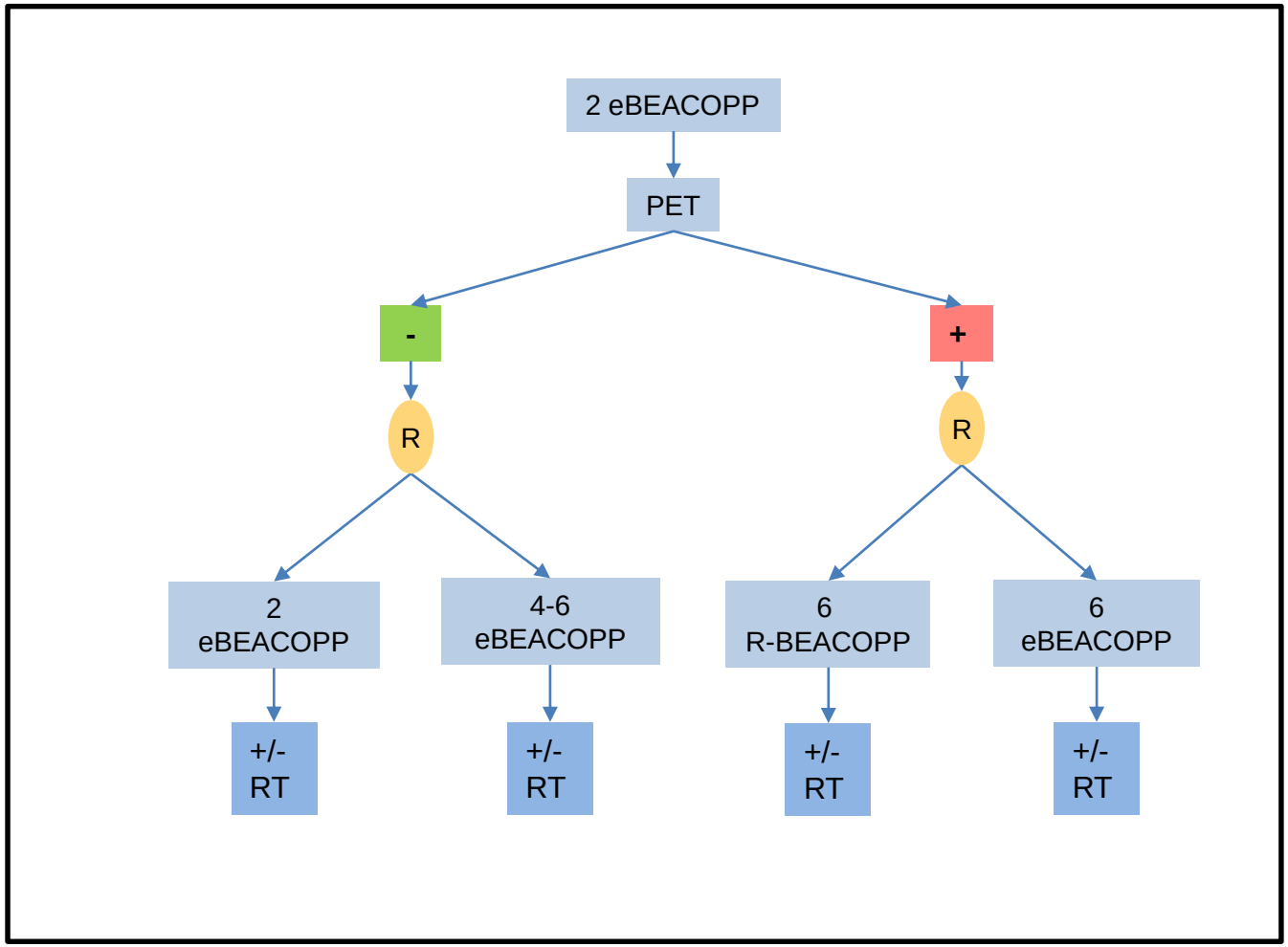


LYSA AHL2011



Randomised trials to test the role of interim PET Advanced stage disease

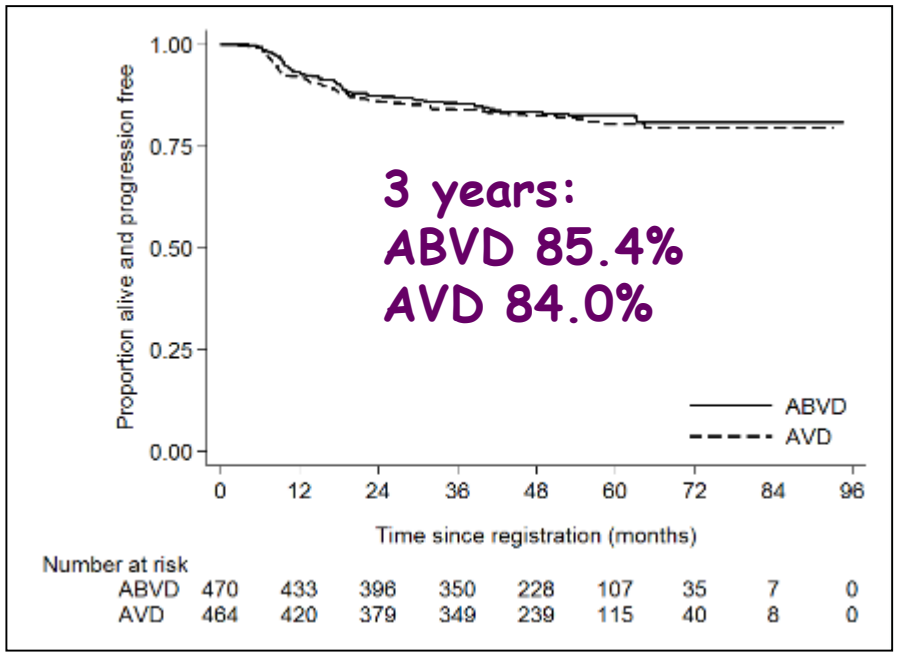
GHSG HD18



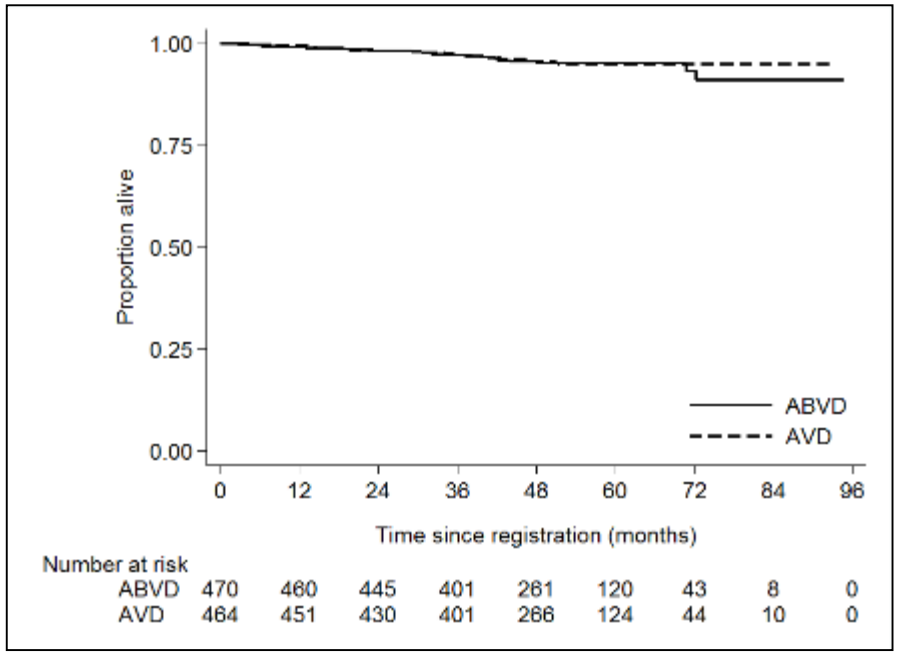
RATHL: Progression-Free and Overall Survival at 3 years for interim PET-negative patients

(median follow up 52 months)

Progression-free survival



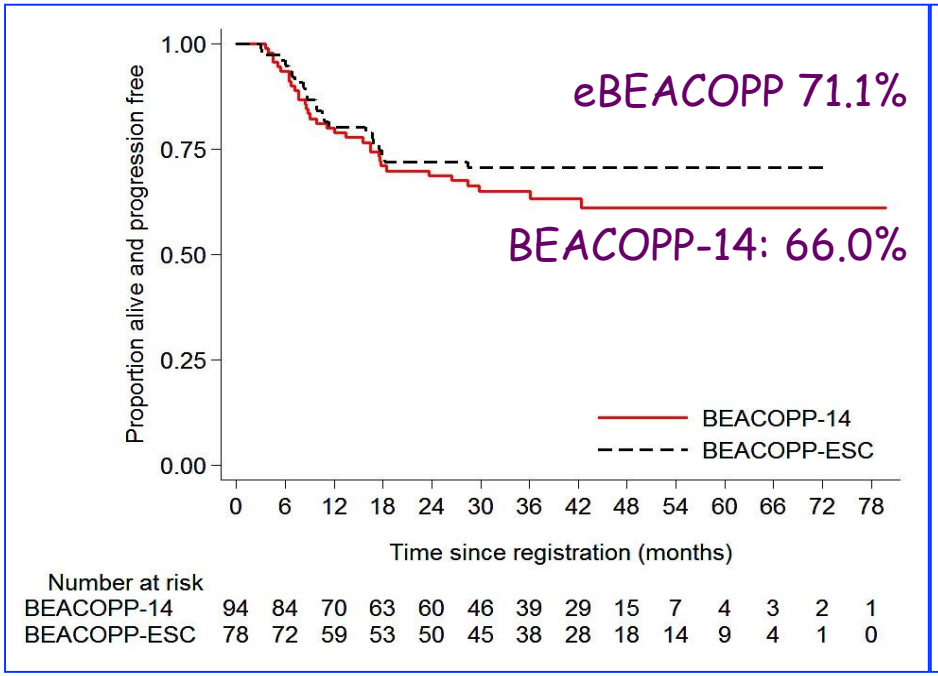
Overall survival

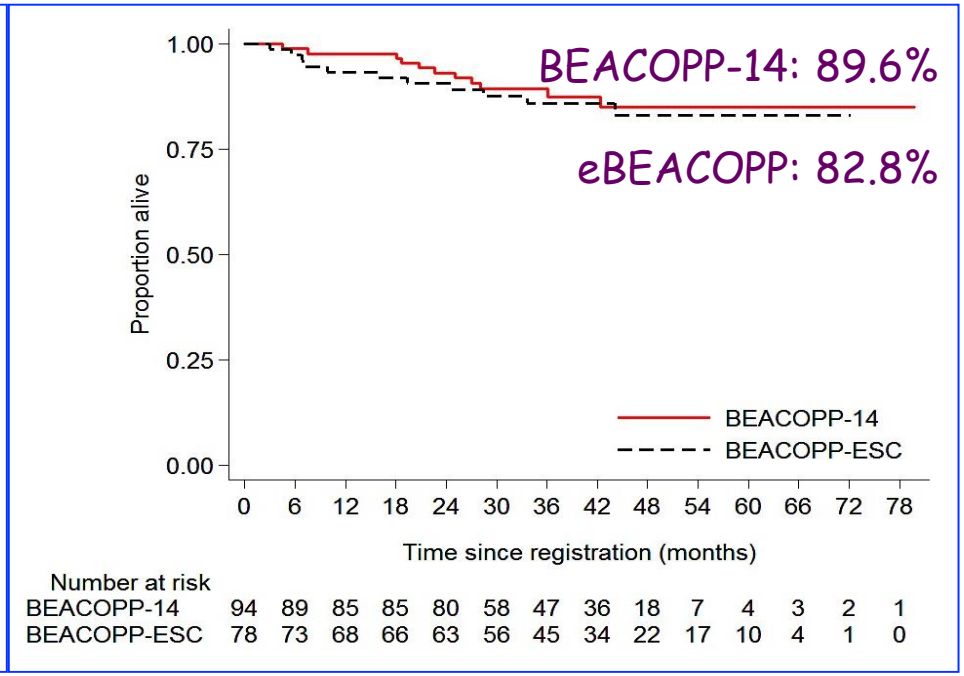


ABVD - AVD = 1.2% (-3.7 to +4.8)
within pre-defined non-inferiority margin of 5%

Johnson P et al. N Engl J Med. 2016;374:2419-29;
Trotman J et al. Hematological Oncology. 2017, 35(S2)

RATHL: Progression-free and overall survival at 3 years for patients with positive PET-2

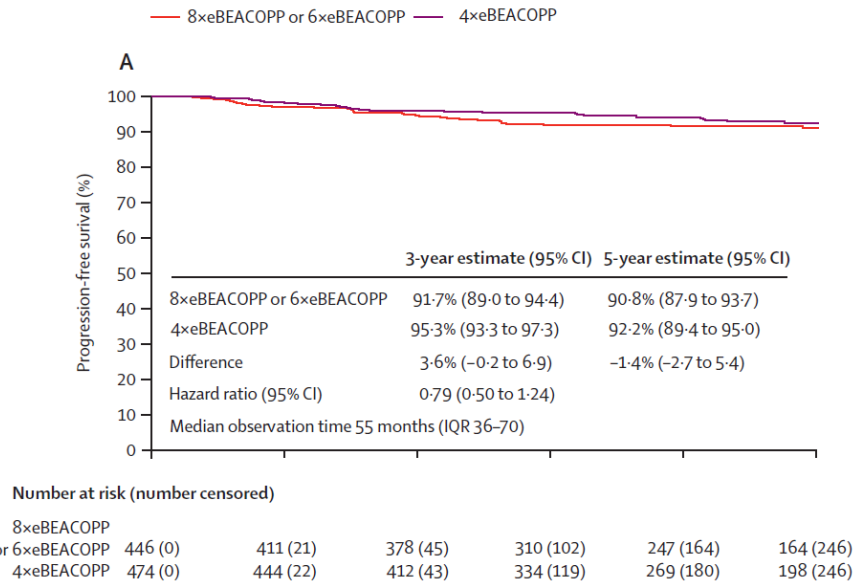


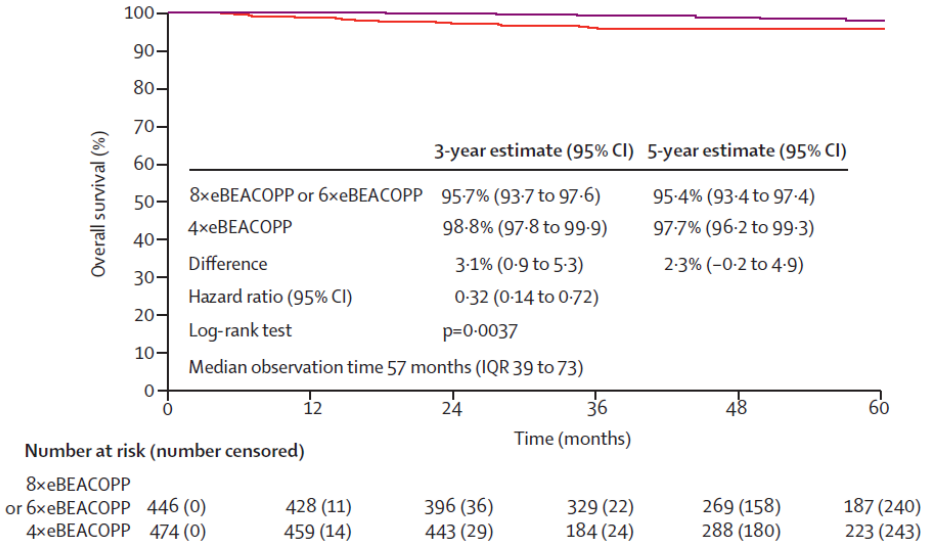


Johnson P. et al., New Engl J Med, 2016. 374:2419-29

GHSG HD 18 trial
Dose reduction starting with escBEACOPP

Deauville score ≤ 2, ~ 60 % of patients



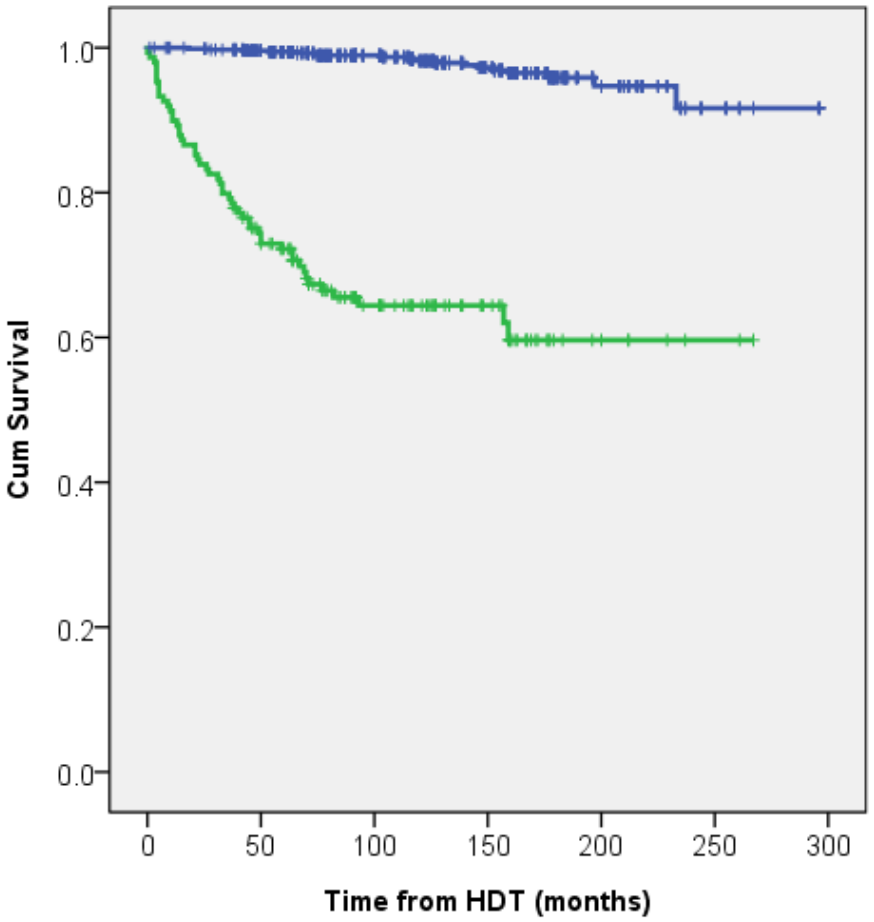


Borchmann P et al., Lancet Oncol 2017; online Oct 20

Residivbehandling

- 1. residiv
  - IGEV + HMAS +/- strålebehandling
  - Brentuximab vedotin som induksjon og vedlikehold
  - IGEV, DHAP, IME, LVPP, BEACOPP +/- strålebehandling
- 2. residiv
  - mange regimer, inklusive brentuximab vedotin, nivolumab, pembrolizumab
  - allogen TX

Langtidsoppfølging etter HMAS for residiv av Hodgkin lymfom



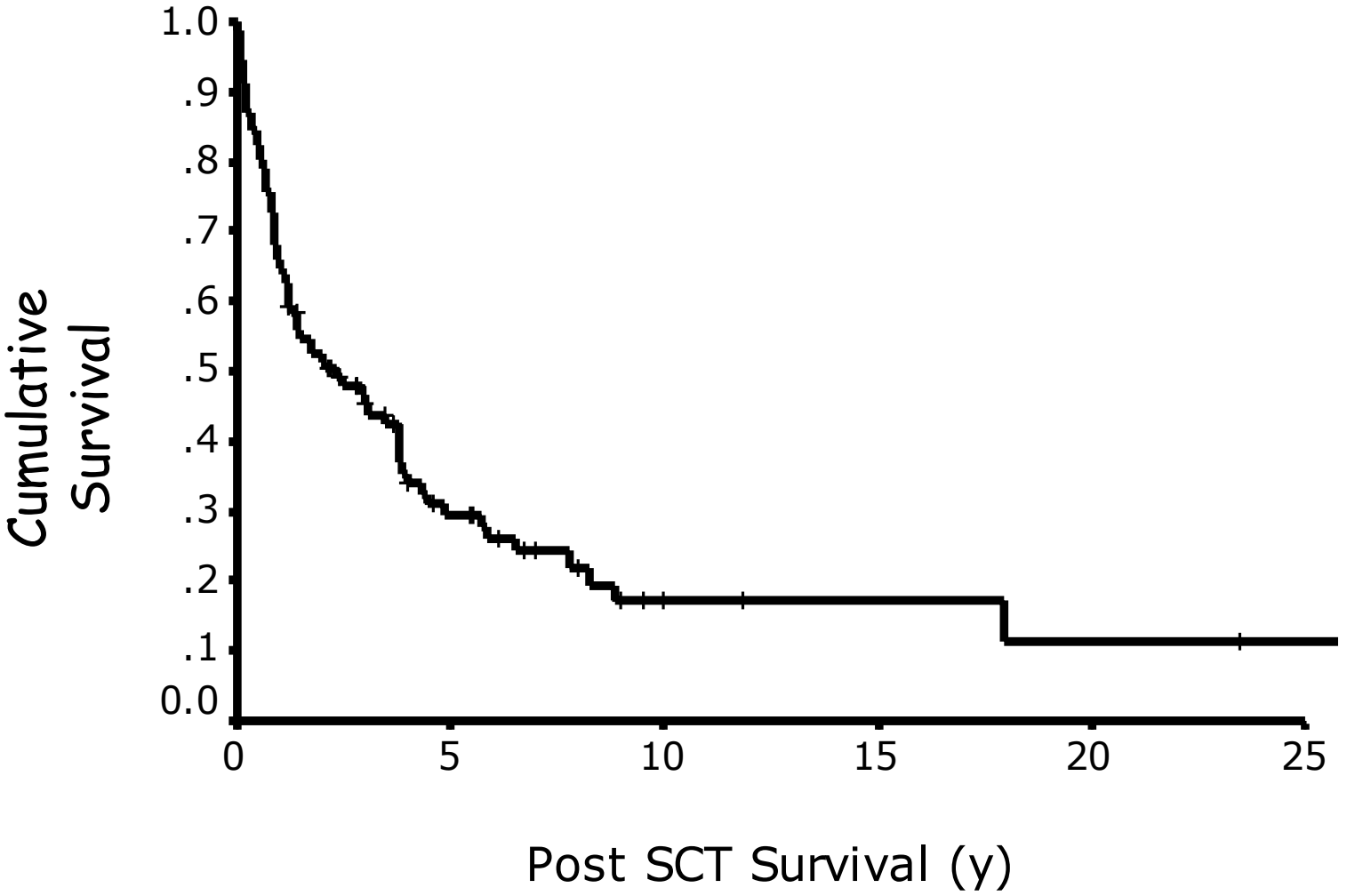
Causes of death:

30 (60 %) HL
9 (18 %) NHL
3 (6%) Hem mal
2 (4%) CVD
6 (12%) other

Overall survival after HDT for Hodgkin's lymphoma in green (n=149) versus age- and gender matched controls in blue (n=745). HR 19 (95% CI: 11-32), p<0.001.

Smeland et al, 2015

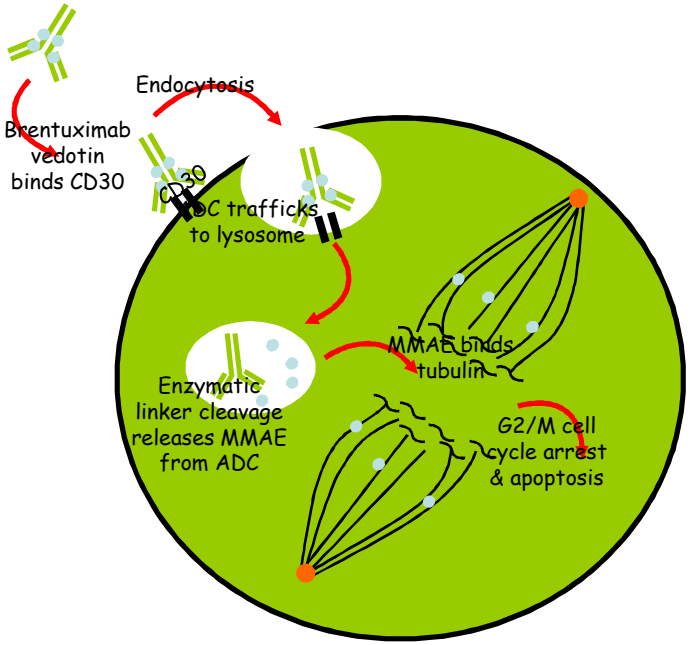
Relapse after high dose therapy and autologous stem cell
Overall survival

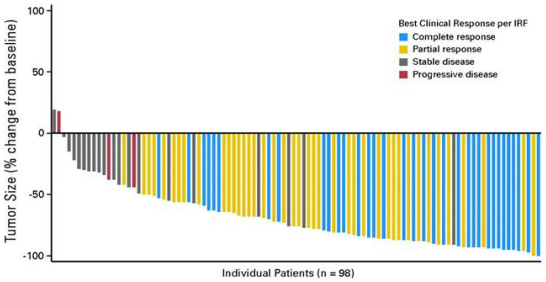


Horning et al. 10th ICML; Lugano, Switzerland; 2008.

New drugs in Hodgkin lymphoma

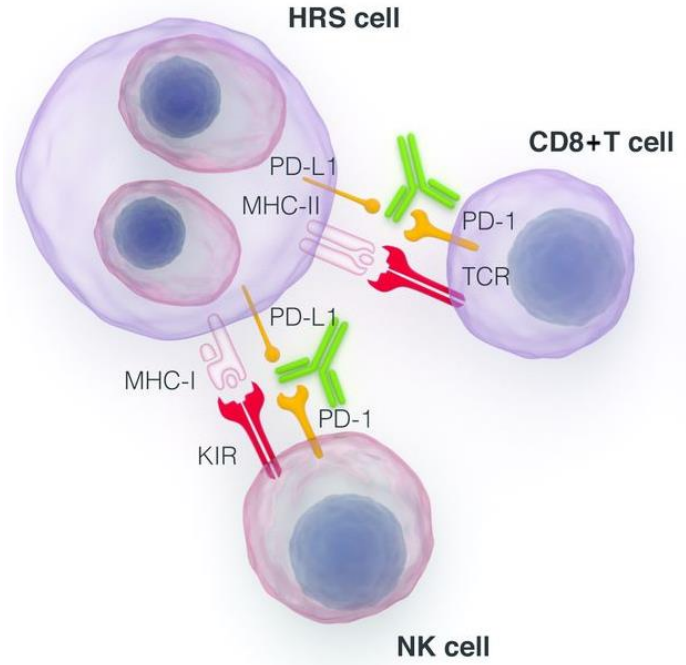
Brentuximab vedotin
Antibody-Drug Conjugate

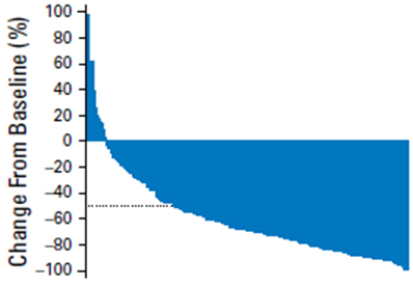




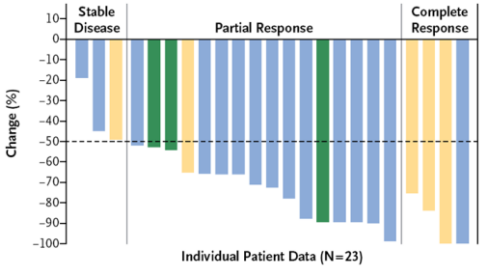
Younes et al; 2012

PD-1 inhibitors
Nivolumab, Pembrolizumab





Chen et al; 2017

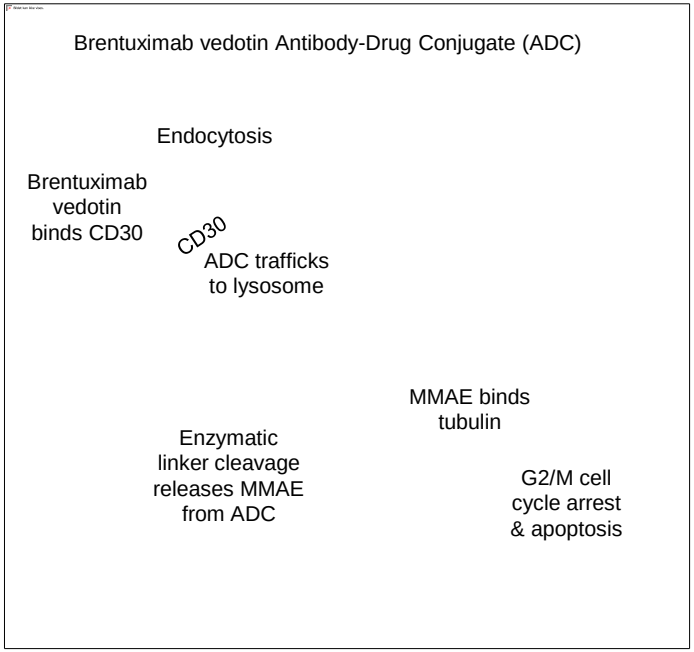


Ansell et al; 2014.

Brentuximab vedotin: oversikt

Tre komponenter:

- Antistoff: binder seg til CD30
- Cytostatikum: monomethyl auristatin E (MMAE), et vinca alkaloid
- Linker: protease-følsom linker binder MMAE til antistoff



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

Brentuximab vedotin: Fase II

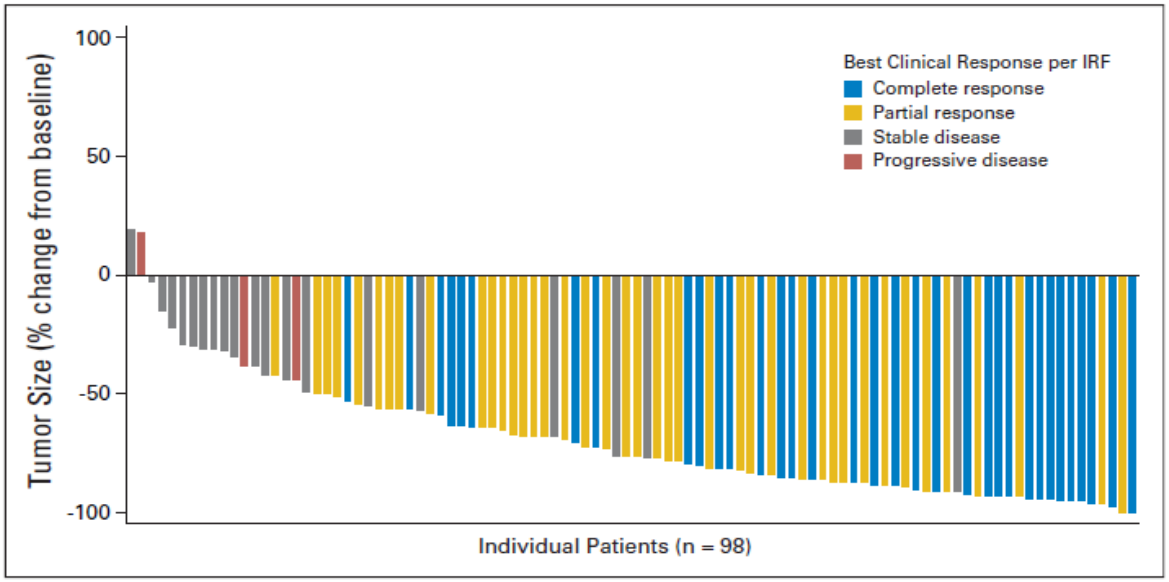
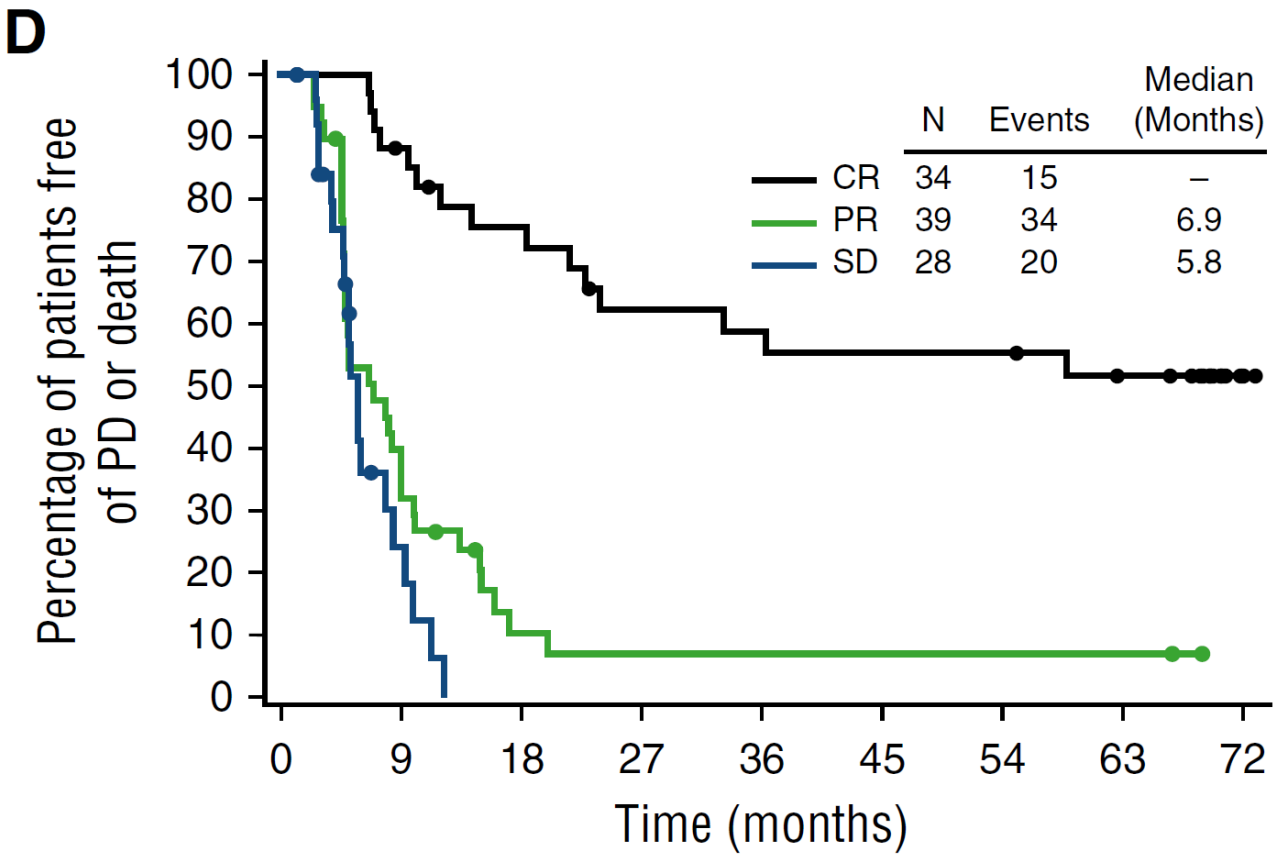


Fig 1. Maximum percent reduction in the sum of the product of diameters in individual patients (n = 98) per Cheson et al.[12] Tumor size reductions were observed in 96 (94%) of 102 patients. Four patients were not included in the analysis; three patients had no measurable lesions per independent review facility (IRF), and one patient had no postbaseline scans.

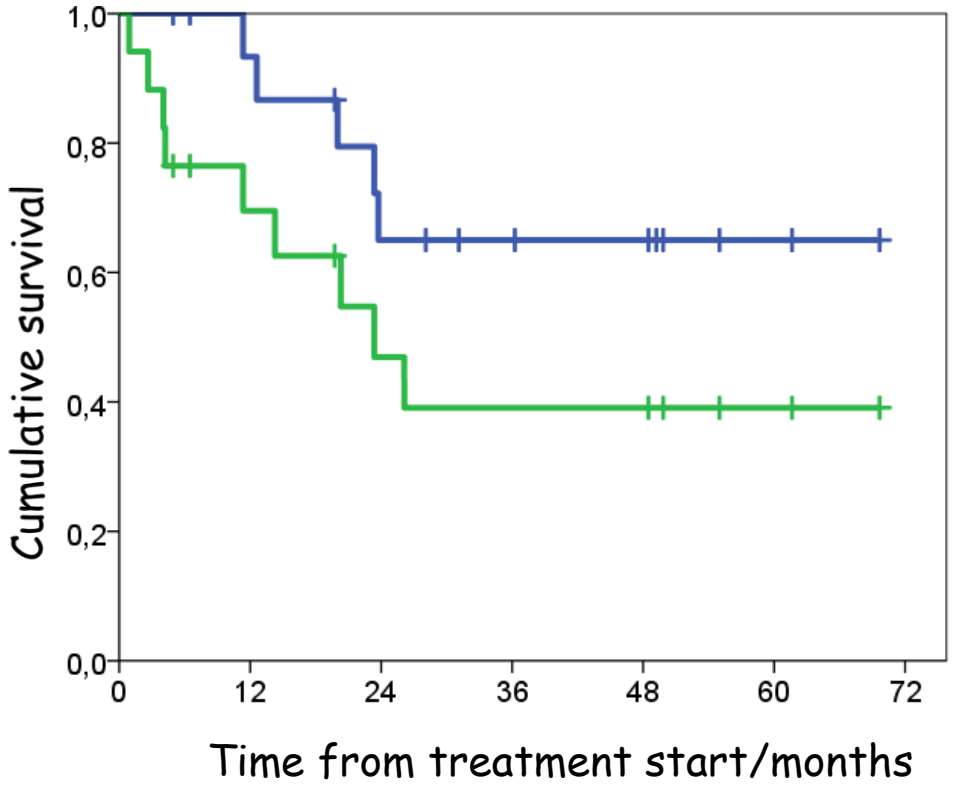
Younes et al, JCO, 2012

Brentuximab vedotin: Phase II



Chen R, et al, 2016

Survival data, cHL patients with post ASCT relapse



All patients:
Median OS not reached
Median PFS 23.4 months
5 year OS 65 %
5 year PFS 39 %

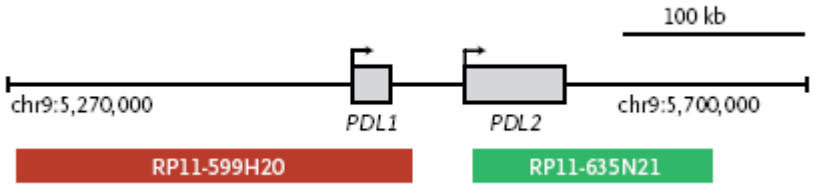
Overall survival, HL patients post ASCT relapse

Progression-free survial, HL patients post ASCT relapse

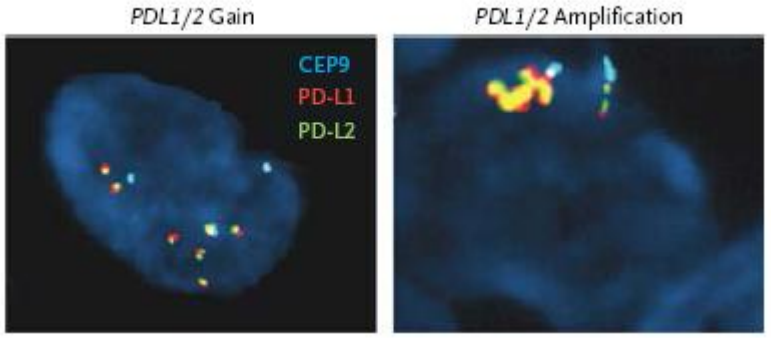
ASCT, autologous stem cell transplantation; cHL, classical Hodgkin lymphoma; PFS, progression free survival; OS, overall survival

PDL1/2 i Hodgkin lymfom

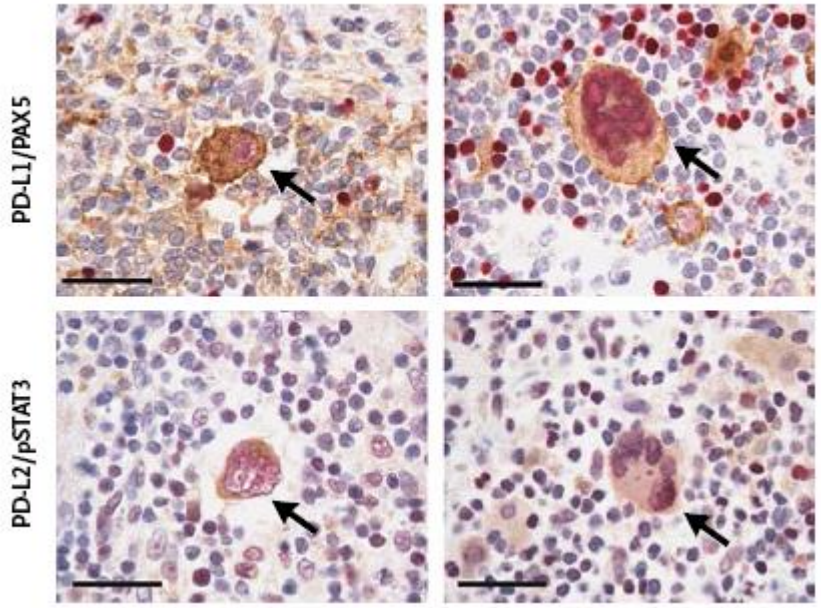
A



B



C

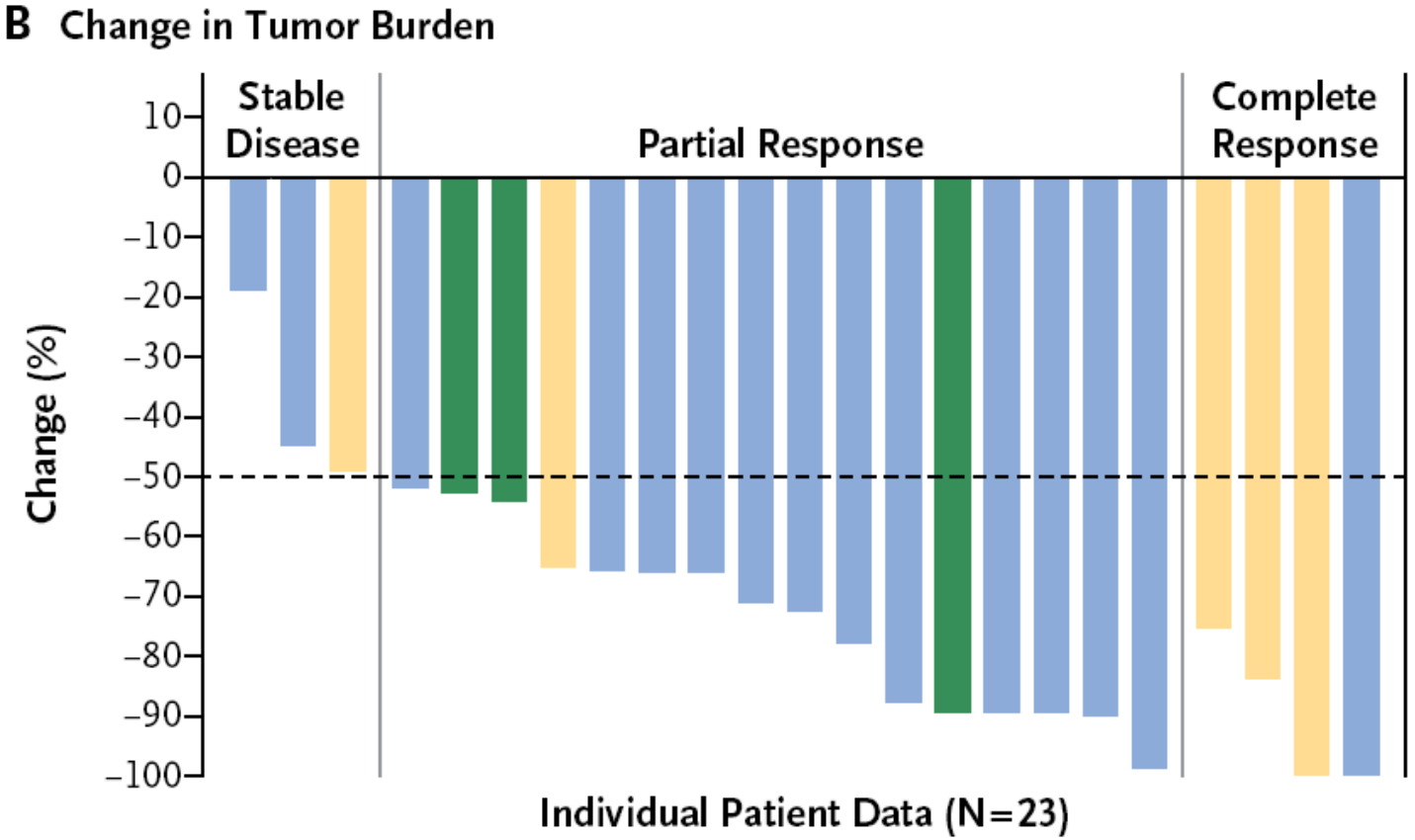


D

Patient No.	Cytogenetic Alterations			IHC-positive HRS cells		Nuclear pSTAT3	EBER
	Polysomy 9p	*PDL1/2* Gain	*PDL1/2* Amplification	PD-L1	PD-L2		
1	+	–	–	+	+	+	–
2	+	–	–	+	+	+	–
3	+	–	–	+	+	+	–
4	+	+	–	+	+	+	–
5	+	+	–	+	+	+	–
6	+	+	–	+	+	+	+
7	+	+	+	+	+	+	–
8	+	+	+	+	+	+	–
9	–	+	+	+	+	+	–
10	–	–	+	+	+	+	–

Ansell et al; 2014.

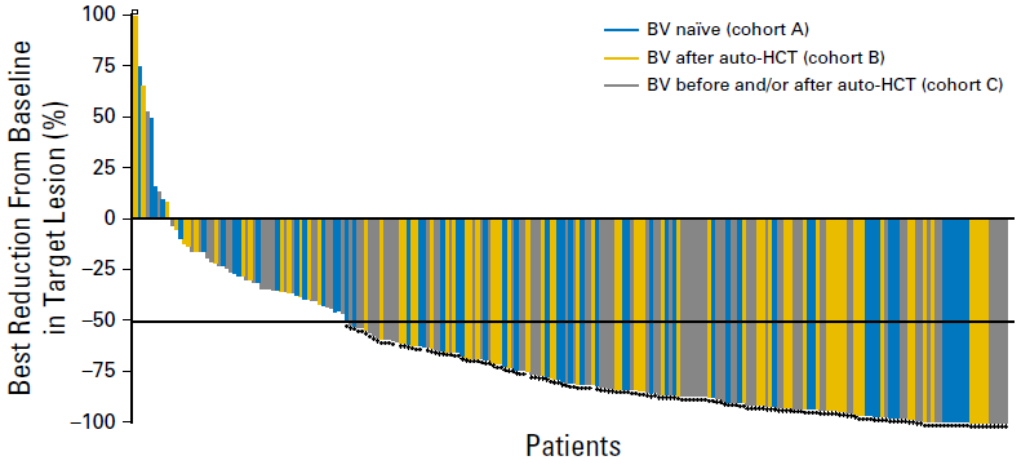
Nivolumab and Hodgkin



Ansell et al; 2014.

Intermediate term results pf PD-1 inhibition i cHL

A



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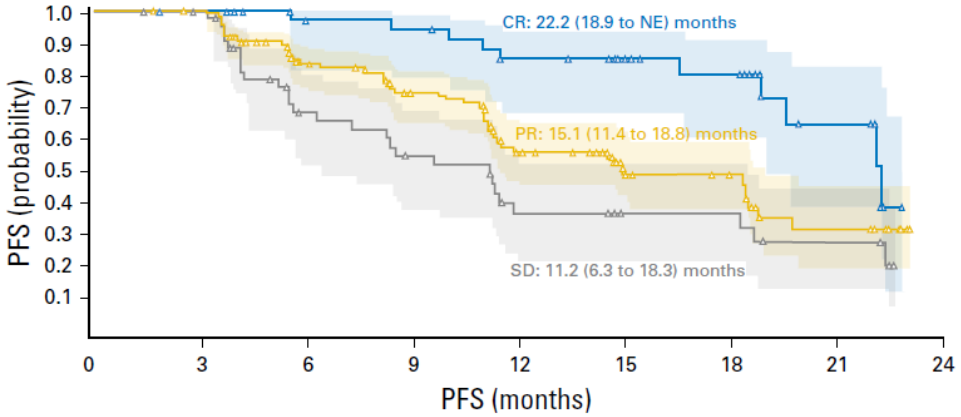
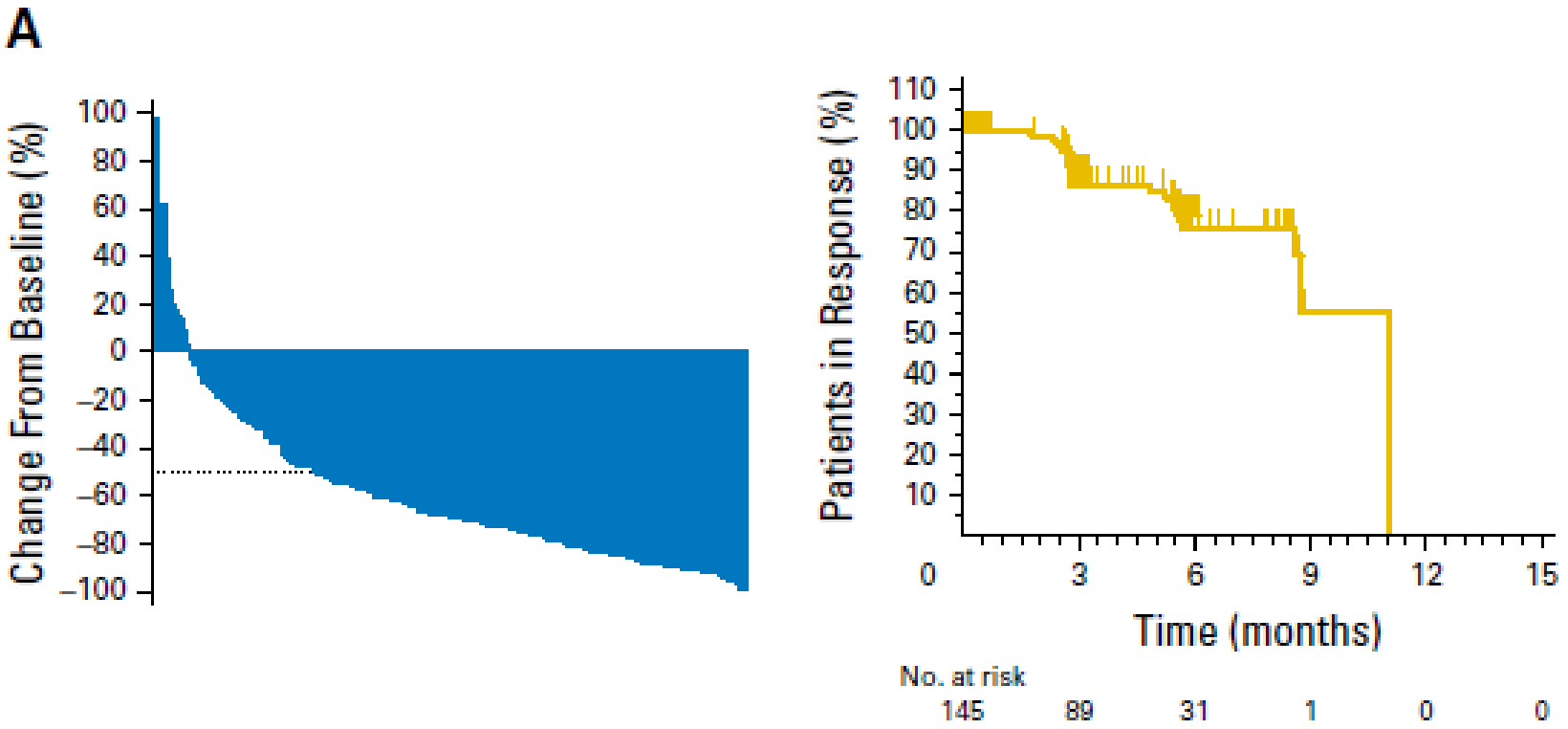


No. at risk:

CR	40	40	33	32	27	20	16	7	0
PR	128	126	89	71	46	25	21	8	0
SD	47	44	25	19	11	8	8	5	0

Ansell et al; 2018.

Pembrolizumab Keynote 087



Chen et al; 2017

Oppsummering

- Gjennomgang av behandlingsstrategier hos voksne og eldre
- Gode behandlingsresultater hva angår kurasjon, PET-respons adaptert
- Nye medikamenter er brentuximab vedotin og PD-1 hemmere
- Fokus på langtidsoverlevere og senskader