Non-Hodgkin lymfomer

Et helhjertet forsøk på å hjelpe LIS-leger til å forstå hvordan man vurderer og behandler pasienter med non-Hodgkin lymfom, samt øke LIS-legers lyst til å satse på lymfom-onkologi!!!!

Arne Kolstad
Radiumhospitalet
2014

Sykehistorie

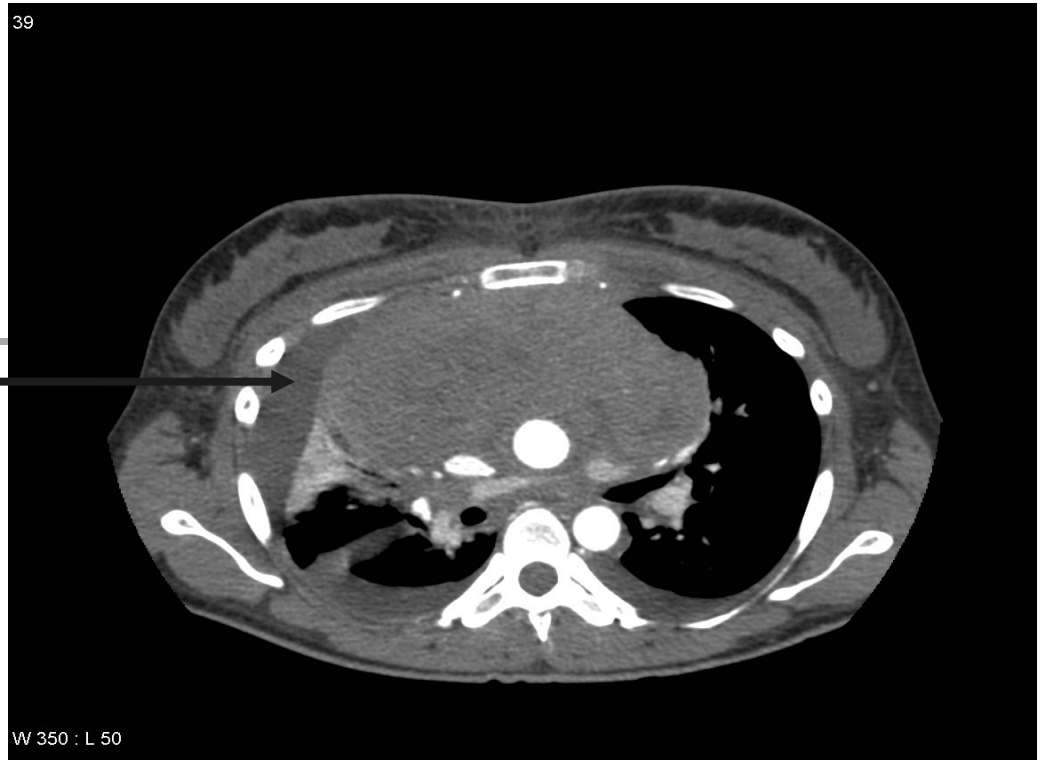
- Ung dame, student, 21 år, tidligere frisk
- Siste 6 mnd slapp, vekttap, hoste, tungpustet, feber. Behandlet med flere antibiotika-kurer uten effekt.
- Innlagt Ø-hjelp oktober 2007 ved Radiumhospitalet. Livstruende syk, vena cava superior syndrom. Tungpustet, hevelse i ansikt/hals

Sykehist

Stor mediastinal tumor komprimerer vitale strukturer, pleura effusion

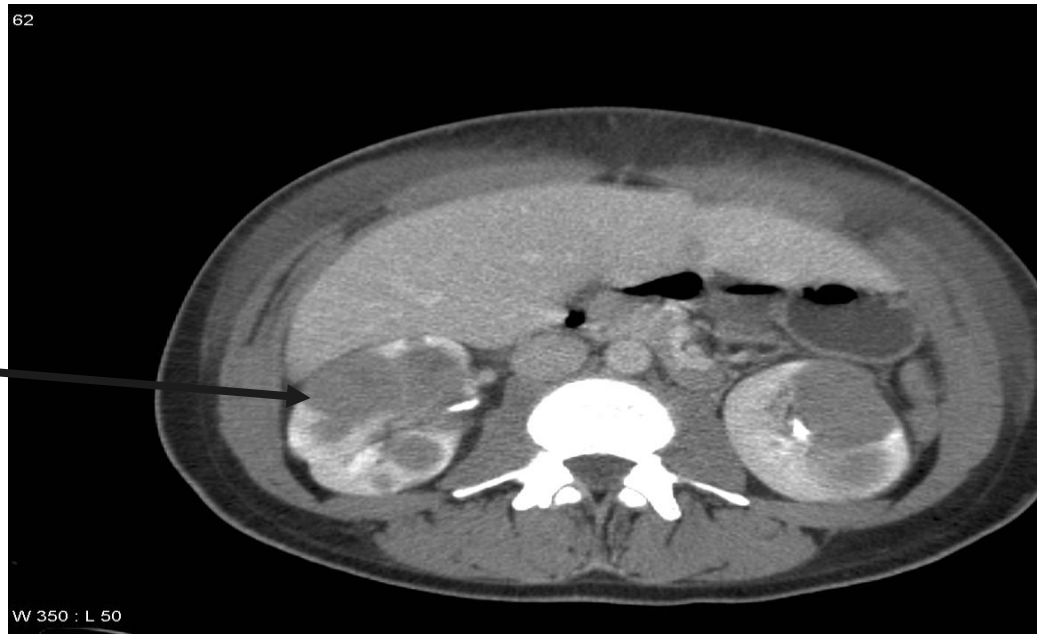
Histologi:

Diffust storcellet B-cell lymfom (primært mediastinalt).



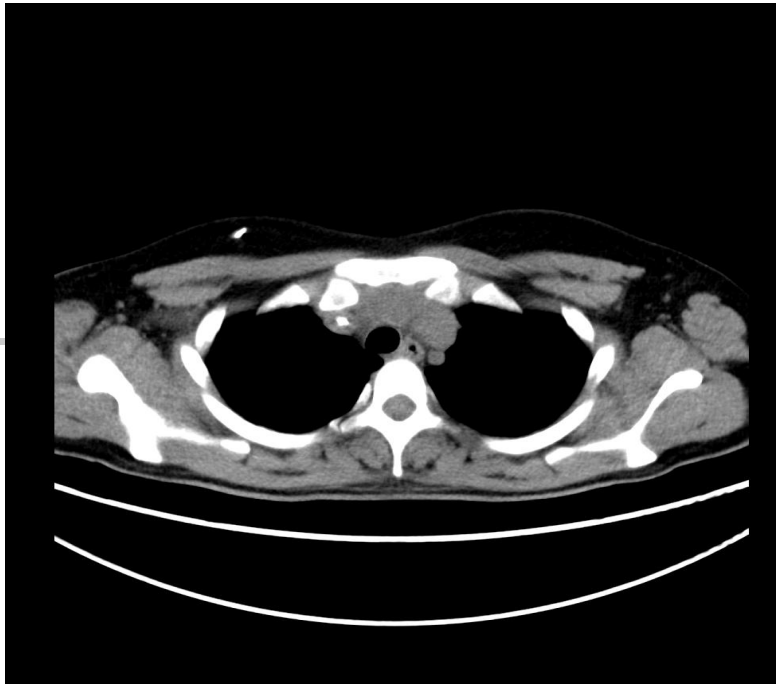
Begge nyrer affisert

Stadium IVB

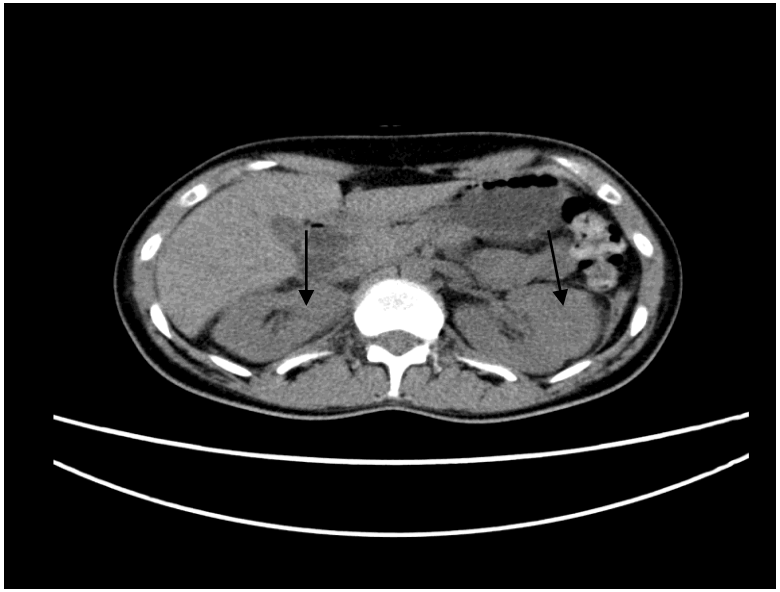


Terapi

CHOEP-14 + rituximab 6 kurer



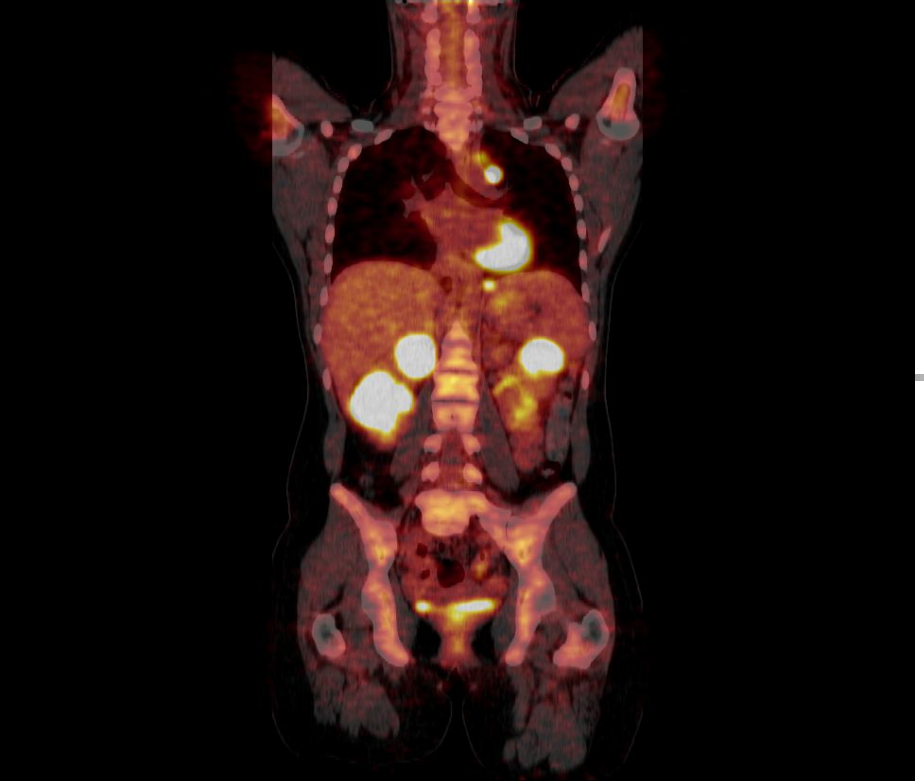
God effekt i mediastinum, uendret mellom 3 og 6 kurer

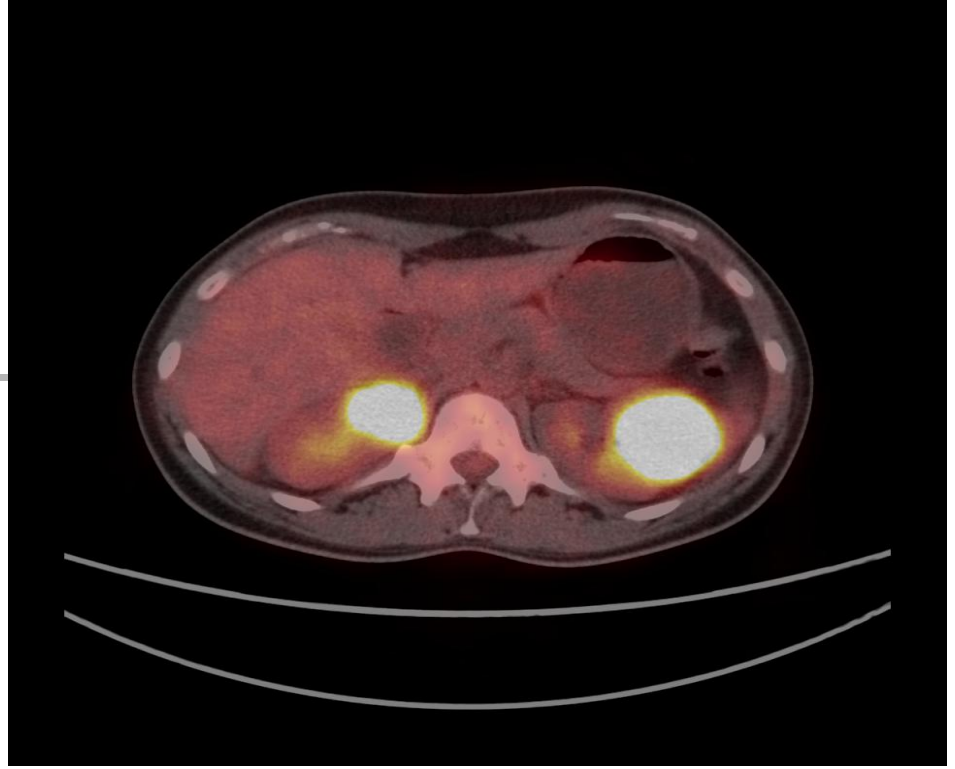


Økning i nyresvulster mellom 3 and 6 kurer?

PET/CT-scan utført

Nyre biopsert

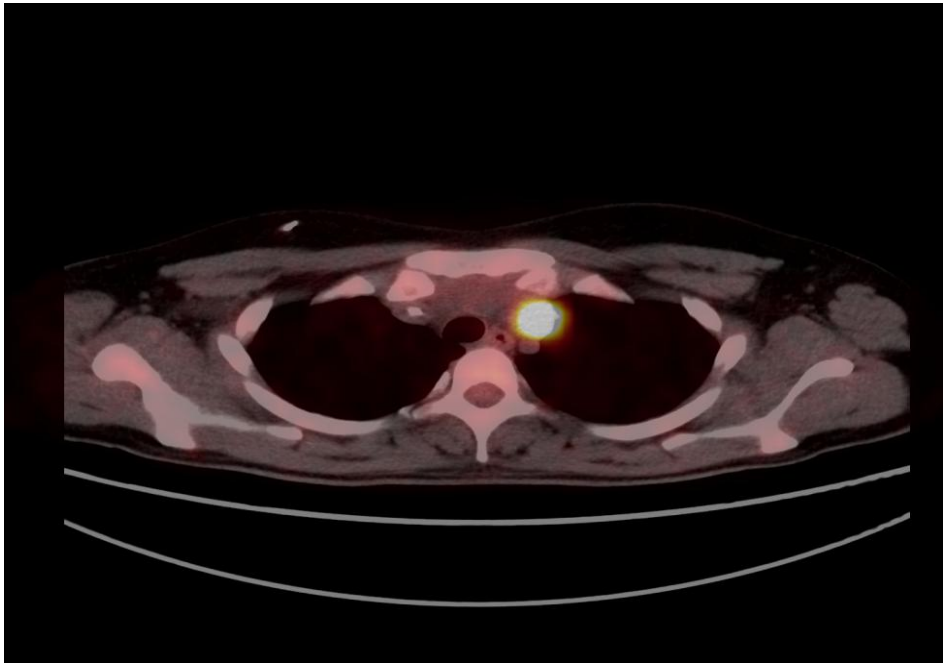




Sykehistorie

PET/CT viste activitet både i mediastinum og i begge nyrer

Biopsi: Aktiv tumor i nyre



Progresjon under terapi – hva nå? Meget dårlig prognose!

- Skifte til nytt kjemoterapi-regime – max intensitet
- Etter 3 blokk-kurer, god effekt. Høstet stamceller fra blod.
- Ny PET/CT viste kun opptak i ett nyre
- Høydosebehandling med stamcellestøtte
- Fjerning av høyre nyre.
- Fullført terapi i mai-08

Kontroll november 2013

- Komplett remisjon 5 år etter avsluttet behandling
- God form
- Fullført masteroppgave i helseøkonomi, signert eksemplar til meg

Behandlingsmål

- Helbredende (kurativ)
- Livsforlengende
- Lindrende

(Palliativ)

Fokus for foredraget: ikke detaljer, men formidle forståelse av hvordan vi vurderer og behandler

- **Aggressive NHL**
  Eks: Diffust storcellet B celle lymfom
- **Indolente NHL**
  Eks: Follikulært lymfom
- **Intermediære NHL**
  Eks: Mantelcelle lymfom
- **Allo-txt ved NHL**
- **Konklusjon**

Malignant lymphoma (2010)

Hodgkin lymphoma

Insidence	
males	76
females	54
Prevalence	
All	2296

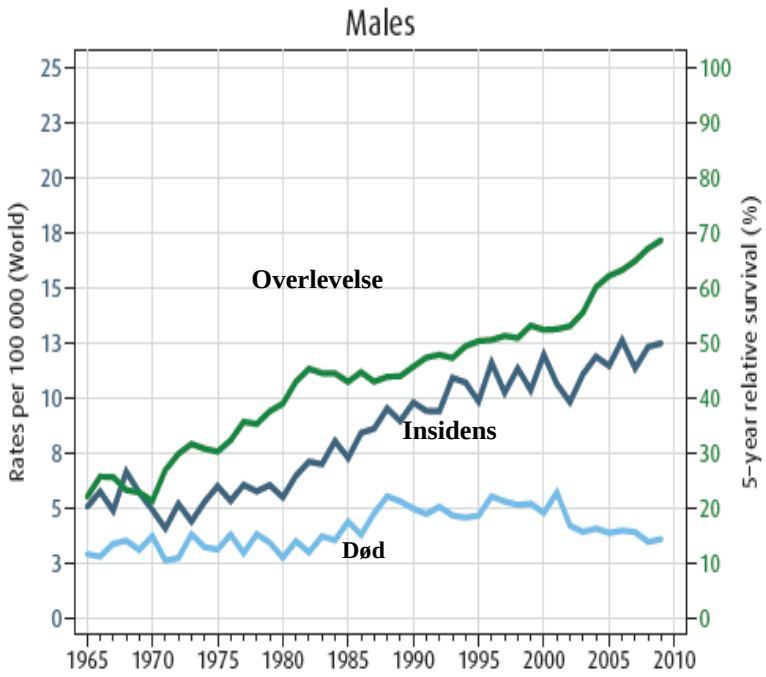
Non-Hodgkin lymphoma

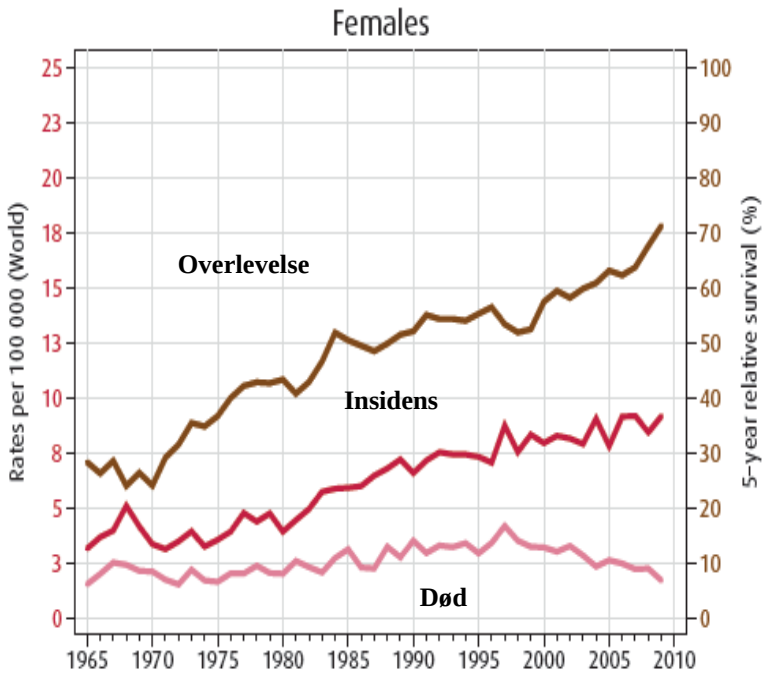
Insidence	
males	547
females	417
Prevalence	
All	7079

Norwegian Cancer Registry, 2010

Non-Hodgkin lymfom

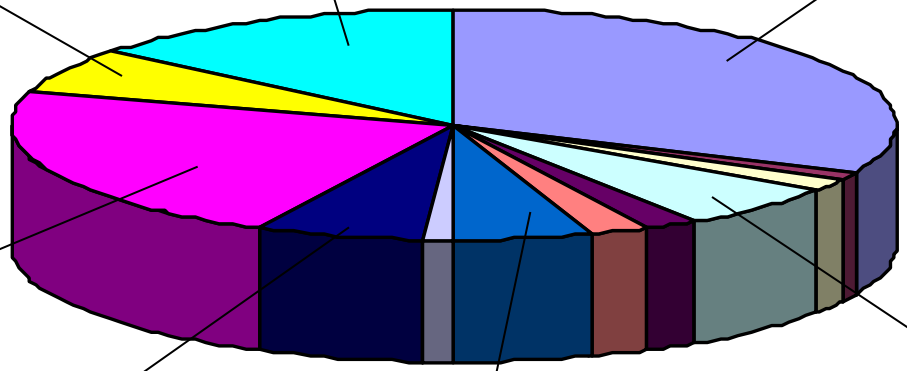
Figure 10-W: Non-Hodgkin lymphoma (ICD-10 C82–85, C96)





WHO for dummies..!

Aggessive
Langsomtvoksende
Hodgkin



Hodgkins lymfom
14 %

Diffust storcellet B-celle lymfom
31 %

Mantelcelle lymfom
6 %

Burkitt lymfom
2 %

Lymfoblast-
lymfom
1 %

Follikulært
lymfom
22 %

Perifert T-celle
lymfom
6 %

Lymfocytært lymfom/
B-KLL
6 %

Anaplastisk storcellet
lymfom
2 %

Lymfoplasmacytisk
lymfom
1%

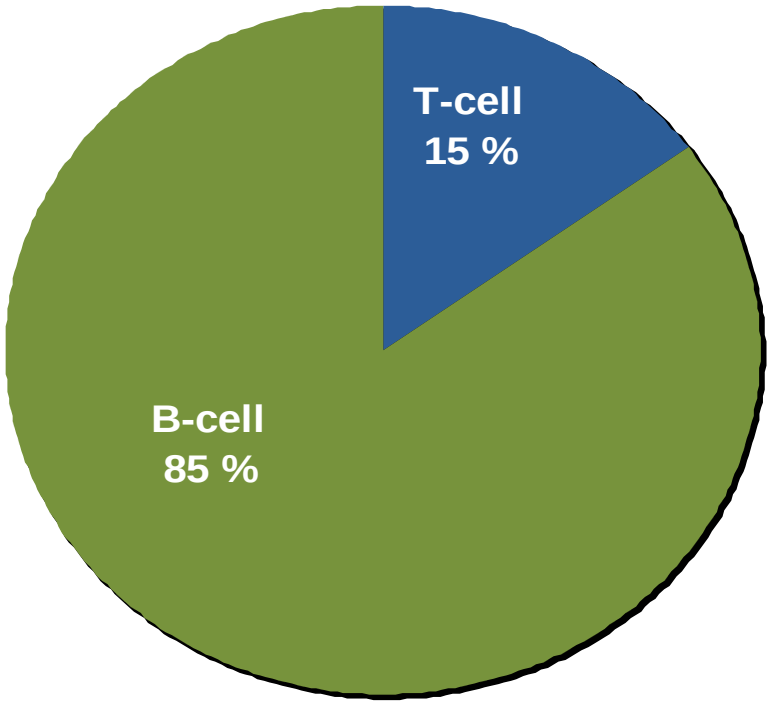
Marginalsone
lymfom
5 %

Inndeling av Non-Hodgkin lymfom

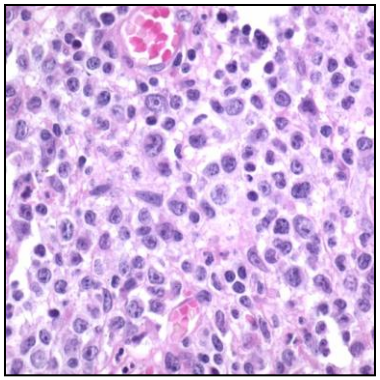
- **B-celle lymfom 85%**
  Lavgradige: **Follikulære lymfom**, mantelcellelymfom, marginalsonelymfom, lymfocyttært lymfom
  Høygradige: **Diffust storcellet B-cellelymfom**, Burkitt lymfom, B-lymfoblast-lymfom

- **T-celle lymfom 15%**
  Lavgradige: Kutant T-cellelymfom
  Høygradige: **Perifert T-cellelymfom**, Enteropatiassosiert T-celle lymfom, Hepatosplenisk T-cellelymfom, Angioimmunoblastisk T-cellelymfom, T-lymfoblastlymfom

Non-Hodgkin lymfomer



Diffust storcellet B celle lymfom (DLBCL)

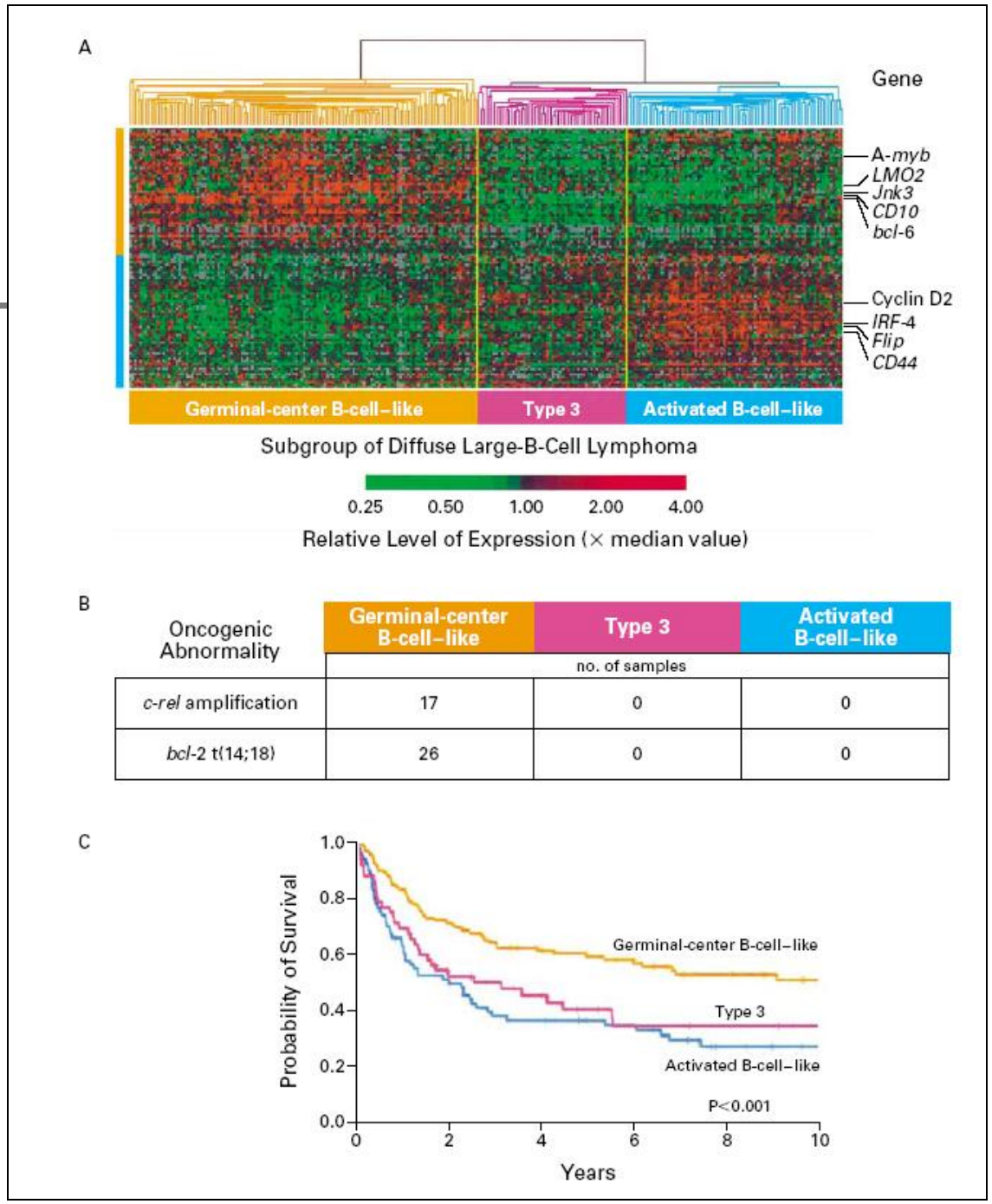


Histologi

Diffuse Large B-cell lymphoma

frequency	31 %
median age	64
age range	14-98
M	55 %
B symptoms	33 %
extranodal site	71 %
bone marrow	16 %

Diffuse Large B cell Lymphoma: survival predictor score



B

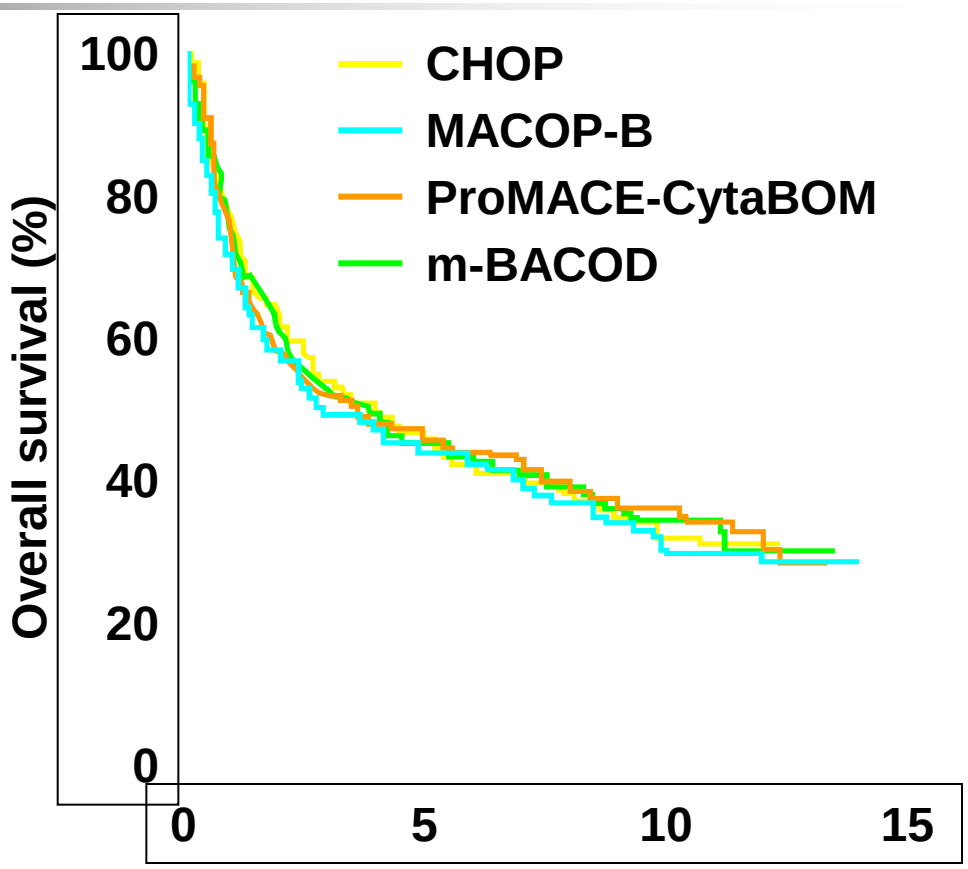
Oncogenic Abnormality	Germinal-center B-cell–like	Type 3	Activated B-cell–like
	no. of samples		
c-rel amplification	17	0	0
bcl-2 t(14;18)	26	0	0

Rosenwald et al. N Engl J Med, 2002, 346, 1937-1947

THE NORWEGIAN RADIUM HOSPITAL

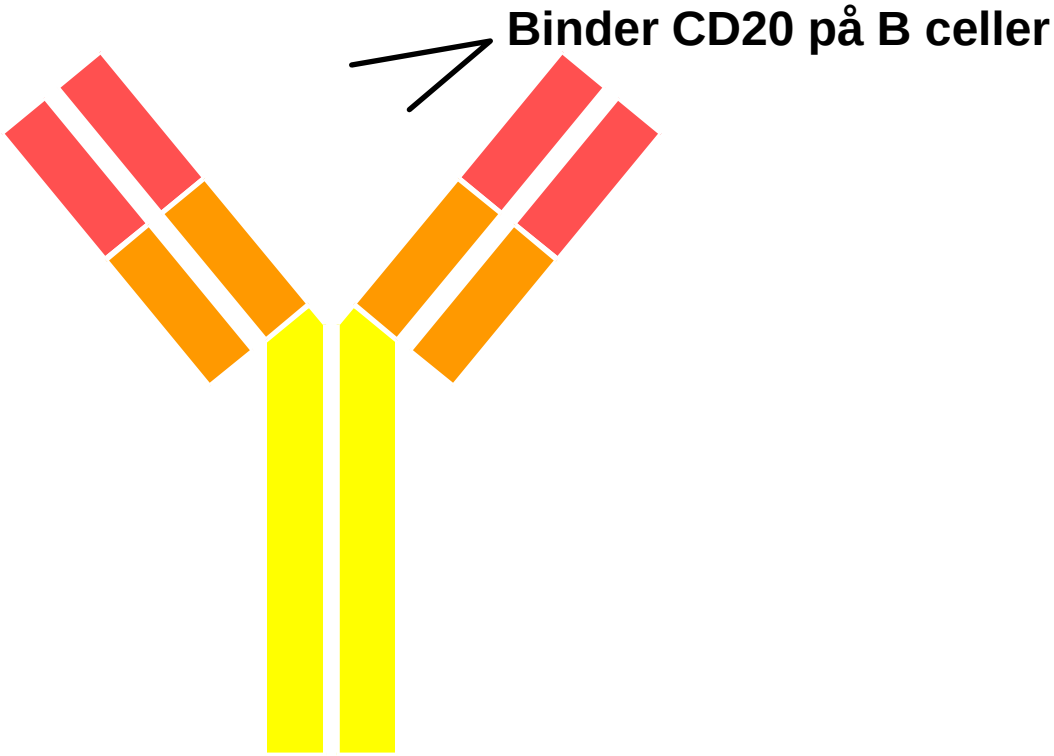
CHOP21 was a good standard

- It was associated with a good efficacy
- It was easy to use
- It gave reproducible results
- But long terms results are insufficient
- So, improvement is possible



Fisher RI et al. N Engl J Med 1993;328:1002–6

Rituximab: Det store fremskrittet i behandlingen av non-Hodgkin lymfom de siste 10 år



Adapted from: Ryback et al. 1992

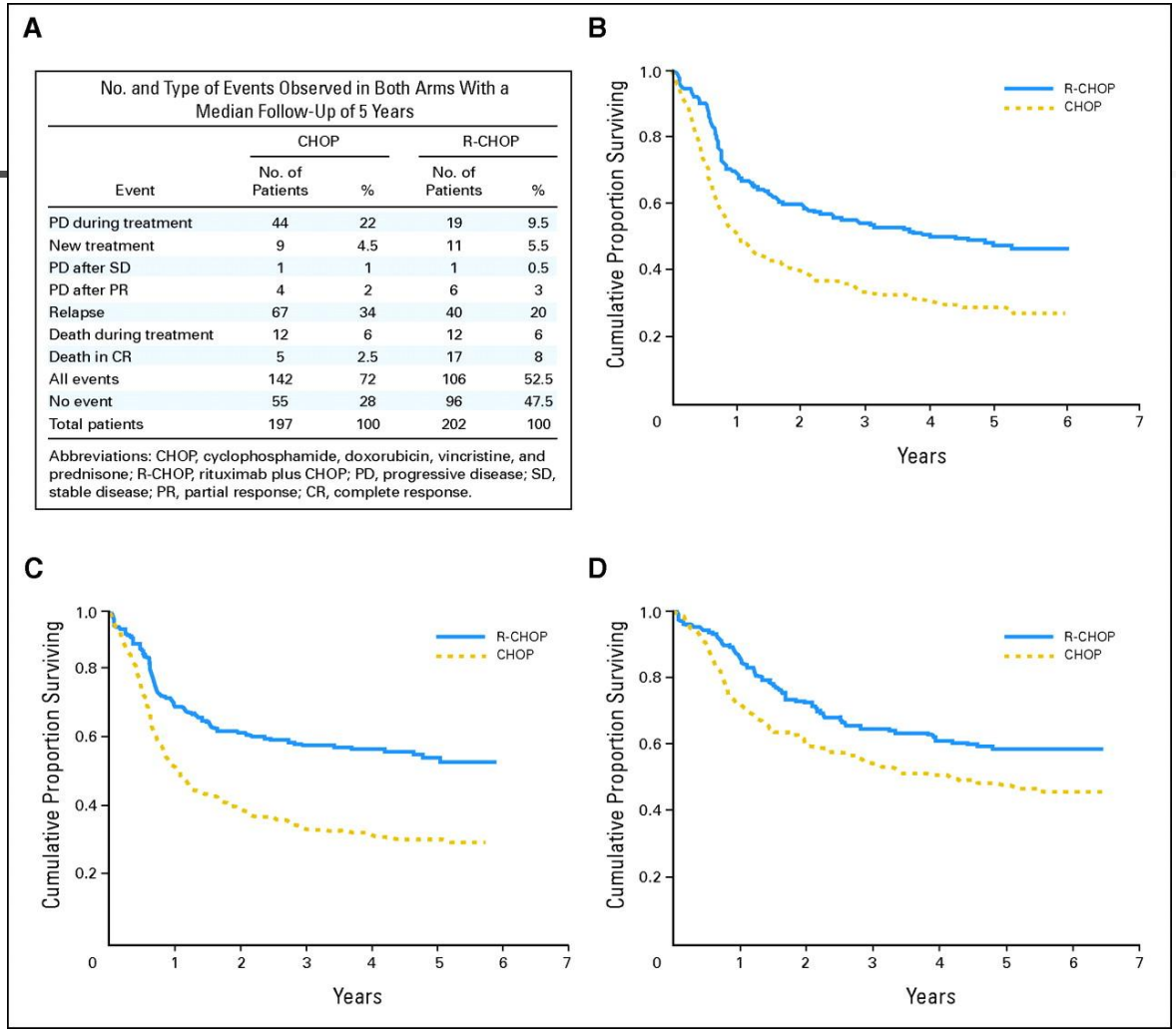
Fig 2. Five-year follow-up results of the Groupe d'Etude des Lymphomes de l'Adulte study in patients 60 to 80 years old comparing cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with the rituximab plus CHOP (R-CHOP) regimen

A

No. and Type of Events Observed in Both Arms With a Median Follow-Up of 5 Years

Event	CHOP No. of Patients	CHOP %	R-CHOP No. of Patients	R-CHOP %
PD during treatment	44	22	19	9.5
New treatment	9	4.5	11	5.5
PD after SD	1	1	1	0.5
PD after PR	4	2	6	3
Relapse	67	34	40	20
Death during treatment	12	6	12	6
Death in CR	5	2.5	17	8
All events	142	72	106	52.5
No event	55	28	96	47.5
Total patients	197	100	202	100

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab plus CHOP; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.



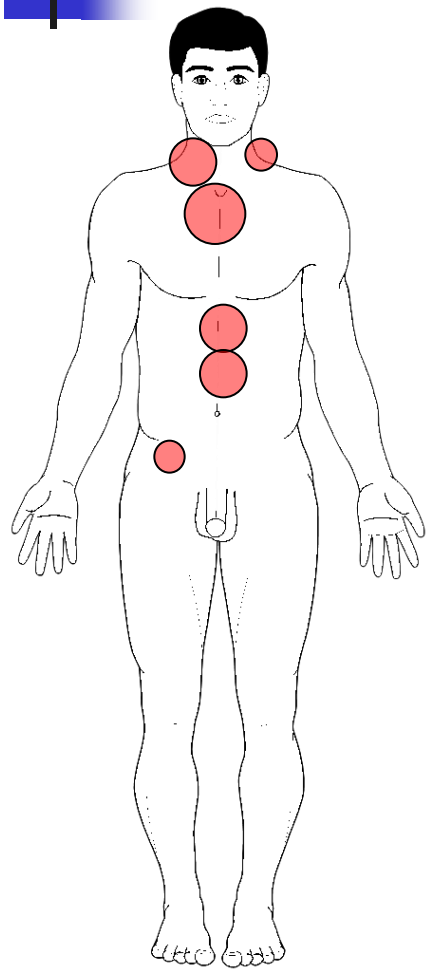
Thieblemont, C. et al. J Clin Oncol; 25:1916-1923 2007

Copyright © American Society of Clinical Oncology

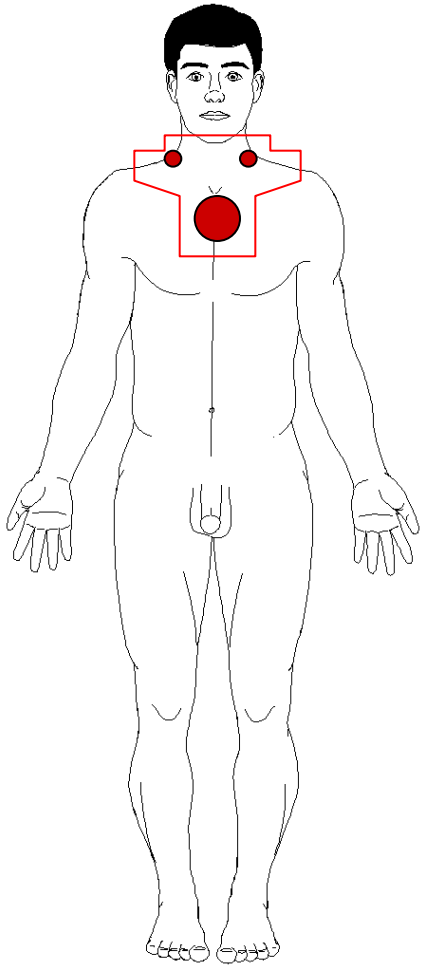
Rituximab i kombinasjon med kjemoterapi ved storcellet B celle lymfom

- Fremskritt i behandlingen, bedrer overlevelse med 10-20%
- Ingen økt toksistet, bortsett fra bivirkninger under første kur med rituximab
  Feber, frysninger, dyspnoe, utslett med mer
- Stadium I/IIA: CHOP-R x 3-4 og stråleterapi (30-40Gy)
- Stadium IIB/IV: CHOP-R x 6-8

DLBCL – avanserte stadier kombinasjon med kjemoterapi



Full kjemoterapi med 6-8 x R-CHOP

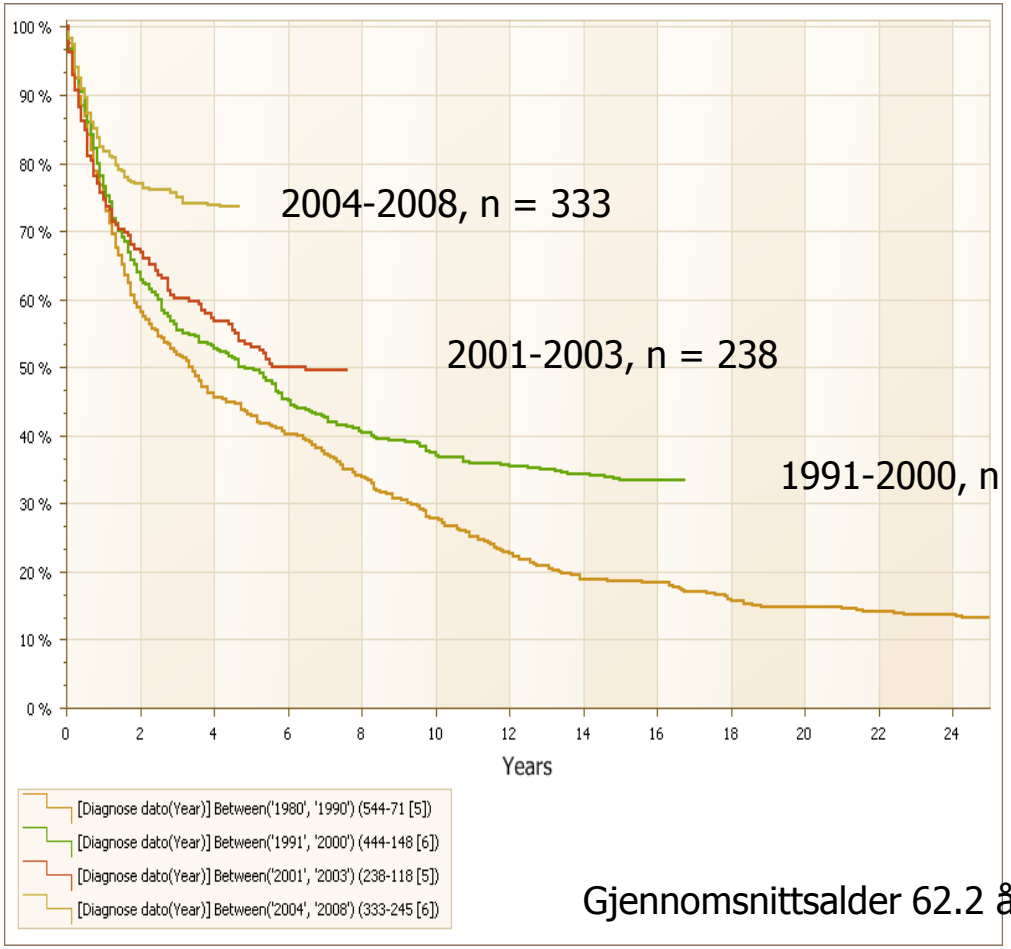


Evt: Konsoliderende radioterapi 2 Gy x 15-20

HMAS ved diffust storcellet B-celle lymfom

- Ved residiv av DLBCL hos pasienter med lite ko-morbiditet ca < 65 år
- Kurativt hos ca 30-40%

Diffuse storcellete B-cellelymfomer ved Radiumhospitalet, totaloverlevelse i grupper etter diagnoseår

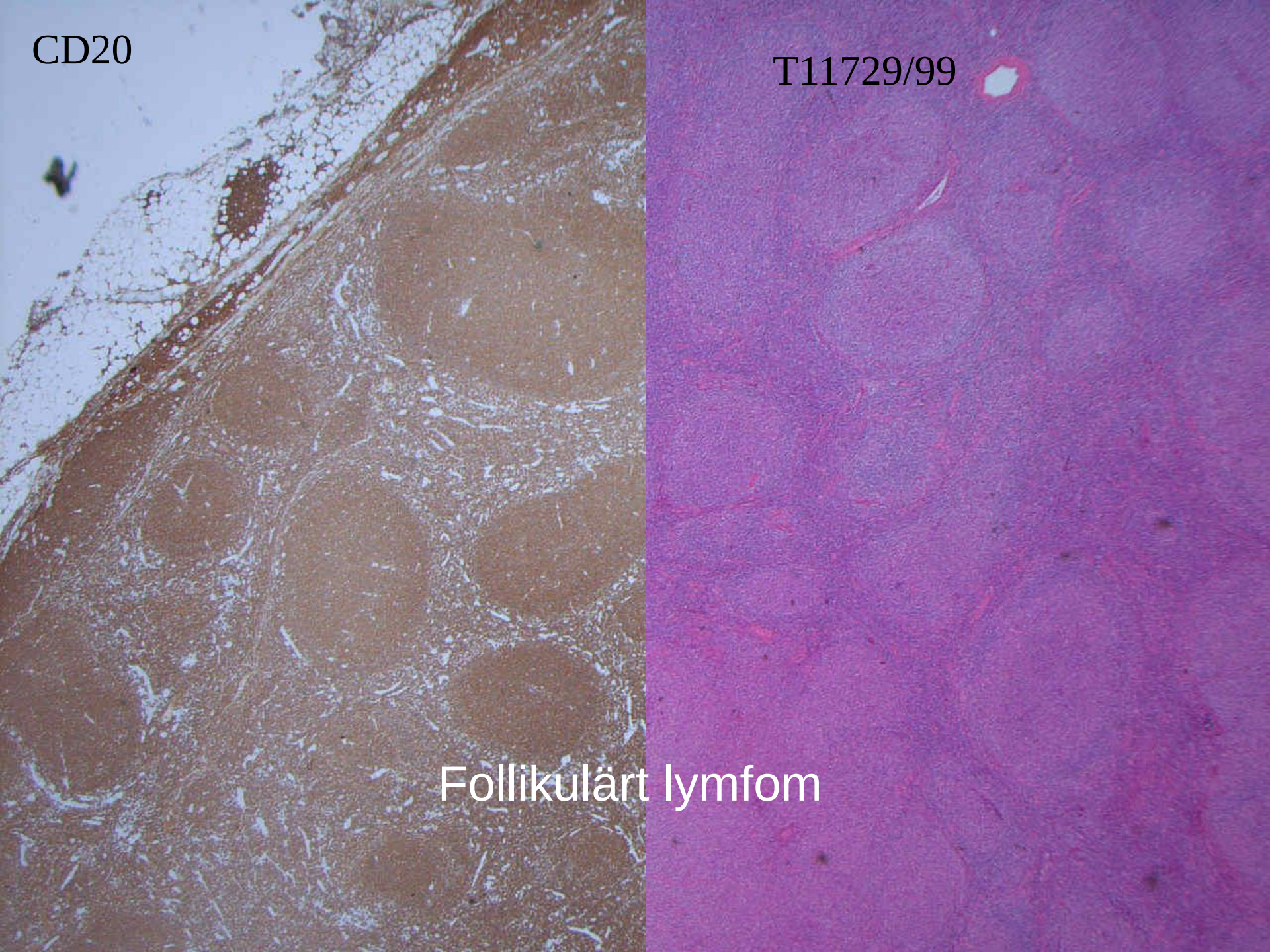


Gjennomsnittsalder 62.2 år

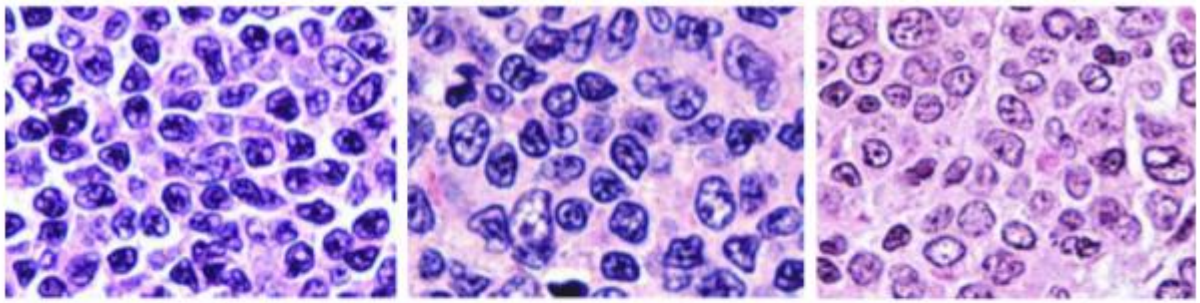
Follikulære lymfomer

Store fremskritt siste 10 år ved å benytte rituximab alene eller i kombinasjon med kjemoterapi

Fortsatt ikke-kurabel sykdom om utbredt stadium III/IV


CD20
T11729/99
Follikulärt lymfom

Follicular Lymphoma: WHO 2008 Classification



	Grade 1 Small Cleaved	Grade 2 Mixed	Grade 3 Large Cell
Large Cells Per High Power Field	<5	5-15	>15
Expert Concordance	72%	61%	60%

1 **2** — **Low Grade**

3A **3B**

Terapi-valg ved follikulære lymfomer

Ingen (WW)

Chlorambucil

R-COP

R-CHOP

R-Fludarabin/Cyklofosfamid

Stråleterapi

?

Rituximab

Allo-transplantasjon

HMAS

R-IME

R-Bendamustin

Zevalin

Utprøvende behandling?

Follikulært lymfom stadium I/II

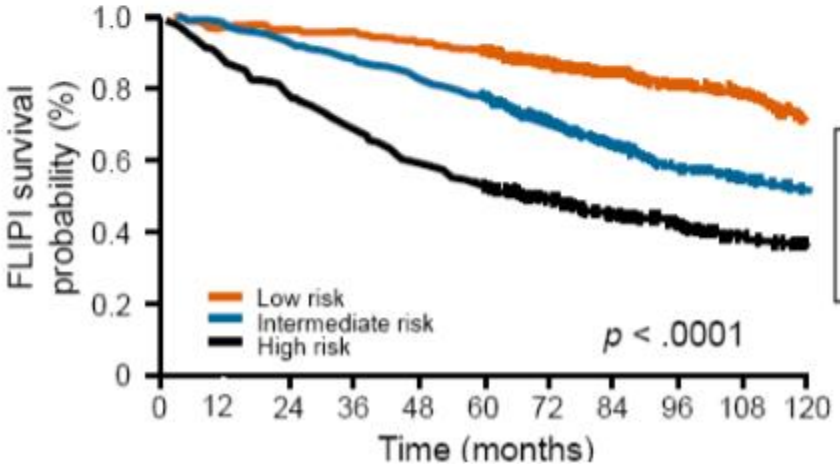
- Strålebehandling alene, moderat dose 2 Gy x 12

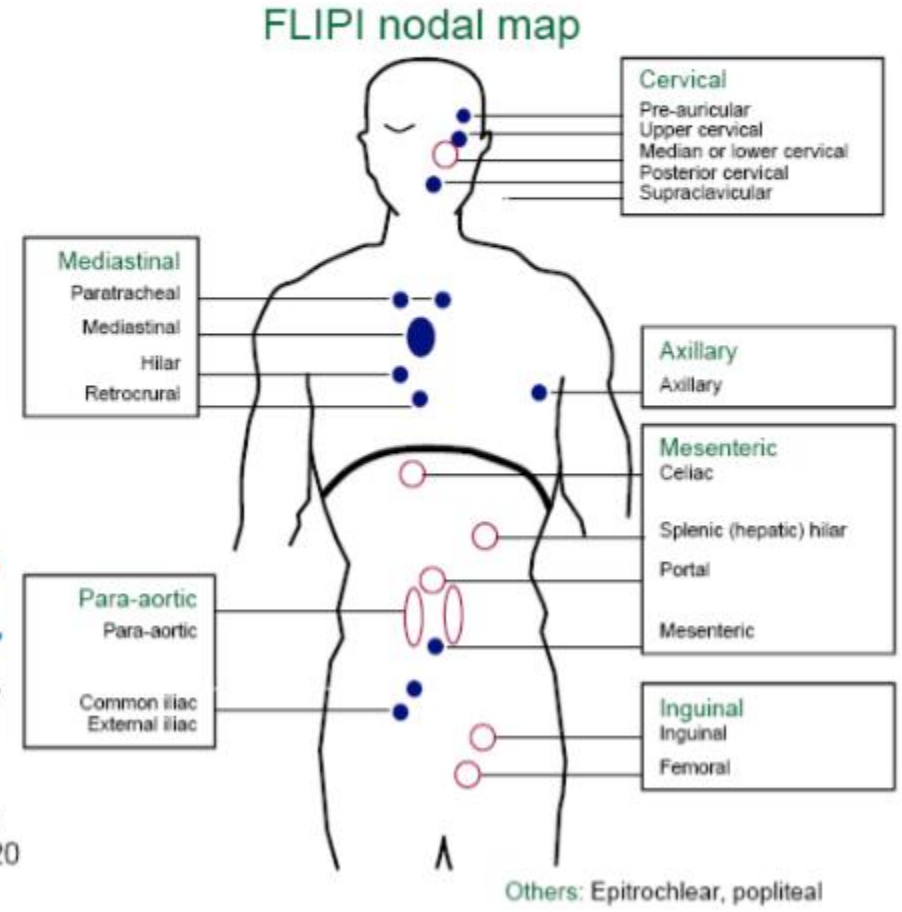
  Hensikt: Kurere sykdommen (50%?)

Follicular Lymphoma International Prognostic Index (FLIPI)

Criteria

- Nodal sites (≤ 4 vs. > 4)
- LDH (≤ normal vs. > normal)
- Age (≤ 60 vs. > 60 years)
- Stage (I or II vs. III or IV)
- Hemoglobin (≥ 12 g/dL vs. < 12 g/dL)

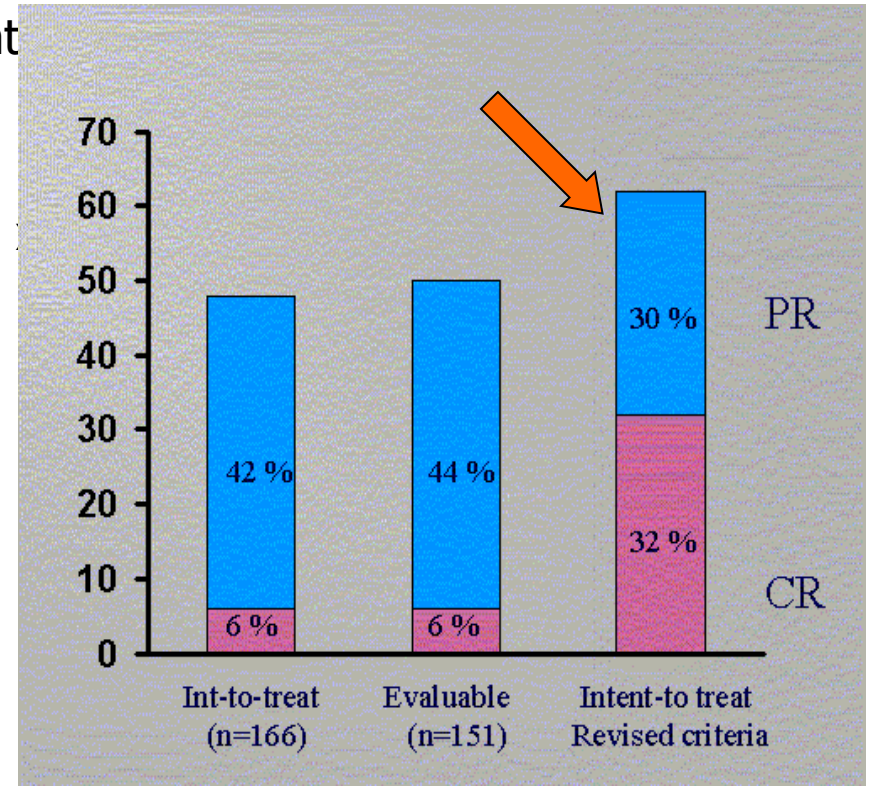




Solal-Celigny et al. Blood 2004;104:1258-1265

Rituximab monoterapi

- Relapsed or refractory indolent NHL (n=166)
- Ukentlig MabThera 375mg/m^2 4
- Overall RR 48% (62%)
- Median TTP 13,0 mths
- Re-analysert med bruk av de nye standardiserte response-kriterier etter Cheson et al (NCI-sponsored International working group)



McLaughlin JCO 1998

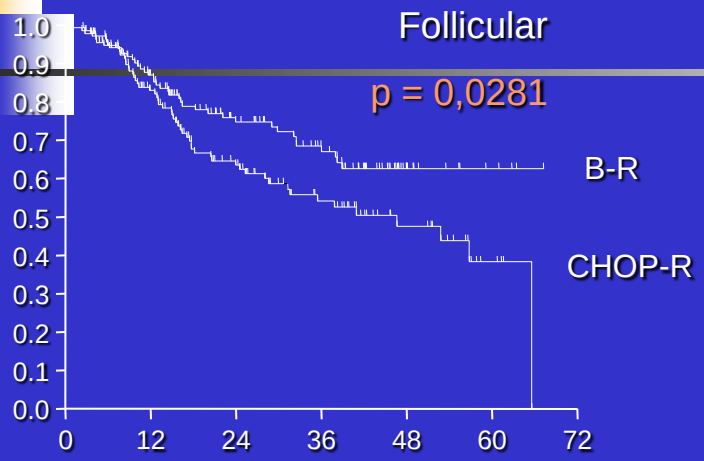
Hvilken immunokjemoterapi?

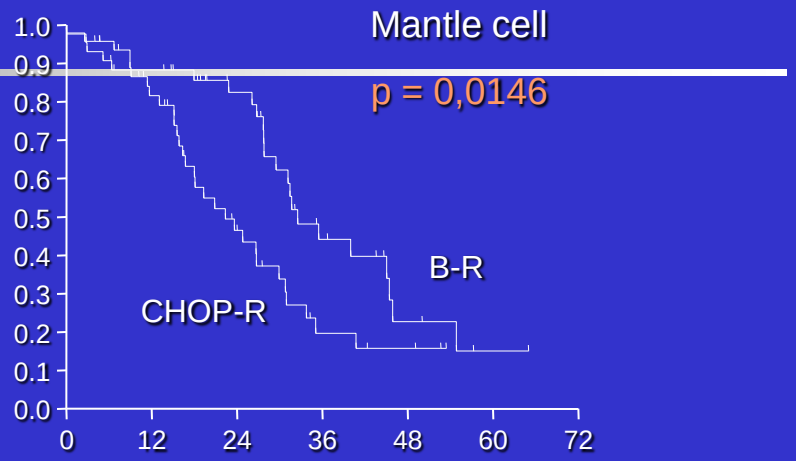
- **CVP + Rituximab?**
- **CHOP + Rituximab?**
- **FC(m) + Rituximab?**
- **Bendamustin + Rituximab?**

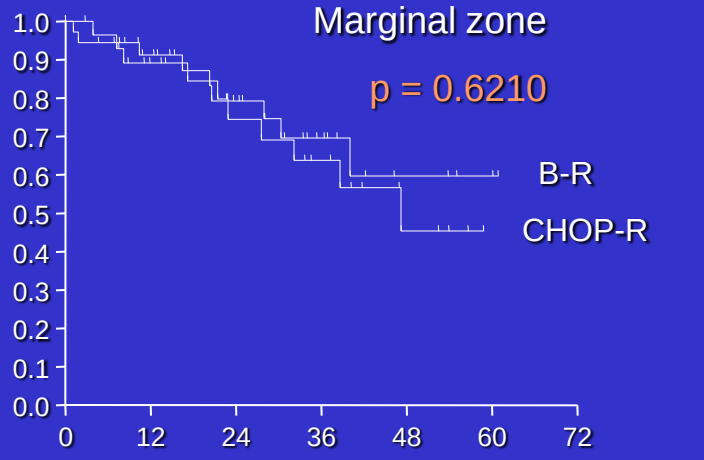
Hva er best?

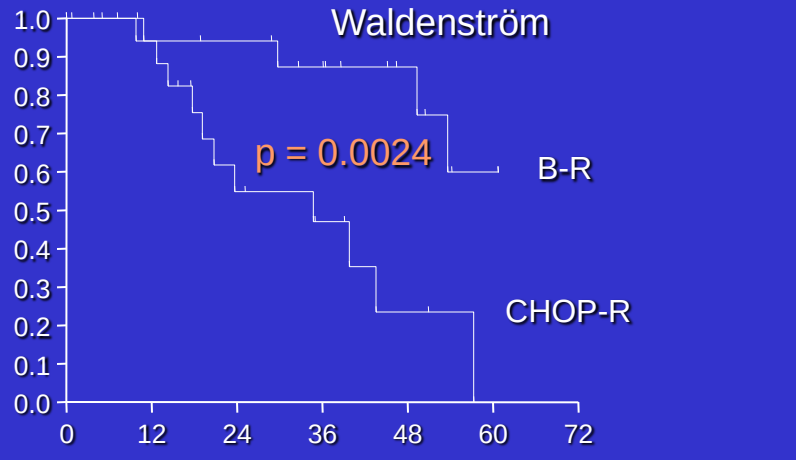
Ingen randomiserte studier som sammenligner forskjellige regimer, bortsett fra en

PFS ved subgrupper for R-bendamustine vs R-CHOP







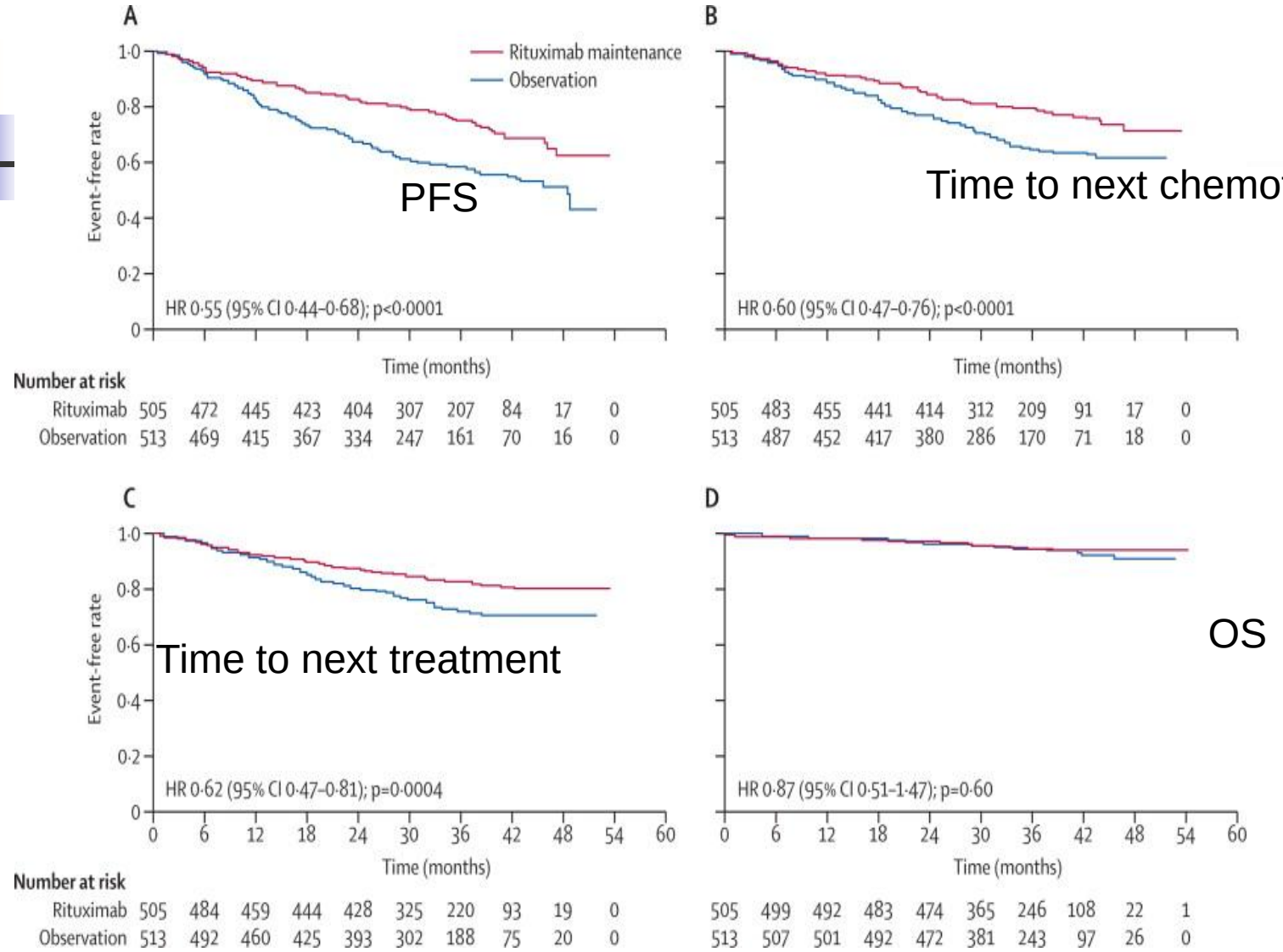


(ASH 2009, Abstract 405, Rummel et al)

Vedlikeholdsbehandling med rituximab

- Hensikt:
  Utsette residiv
  Forlenge overlevelse?
- 375 mg/m2 hver 2. mnd

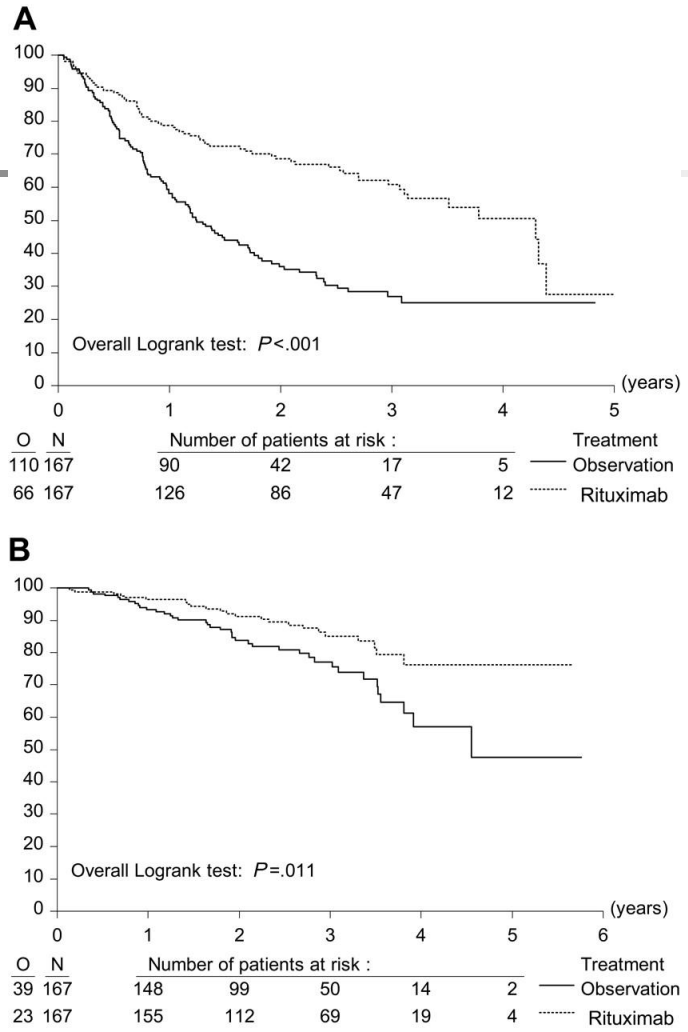
Effect of R (rituximab) maintenance treatment 1st remission



Salles et al. Lancet 2010

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

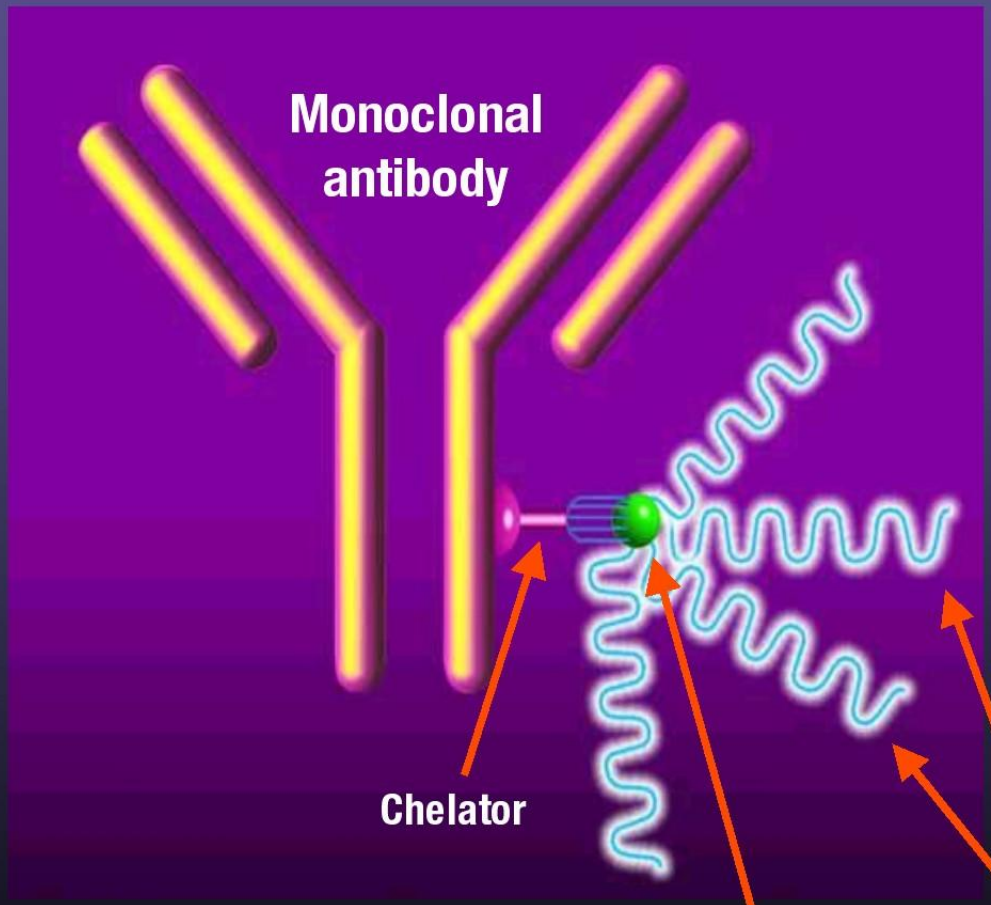
Figure 2. Effect of R (rituximab) maintenance treatment 2. or later remission on progression-free survival and overall survival



van Oers, M. H. J. et al. Blood 2006;108:3295-3301

Copyright ©2006 American Society of Hematology. Copyright restrictions may apply.

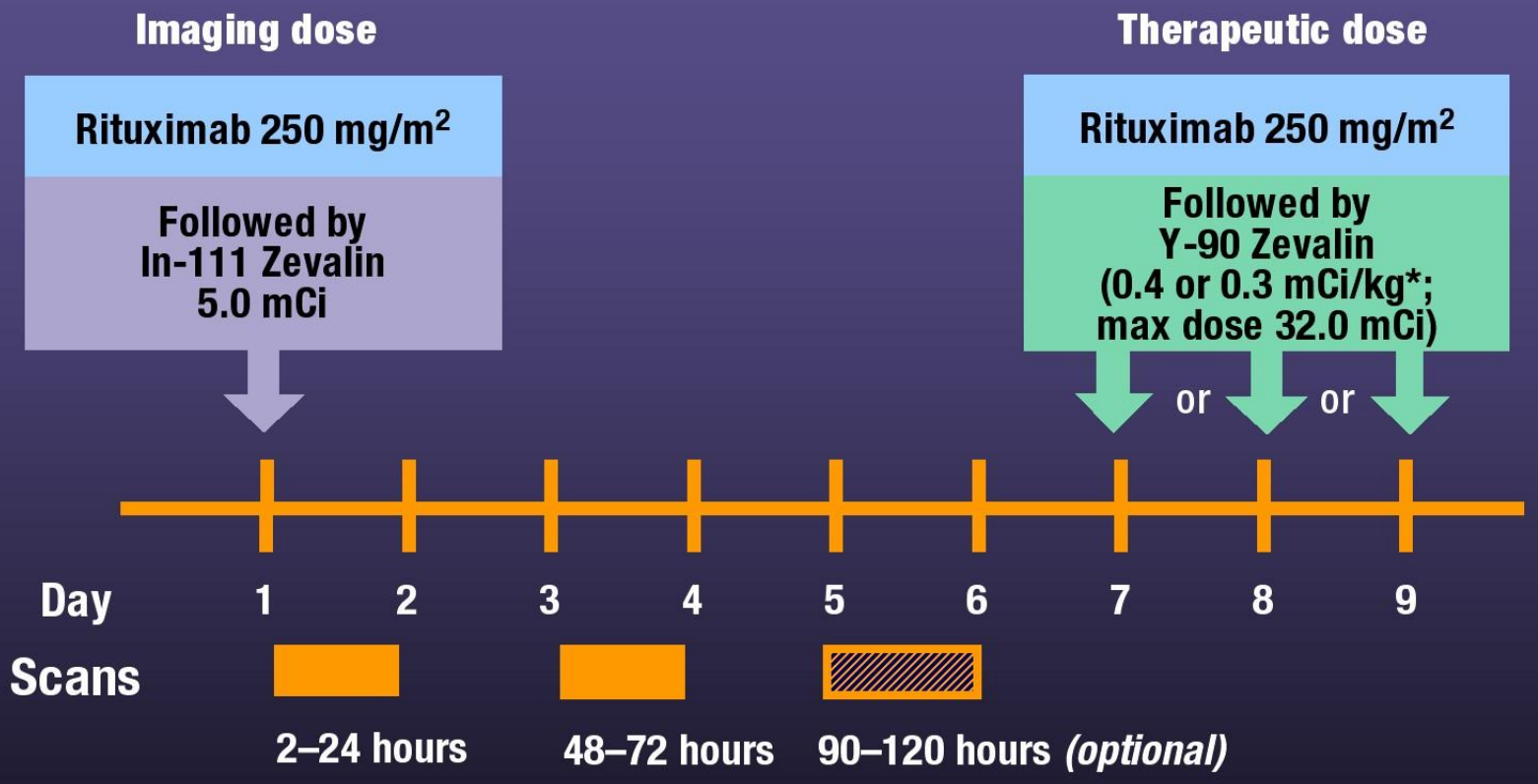
Yttrium-90 (Y-90) Zevalin Radioimmunotherapy Delivers Increased Cytotoxicity by Antibodies



- Ibritumomab
  - Murine monoclonal antibody parent of Rituximab
- Tiuxetan
  - Conjugated to antibody, forming strong urea-type bond
  - Stable retention of Y-90

ZEVALIN™
Ibritumomab tiuxetan

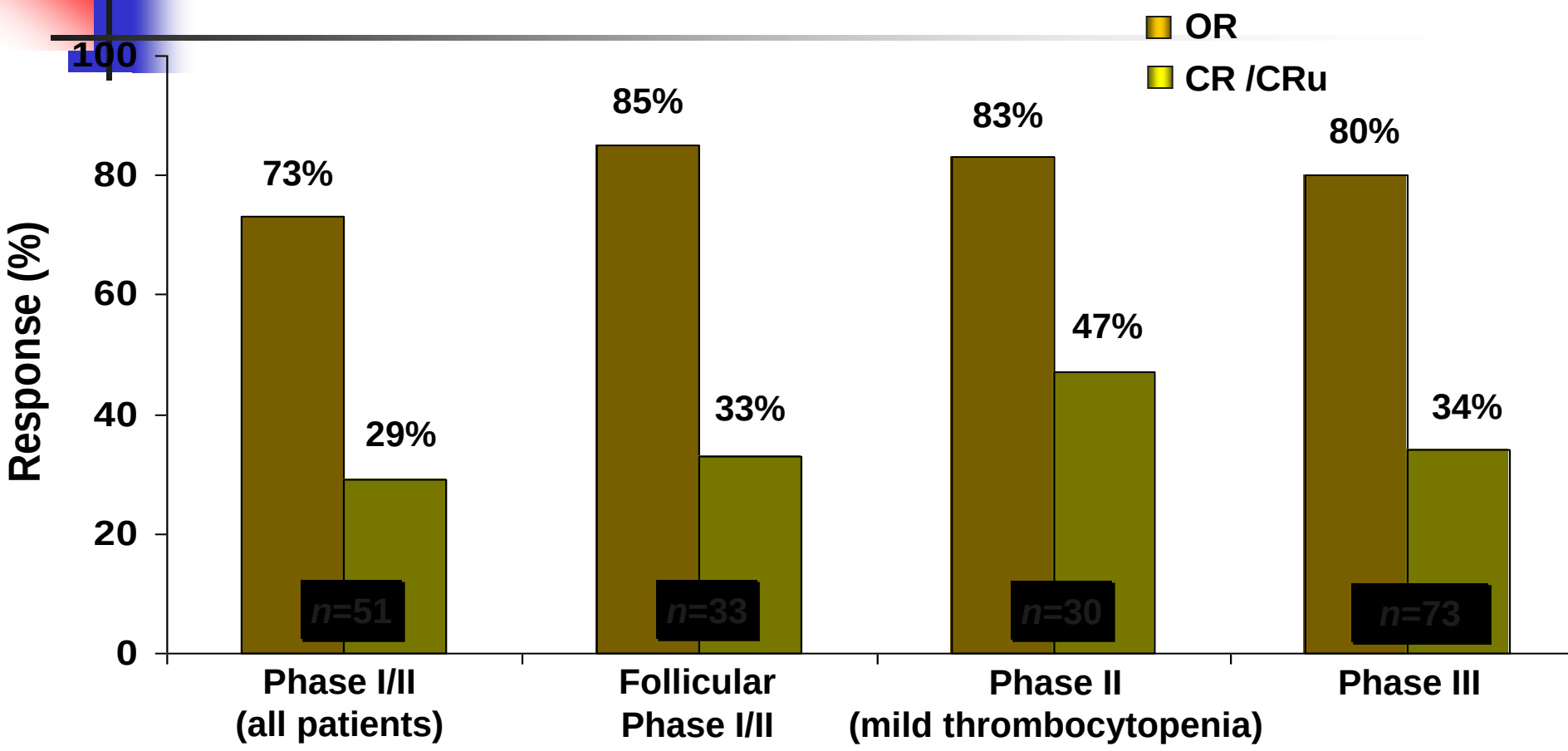
The Zevalin Therapeutic Regimen



*0.4 mCi/kg in patients with a platelet count ≥150,000 cells/mm^3 or 0.3 mCi/kg with a platelet count 100,000–149,000 cells/mm^3. Maximum dose is 32.0 mCi.

ZEVALIN™
Ibritumomab tiuxetan

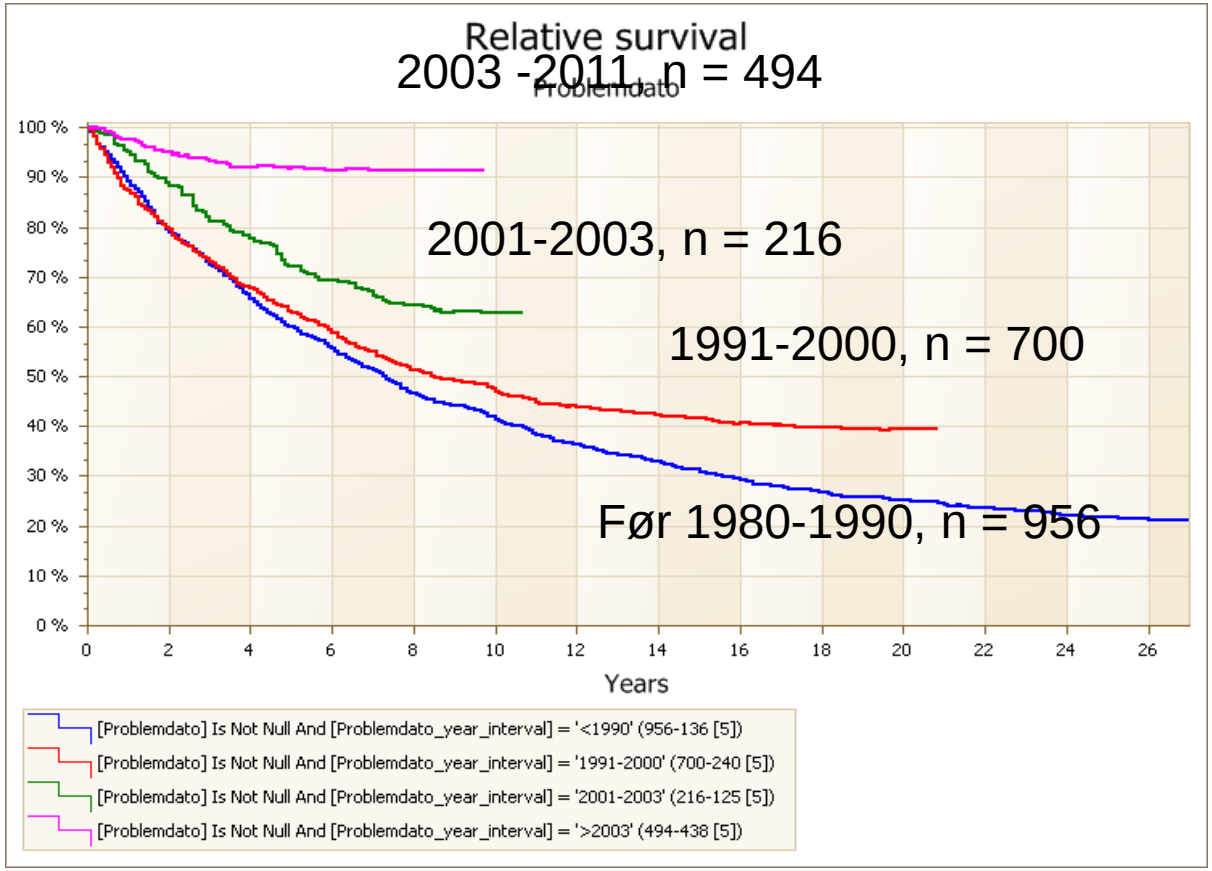
Updated response rates* in Ibritumomab tiuxetan trials



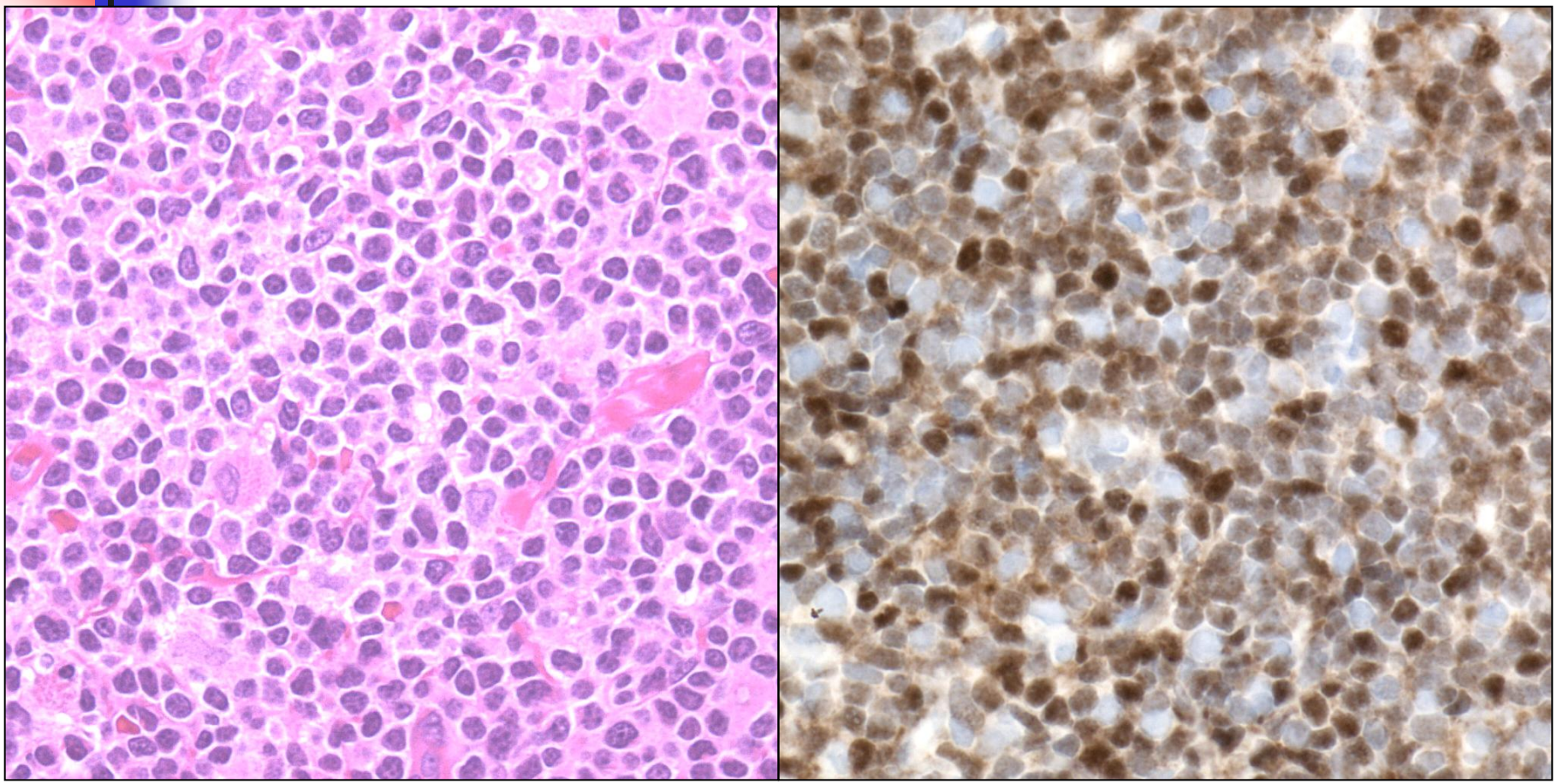
*International Workshop Response Criteria

Witzig, ASCO 2003

Indolente lymfomer, relativ overlevelse, tidsperioder



Mantle cell lymphoma



CyclinD1

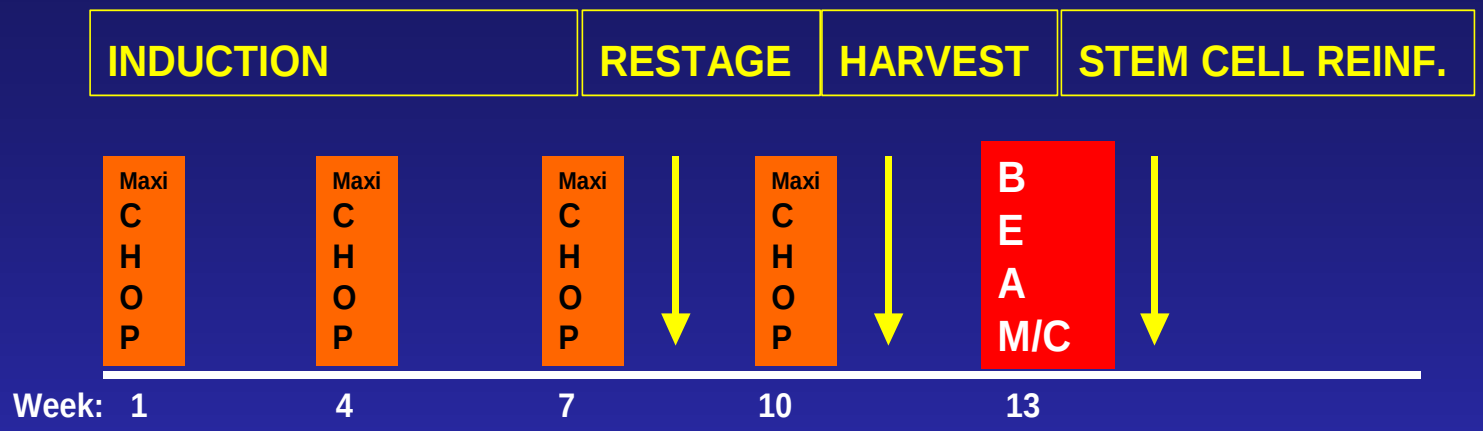
Mantle cell lymphoma

frequency	6%
median age	63
age range	37-82
M	74 %
B symptoms	28 %
extranodal site	81 %
bone marrow	64 %
immunophenotype	CD20+, CD5+, CD23-, cyclinD1+
cytogenetics	t(11;14)(q13;q32)
oncogenes	bcl-1 (cyclinD1)

Three Nordic phase II studies; frontline therapy in MCL

- 1996 – 2000 MCL-1 41 pts
- 2000 – 2006 MCL-2 160 pts
- 2006 - 2009 MCL-3 160 pts

Nordic MCL1 Trial 1996-2000



Dose-intensified CHOP ("Maxi-CHOP"):

Cyclophosphamide 1200 mg/m^2 D1

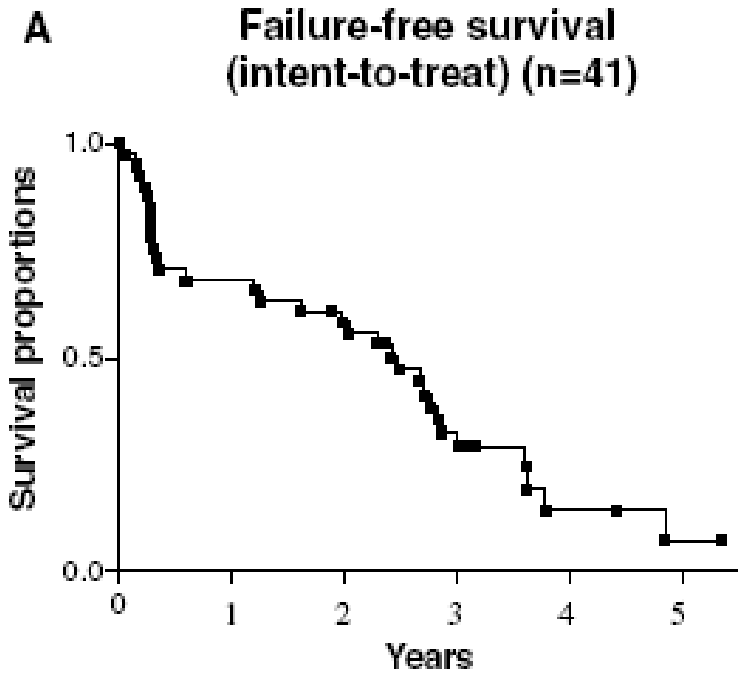
Doxorubicin 75 mg/m^2 D1

Vincristin 2 mg D1

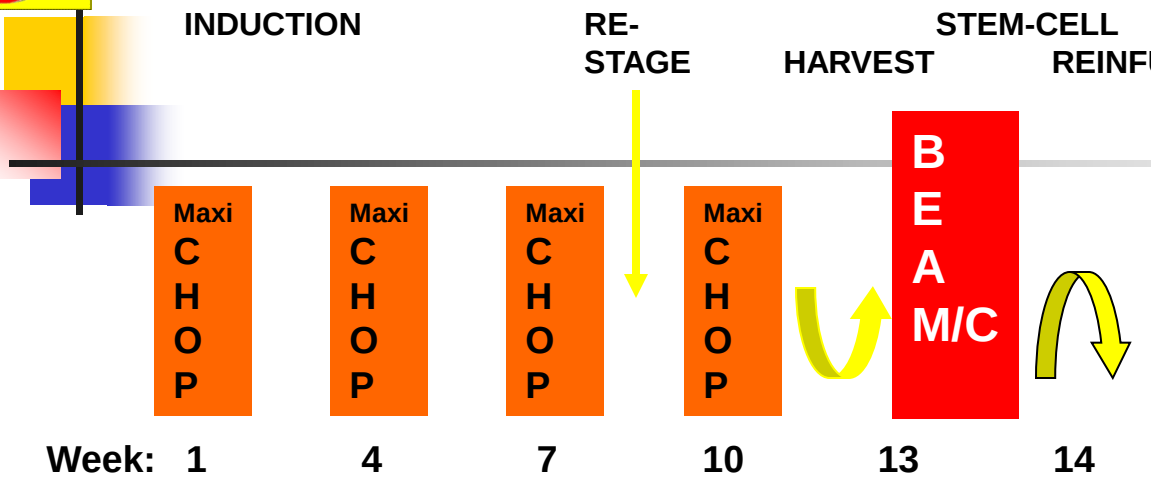
Prednisone 100 mg D1-5

Andersen et al Eur J Haematol 2003

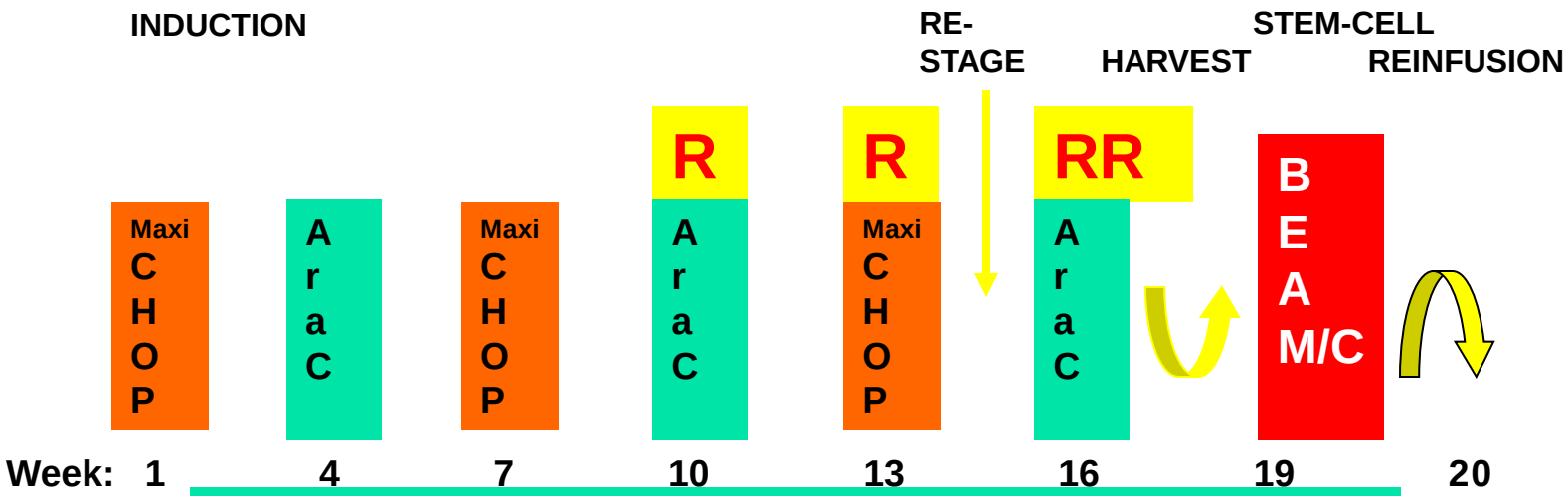
MCL1 results



MCL-1 TRIAL 1996-2000



MCL-2 TRIAL 2000-2006



AraC: 4 Infusions: ≤ 60 years 3g/m², > 60 years 2g/m²

Nordic MCL Project

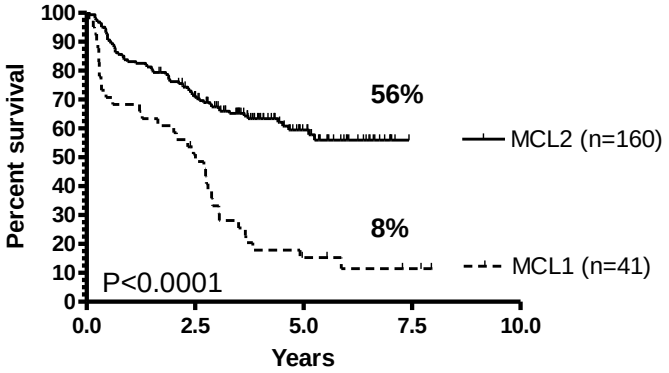
Intent-to-treat: Event-free and overall survival

Database closed March 12, 2008

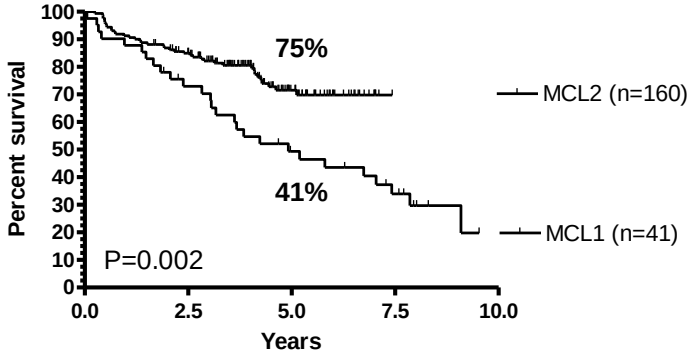
Relapse/PD	**48 (30%)**
Non-relapse events	**13 (8%)**
Off due to: Toxicity 7	
Harv. fail. 4	
Graft fail.1	
Pulm emb 1	

Deaths:	**39 (24%)**
Lymphoma	**31**
Non-relapse deaths	**8 ➔**
Infection 3	**NRM: 5%**
Vasc. Inc.2	
Graft fail. 1	
Pulm. Emb. Year + 5: 1	

A: Event-free Survival proportions

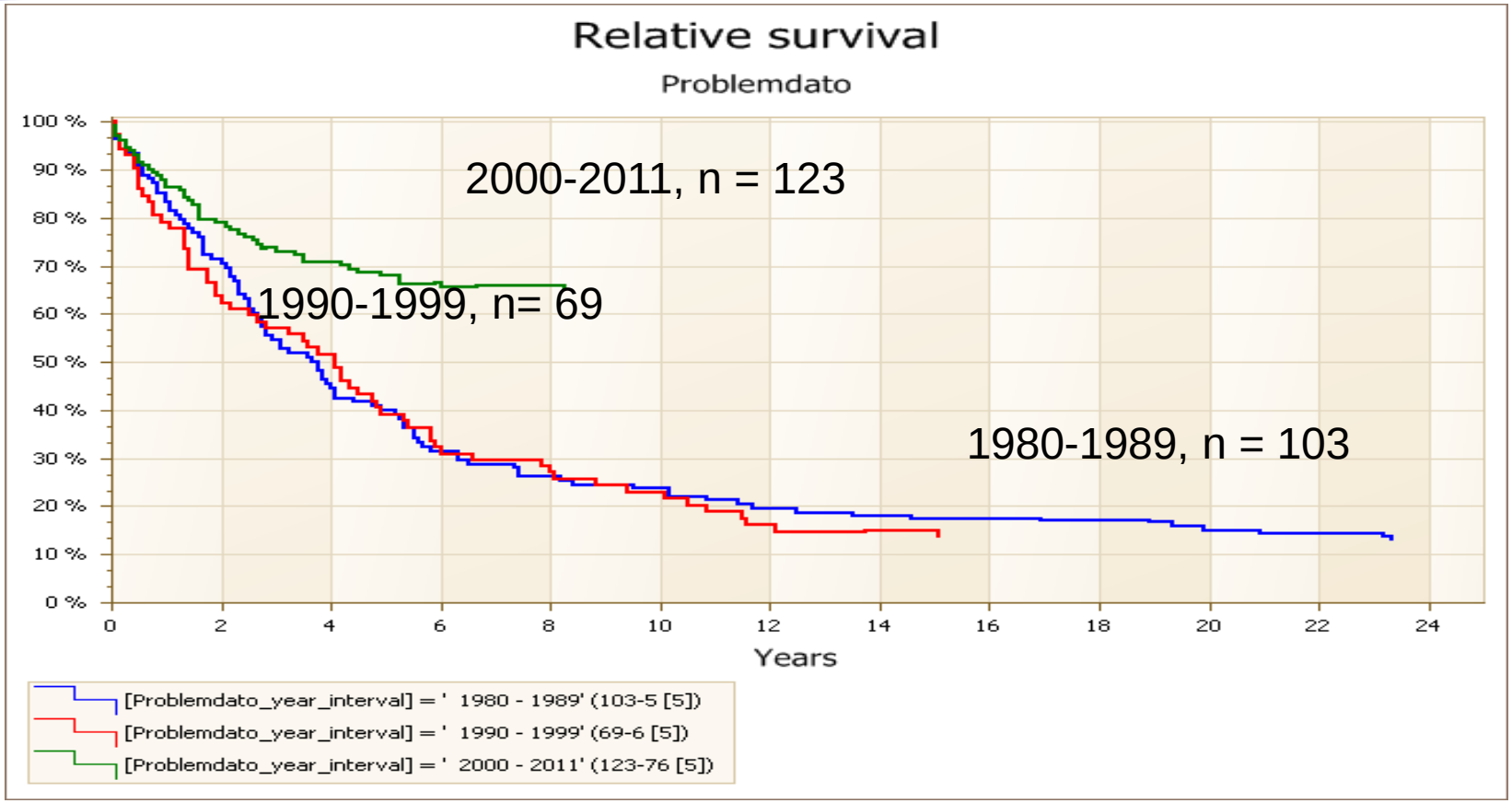


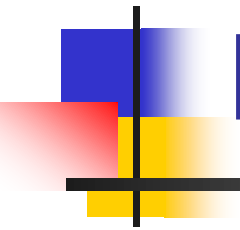
B: Survival



Geisler et al Blood 2008

Mantelcellelymfom, relativ overlevelse, tre perioder





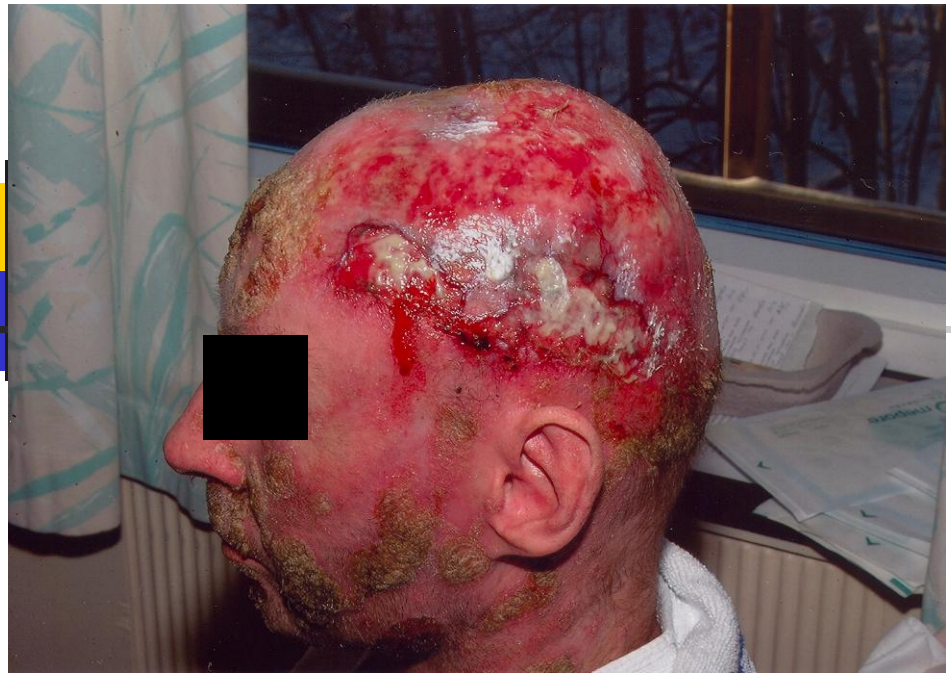
RIC-allo txt ved lymfom

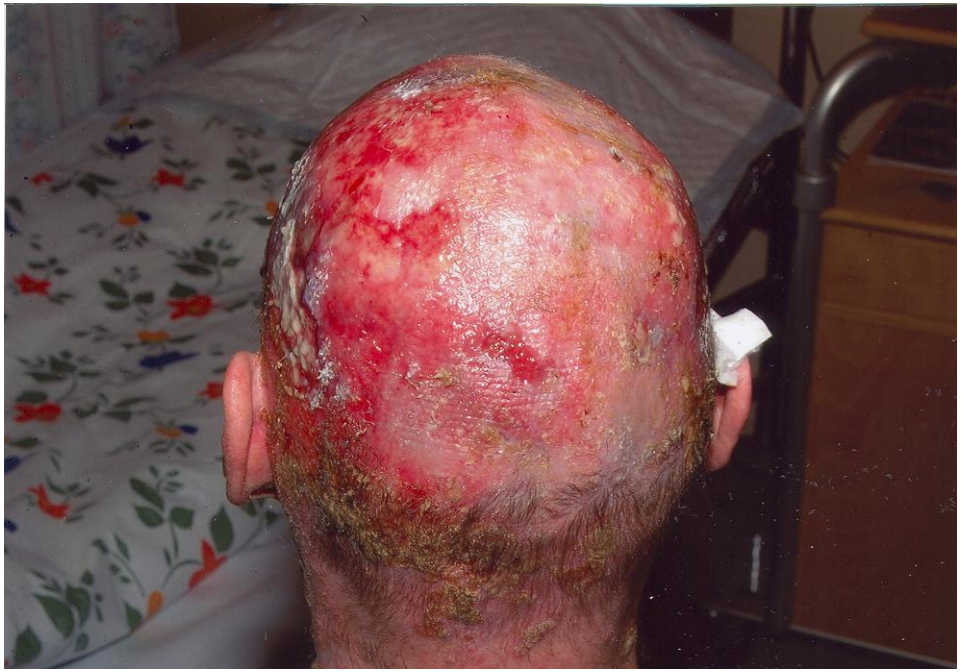
Allo-TX ved lymfom

- Økende siste 5 år
- Dokumentasjon for mange subtyper, mange fase II studier og EBMT-materialer
- RIC-allo dominerer

Case: 47 y male with MF

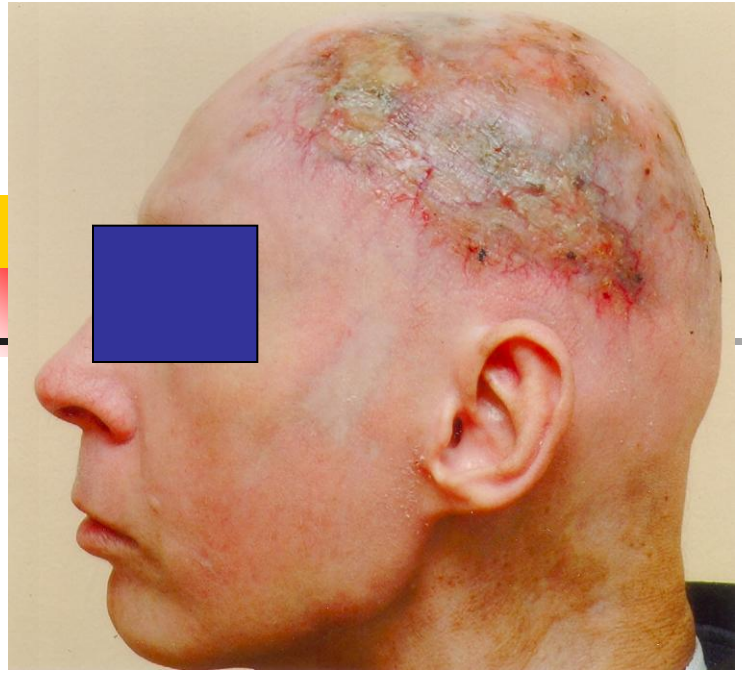
- Very aggressive Mycosis fungoides, chemoresistant
- 1 cycle EPOCH-fludarabin
- RIC-allo in January 2005
- Full donor chimerism achieved at day 15
- 9 mo: CR, no GVHD, good condition
- Developed PjP and chronic GVHD, pulmonary failure, died at 10 mo

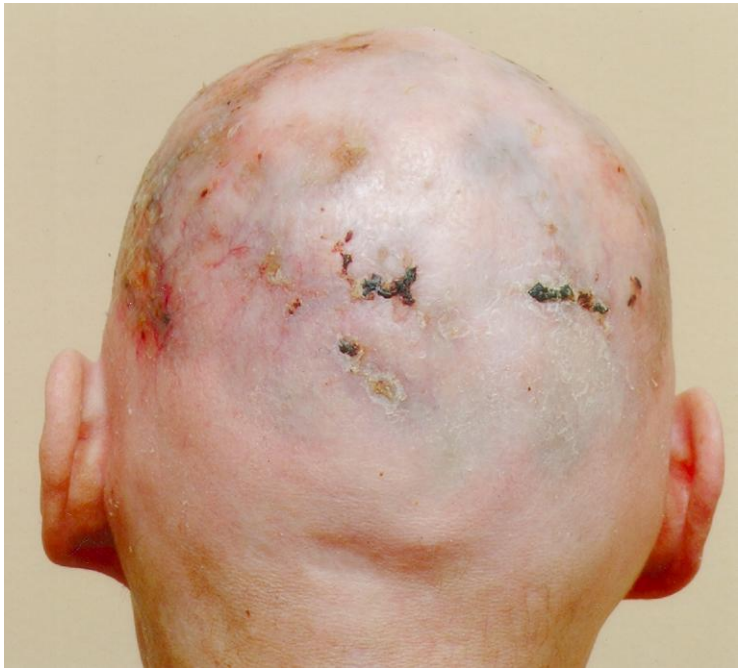




Photos taken before start of treatment

Large plaques and generalized infected lesions





Photos taken 3 months post-transplant

Healing of all lymphoma lesions

GVL-effect

Pasient karakteristika

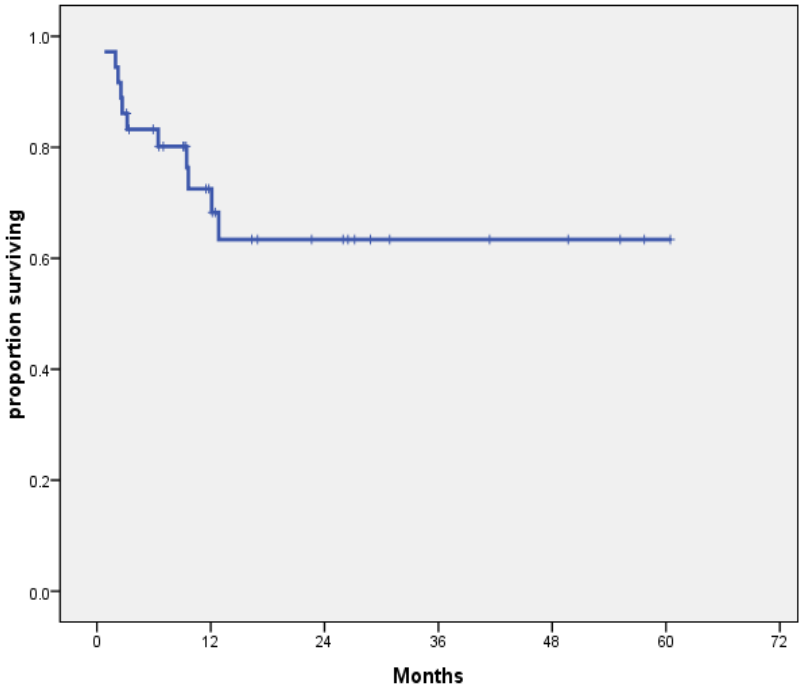
Table 1. Patient characteristics

Characteristics	*N (%) or median (range)*
No. of patients	37
Patient age (years)	52 (19–67)
Patient sex	
Male	27 (73)
Female	10 (27)
Disease	
Follicular lymphoma	10
Hodgkins lymphoma	7
Diffuse large B-cell lymphoma	7
Transformed follicular Lymphoma	6
T-cell lymphoma	3
Mantle cell lymphoma	2
Mycosis fungoides	2
No line therapy before allo-SCT, median (range)	4 (2–7)
No. of patients with auto-SCT before allo-SCT	27 (73)
Donor type	
HLA-matched family	22 (60)
HLA-matched unrelated	15 (40)
HCT co-morbidity index	
0	14 (38)
1 or 2	17 (46)
⩾3)	6 (16)
Median follow-up for patients alive (range)	28 (14–78)

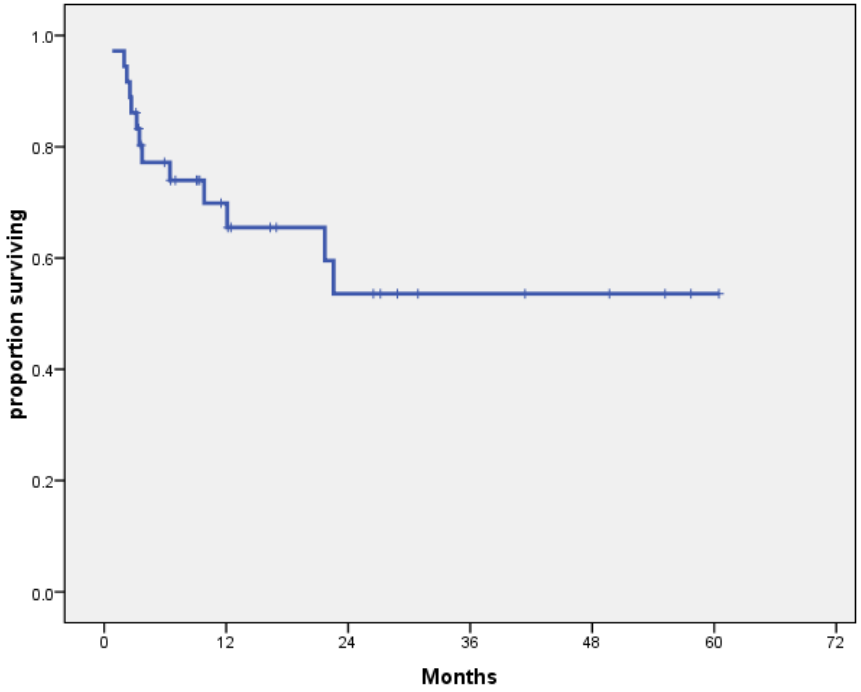
Abbreviation: HCT = hematopoietic cell transplant.

OS and PFS for lymphoma patients

Overall survival

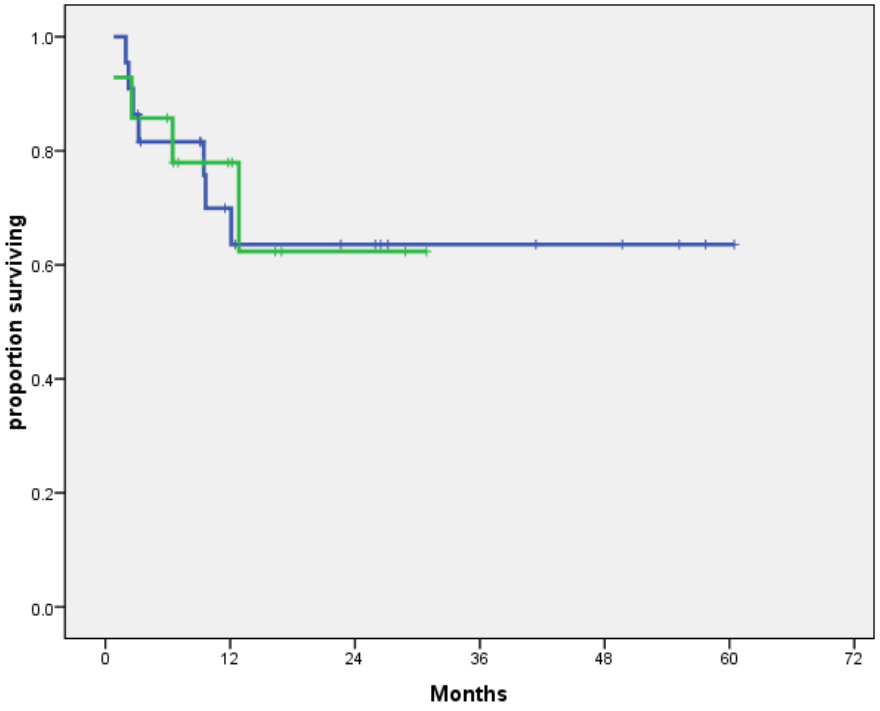


Progression-free survival

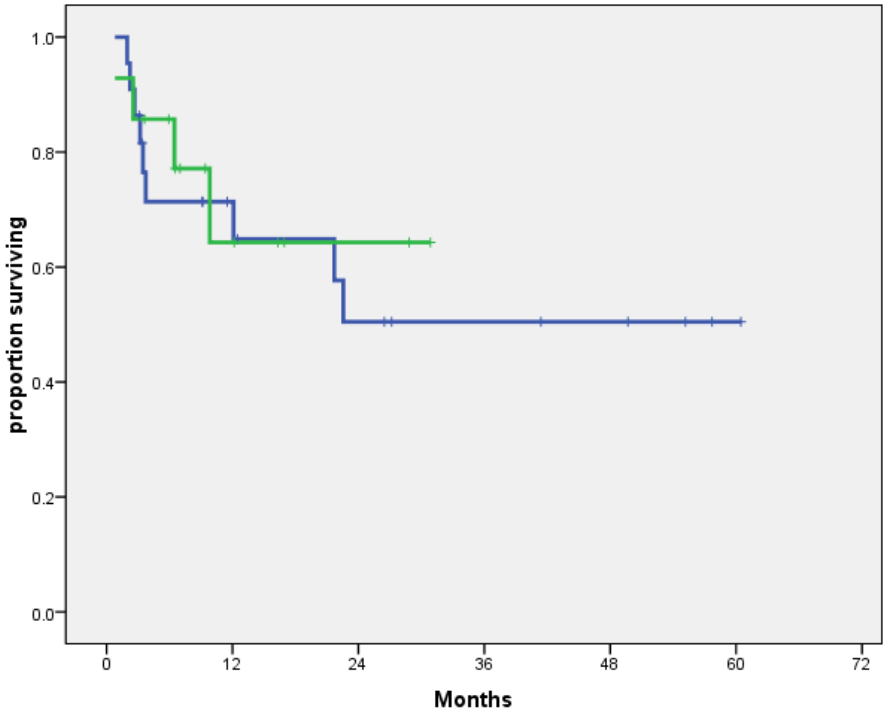


Family donor versus MUD transplants

Overall survival



Progression-free survival



Causes for mortality

- 11 cases

Relapse	3
TRM	8
Multiorgan failure	5
Cardiac	2
Chronic GVHD	1

Konklusjon

- Ved nøye utvelgelse av pasienter med residiv av lymfom kan man kurere ca. 50% av pasientene med RIC-allo, TRM er ca 20%
- Best resultater ved indolente lymfomer
- Aggressive lymfomer bør oppnå en god respons (PR/CR) på induksjonsbehandling før RIC-allo
- Residiv av Hodgkin lymfom er kanskje ikke godt egnet

Behandlingsstrategier

- **DLBCL – kurativt mål**
  - Intensiv kjemoterapi + rituximab
  - Strålebehandling mot mindre felter hos noen pasienter
- **Follikulært lymfom – ikke kurativt mål ved utbredt sykdom**
  - Strålebehandling ved begrenset sykdom - kurativt
  - Utbredt sykdom: -Avvente utviklingen når sykdommen ikke gir plager. Rituximan alene eller kombinert med kjemoterapi ved symptomer
- **Mantelcelle lymfom – ikke kurativt mål?**
  - Intensiv kjemoterapi + rituximab etterfulgt av HMAS hos yngre pasienter

Takk for oppmerksomheten

(i all beskjedenhet)