LYMFOOMAN SYNTY, UHO JA TUHO

Sirpa Leppä
HYKS, Syöpäkeskus &
HY, Genomibiologian tutkimusohjelma

ONKOLOGIPÄIVÄT 29-30.8.2014

Kiitokset

- Suomen lymfoomaryhmä, ideariihi
- Marja-Liisa Karjalainen-Lindsberg, HUS Lab Patologian osasto
- Sirkku Jyrkkiö, TYKS Onkologia
- Rita Janes, HYKS Syöpäkeskus
- Nea Malila, Syöpärekisteri
- Francesco d'Amore, Aarhus University Hospital
- Siddhartha Mukherjee, Columbia University: *The Emperor of All Maladies, A Biography of Cancer (2010)*

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UNIVERSITY OF HELSINKI

HUS

Lymphoma Biology and Prognosis

/Group Leppä

Research Group

- Minna Taskinen, postdoc, 2011-
- Susanna Mannisto, MD, postdoc, 2011-
- Annika Pasanen, MD, postdoc, 2013-
- Suvi-Katri Leivonen, post-doc, 2014-
- Kukka Maille, post-doc, 2014-
- Sari Riihijärvi MD, 2007-
- Kristiina Karihtala MD, 2009-
- Heli Vajavaara, MD, 2011-
- Pauli Vähämurto, MD, 2013-
- Ilari Siren, MSc, 2014-
- Kaisa Hirvonen, nurse, 2007-
- Anne Aarnio, tech, 2010-

PhDs

- Minna Eriksson, MSc 2005
- Antti Sommarhem MD 2007
- Heidi Nyman, MD 2009
- Risto Kajanne, MSc 2009
- Minna Taskinen, MSc 2011

Major Collaborators

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  - Sampsa Hautaniemi
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- University of Helsinki, Haartman Institute
  - Marja-Liisa Karjalainen-Lindsberg
- Aarhus Univ Hosp, Dept of Hematology
  - Francesco d'Amore
  - Judit Jorgensen
- Oslo Univ Hosp, Depts of Oncology and Pathology
  - Harald Holte
  - Jan Delabie
- Lund Univ Hosp, Dept of Oncology
  - Mats Jerkeman,
- Nordic Lymphoma Group
- Suomen Lymfoomaryhmä

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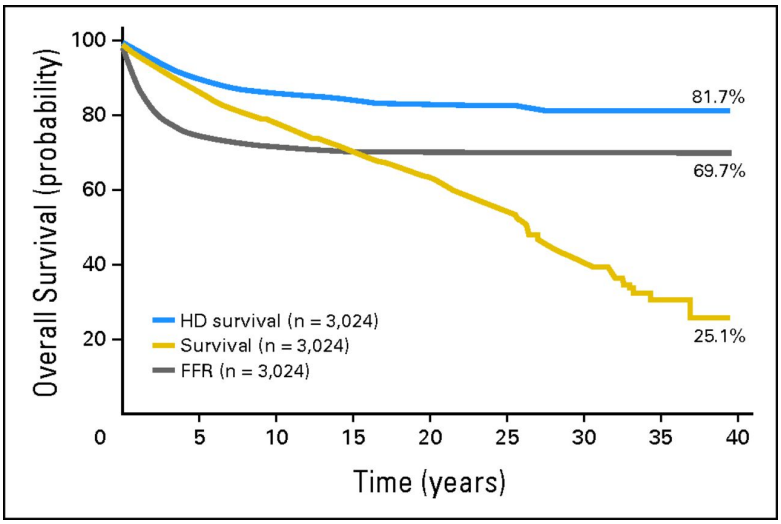
Changes in survival of all patients with all stages of Hodgkin disease (HD) treated by radiotherapy and/or combination chemotherapy at Stanford from 1960 to 2006



Canellos G P et al. JCO 2014;32:163-168

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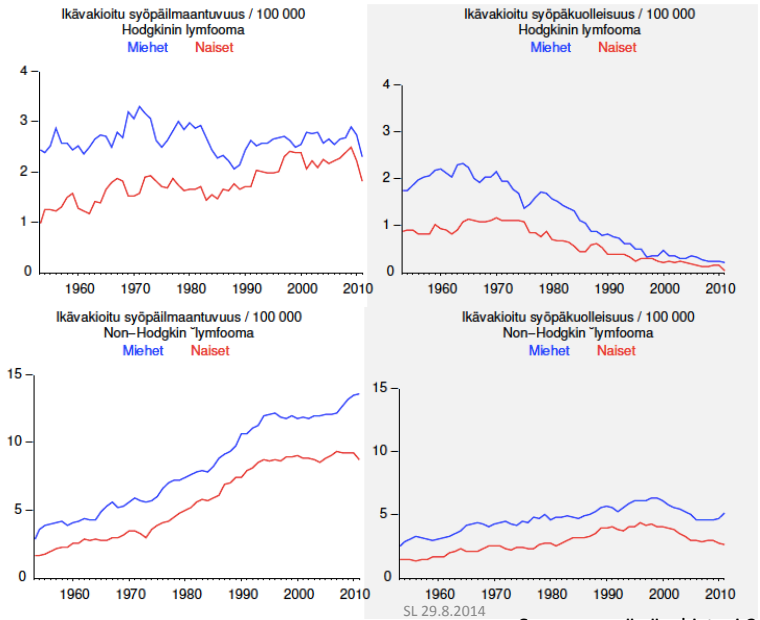
Ilmaantuvuus ja kuolleisuus



5 v OS

HL 88%

NHL 71%

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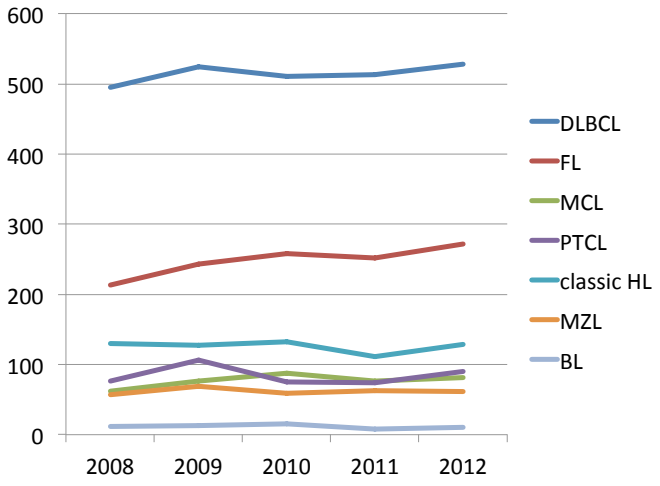
Suomen syöpärekisteri 2012/Nordcan

Ilmaantuvuus 2008-2012

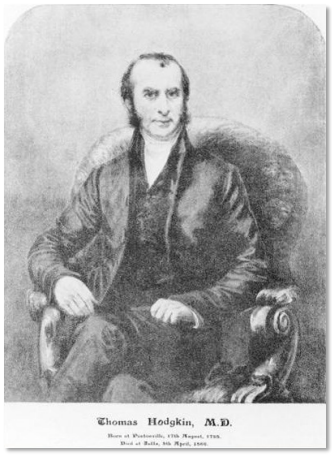


Suomen syöpärekisteri/Malila

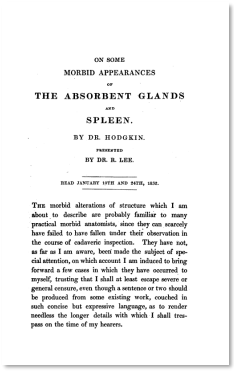
Hodgkinin lymfooma

Sir Robert Carswell's original paintings showing enlarged cervical and axillary lymph nodes

Thomas Hodgkin
(1798-1866)



v. 1832



ON SOME
MORBID APPEARANCES
OF
THE ABSORBENT GLANDS
AND
SPLEEN.

BY DR. HODGKIN.

PRESENTED
BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

The morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.

1823	Thomas Hodgkin publishes his doctoral thesis “Dissertatio Physiologica Inauguralis De ABSORBENDI FUNCTIONE”
1832	Hodgkin publishes a paper titled “Some Morbid Appearances of the Absorbent Glands and Spleen”
1838	Richard Bright publishes a paper on lymphatic disease titled "Observations on abdominal tumors and Intumescence, Illustrated by Cases of Disease of the Spleen"
1856	Samuel Wilks publishes a paper titled "Cases of Lardaceous Disease and Some Allied Affections with Remarks"
1898	Carl Sternberg first describes giant cells now called Reed-Sternberg cells
1902	Dorothy Reed independently describes Reed-Sternberg cells

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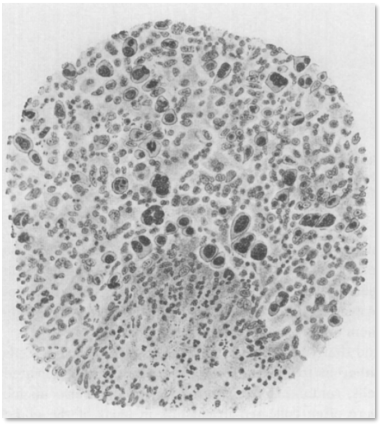
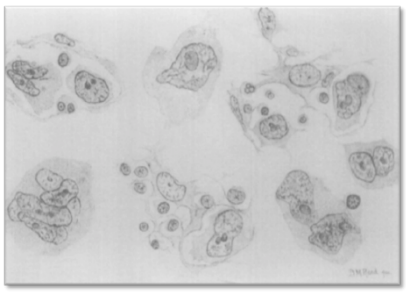
Carl Sternberg (1872-1935)

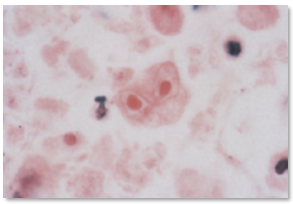


An illustration from Sternberg's paper, published in 1898, clearly showing multi-nucleated cells as well as mononuclear variants

Dorothy Reed (1873-1964)



Dorothy Reed's drawings (1902)



A classical Reed-Sternberg cell in a preparation made from Hodgkin´s original material

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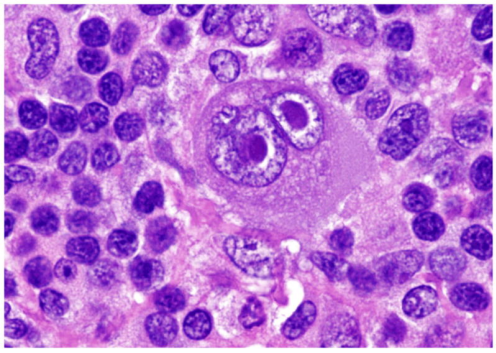

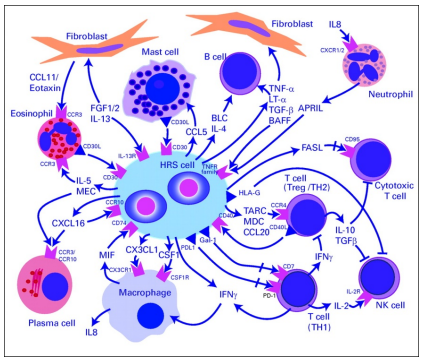

History of chemotherapy

II World war

Explosion in Bari, Italy exposes servicemen to toxic effects of mustard gases.

1943

Nitrogen mustard was submitted to Goodman and Gilman at Yale for treatment of Hodgkin's disease and lymphosarcoma

History of chemotherapy

1946	Goodman et al. and Gilman et al publish papers on the use of Nitrogen Mustard for treatment HL, lymphosarcoma and leukemia
1964	MOPP is developed-by DeVita> 1967 first results reported
1964	Johnson and colleagues publish a paper on vinca-alkaloids
1968	Doxorubicin becomes available
1975	Milan group led by Bonadonna reports the first results from a randomized study comparing ABVD and MOPP
1976	The first report on CHOP regimen (McKelvey et al.)
1992	GHSG led by Volker Diel introduces BEACOPP
2010	Bendamustine is approved for indolent NHLs

The 1950s - Discovery of corticosteroids

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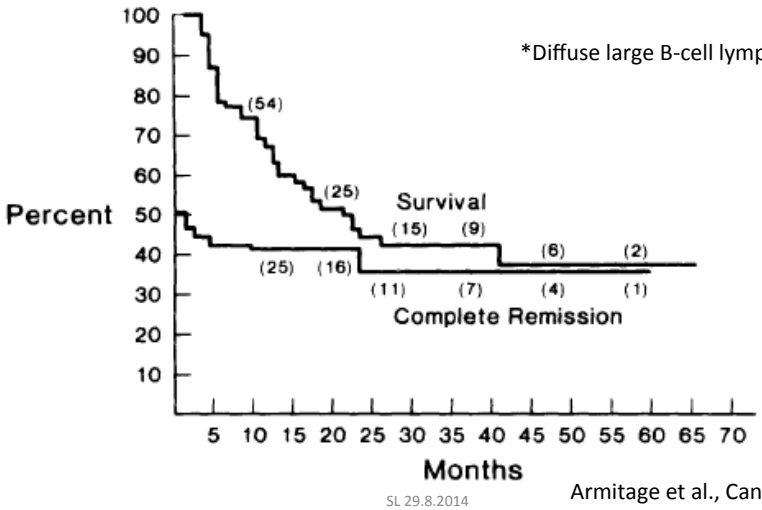
Predicting Therapeutic Outcome in Patients with Diffuse Histiocytic Lymphoma* Treated with CHOP



*Diffuse large B-cell lymphoma

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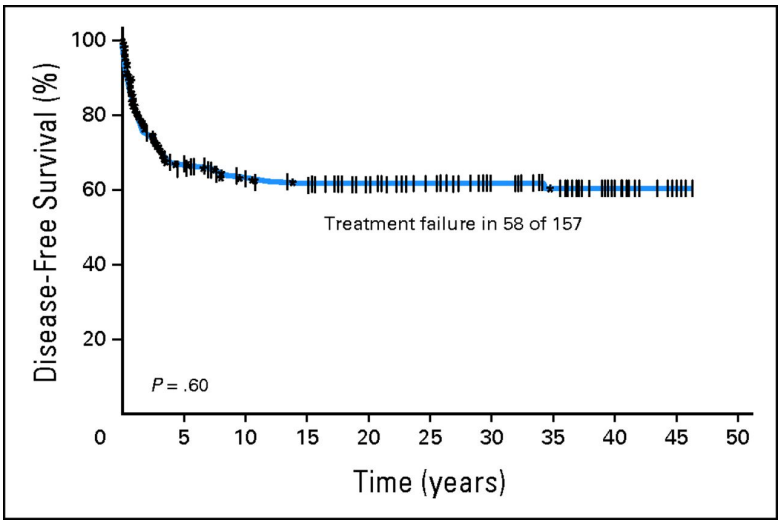
Armitage et al., Cancer 1982

The 40-year disease-free survival of patients who achieved a complete remission with mechlorethamine, vincristine, procarbazine, and prednisone chemotherapy at the NCI (DeVita, personal communication)



Canellos G P et al. JCO 2014;32:163-168

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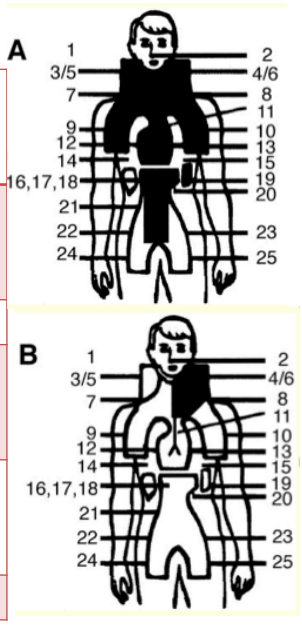
History of radiotherapy

1931	Gilbert reports irradiation of nodes and surrounding areas to result in 5 y survival of 25-35%
1950	Peters publishes a paper titled "Study of survivals in HD treated radiologically"
The 1960s	Linear accelerator is introduced
1966	Kaplan and Rosenberg demonstrate that high dose extended field RT is a curative modality
1975	Rosenberg and Kaplan introduce the concept of combining radiotherapy with chemotherapy
1980	CT-based planning



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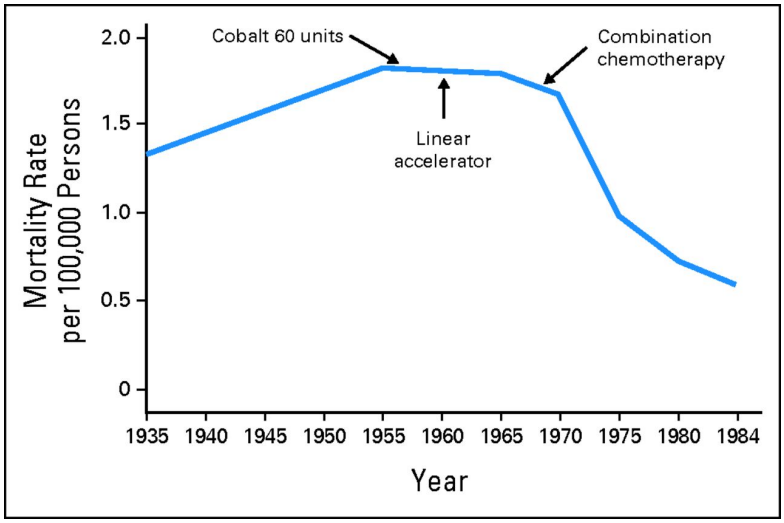
Hodgkin lymphoma mortality rates from 1935 to 1984 related to the introduction of modern RT and combination of RT with MOPP



Canellos G P et al. JCO 2014;32:163-168

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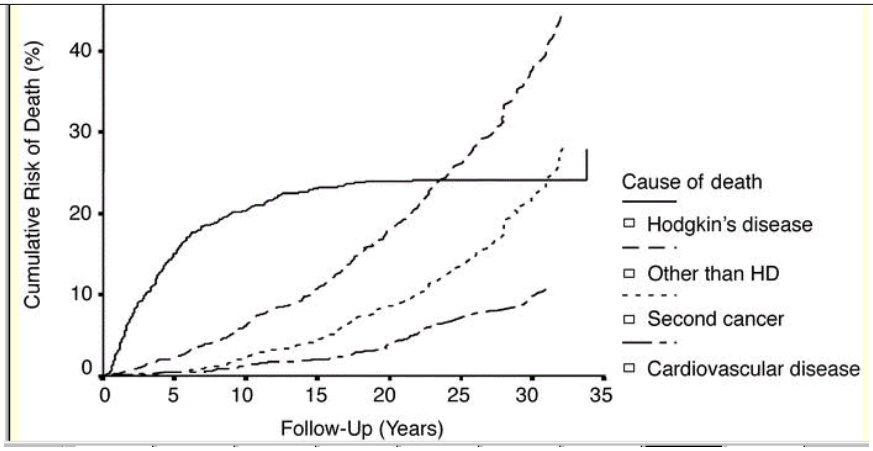
Mitä haittaa säde ja MOPP hoidoista seurasi?

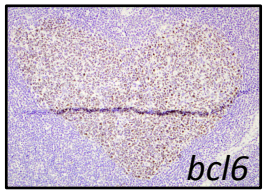
Fertiliteetti, sydän-ja verisuonihaitat, sekundaarimaligniteetit

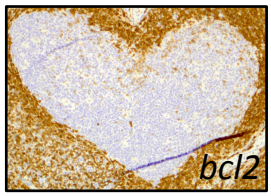
Aleman JCO 2003: 1261 alle 41v potilasta, hoidettu 1965-87, mediaani 17.8v
534/1261 eli **42% kuollut**; **HD**: 294/1261 eli **23%**; **muu syy**: 240/1261 eli **20%**



History of antibody-based therapies

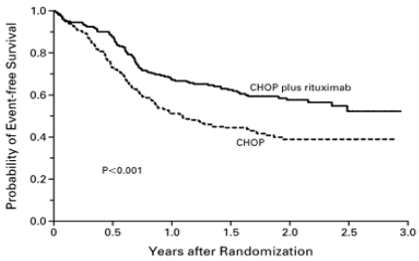
1974	Mason and colleagues introduce immunoperoxidase technique for the use on FFPE tissue slides
1975	Discovery of monoclonal antibodies by Köhler and Milstein
1997	CD20 mAb rituximab is approved for NHLs-> RITUXIMAB ERA
2002	Coiffier et al demonstrate the survival benefit of R-CHOP vs CHOP in DLBCL
2004	Radioimmunotherapy (Zevalin) is approved for indolent NHLs
2012	Brentuximab vedotin is approved for relapsed HL

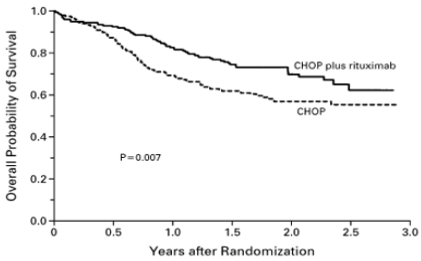




70% DLBCL potilaista paranee

LNH-98.5: CHOP21 vs R-CHOP21 (>60v)





No. at Risk						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17

No. at Risk						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Coiffier et al., NEJM 2002& Feugier et al., JCO 2005

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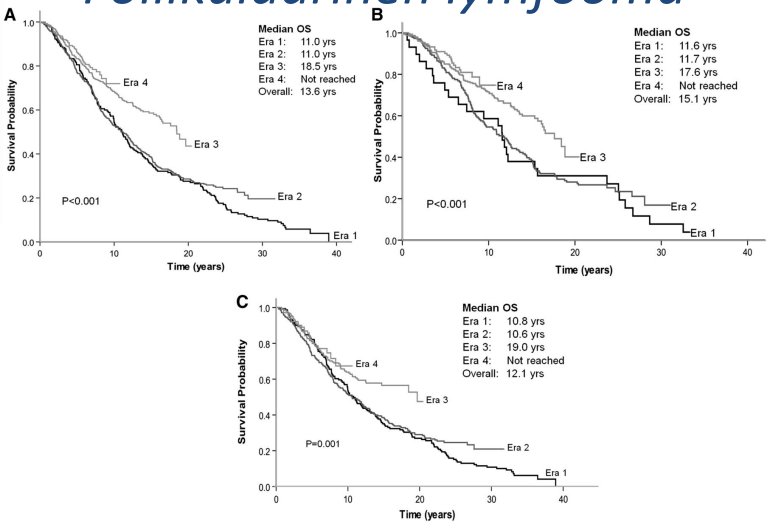
Follikulaarinen lymfooma



Tan D et al. Blood 2013;122:981-987

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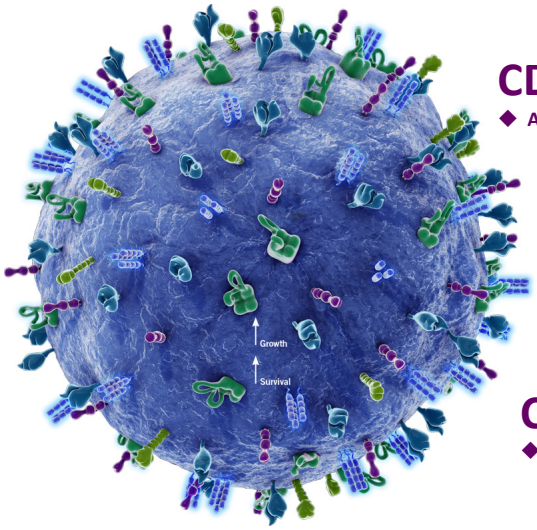
B & T-cell surface antigens as therapeutic targets in lymphomas

CD20
- Rituximab (iv&sc)
- Ofatumumab
- Obinutuzumab

CD20*
- ^{90}Y-Ibritumomab -tiuxetan
- ^{131}I-Tositumomab



CD52
- Alemtutsumab

CD30
- Brentuximab vedotin

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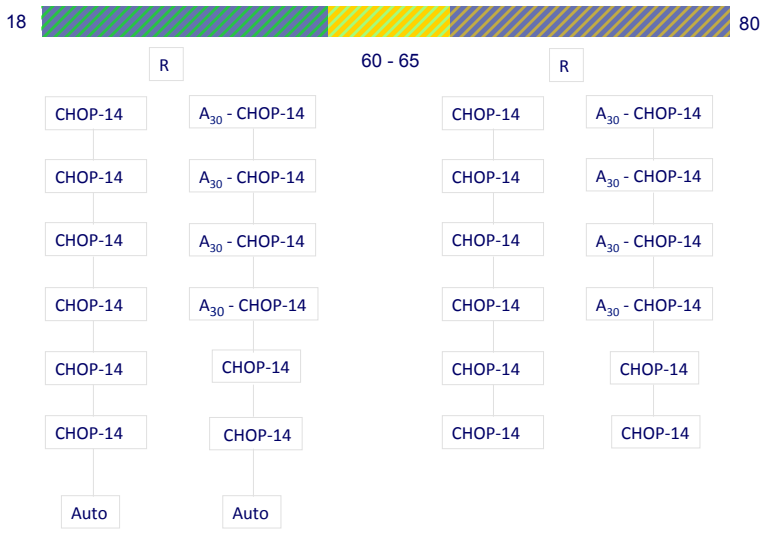
NORDIC LYMPHOMA GROUP

The ACT trials for PTCL

AFTER the dose/age amendments

GERMAN HIGH-GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP



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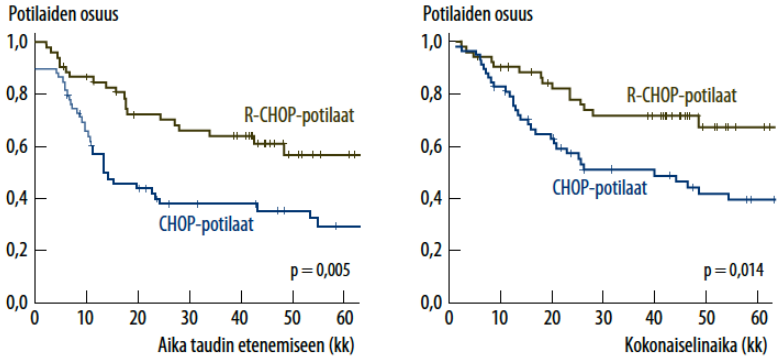
HYKS Syöpäkeskuksen hoitotulokset (DLBCL)

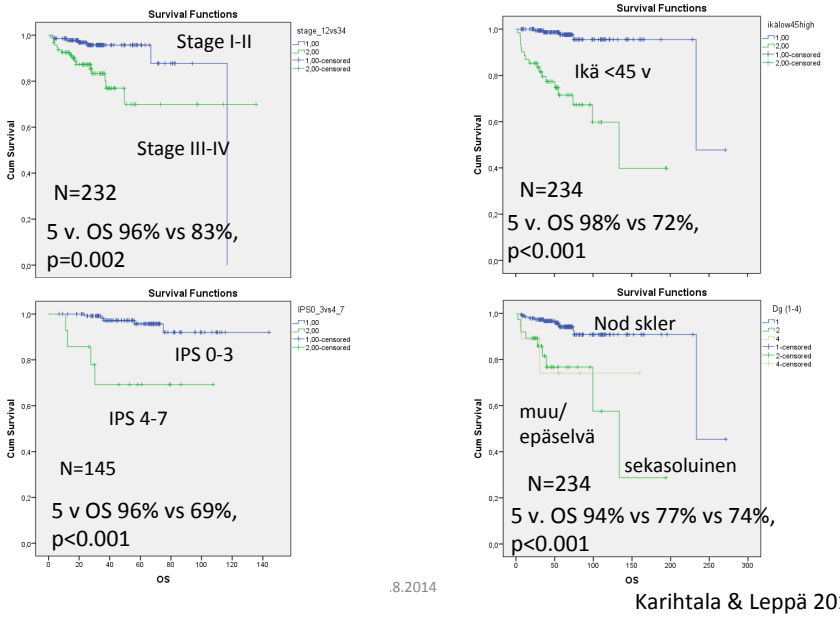


KUVA. CHOP-hoitoa sekä CHOP:n ja rituksimabin yhdistelmää primaarivaiheessa saaneiden diffuusia suurisoluista B-solulymfoomaa sairastavien potilaiden tauditon ja kokonaiselinaika. R = rituksimabi, CHOP = syklofosfamidi + doksorubiniini + vinkristiini + prednisoni.

Paraneeko lymfooma vasta-ainehoidolla?

Lääketieteellinen Aikakauskirja Duodecim
2009;125(3):267-73
Sirpa Leppä, Heidi Nyman ja Marja-Liisa Karjalainen-Lindsberg
Katsaus

HYKS Syöpäkeskuksen hoitotulokset (HL)



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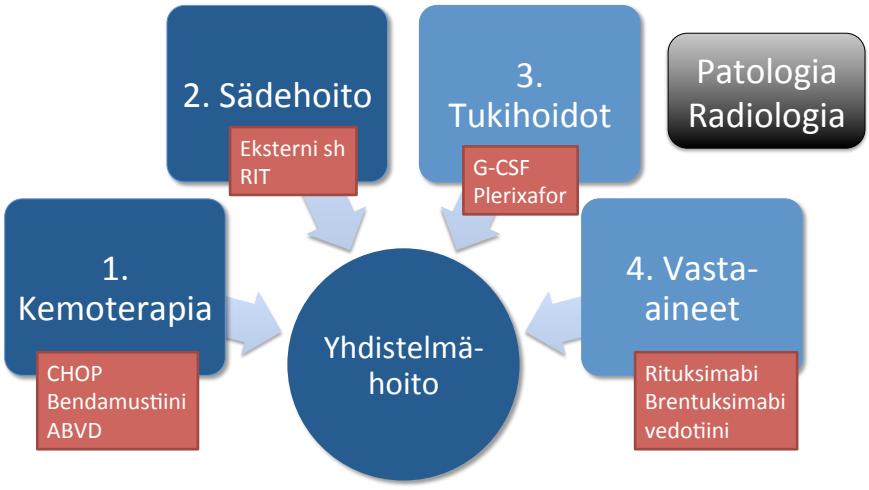
Karihtala & Leppä 2014

Lymfoomahoitojen kulmakivet



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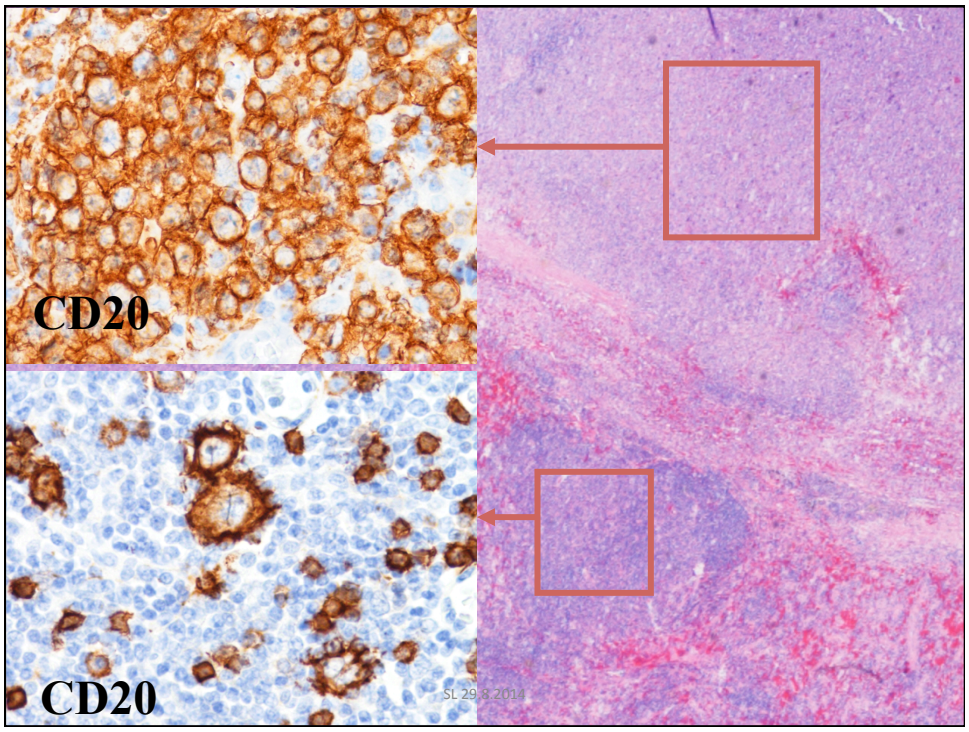

History of Lymphoma Classifications	
1956	Rappaport
1974	Kiehl classification (Lennert)
1978	Lukes-Collins classification
1983	Concordance of Kiehl and Lukes-Collins classifications
1994	Revised European-American LYMPHOMA Classification (REAL)
2001	WHO classification
2008	WHO version 2

HD and NHLs separated

B and T cells recognized

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Diffuse large B-cell lymphoma, not otherwise specified (NOS)

- Common morphologic variants
  - Centroblastic
  - Immunoblastic
  - Anaplastic
- Rare morphologic variants
- Molecular subgroups
  - Germinal centre B-cell-like (GCB)
  - Activated B-cell-like (ABC)
- Immunohistochemical subgroups
  - CD5-positive DLBCL
  - Germinal centre B-cell-like (GCB)
  - Non-germinal centre B-cell-like (non-GCB)

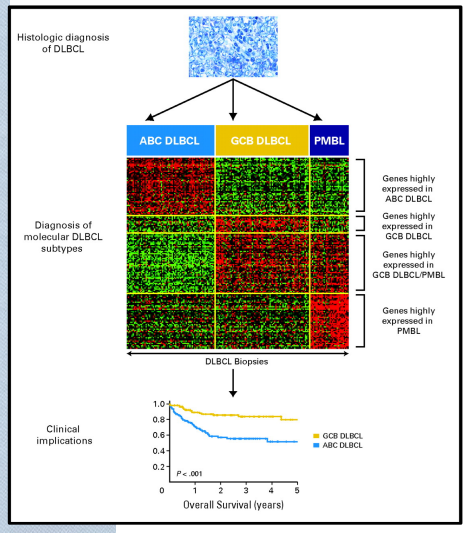
Diffuse large B-cell lymphoma subtypes

- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly

Other lymphomas of large B cells

- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- ALK-positive LBCL
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma

Application of gene expression profiling allows the distinction of histologically undistinguishable molecular subtypes.



Nogai H et al. JCO 2011;29:1803-1811

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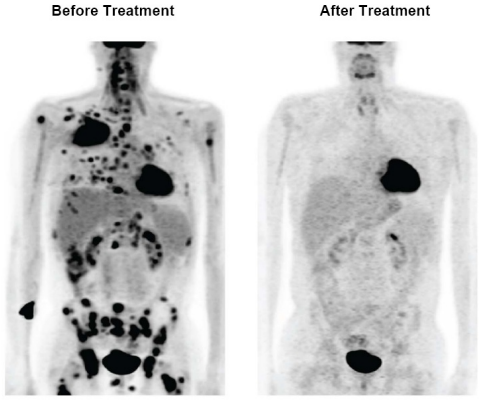
Staging

1960-1970	Lymphagiogram
1966	Rye meeting-> definition of stages I-IV
1971	Ann-Arbor meeting ->staging laparotomy
Early 1980s-1990	CT Gallium Scans
The 2000th	PET ja PET-CT



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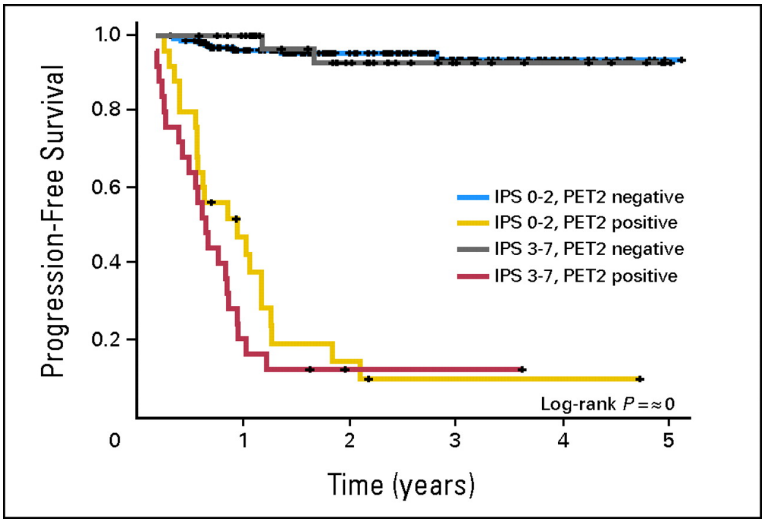
Early interim PET with IPS and prognosis in HL



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Gallamini A et al. JCO 2007;25:3746-3752

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Kuvasaalista hakusanalla ”PET”

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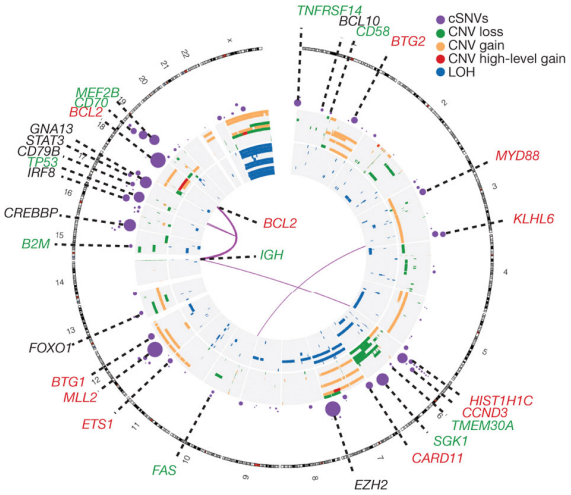
Biologiset riskitekijät/Genomiikka



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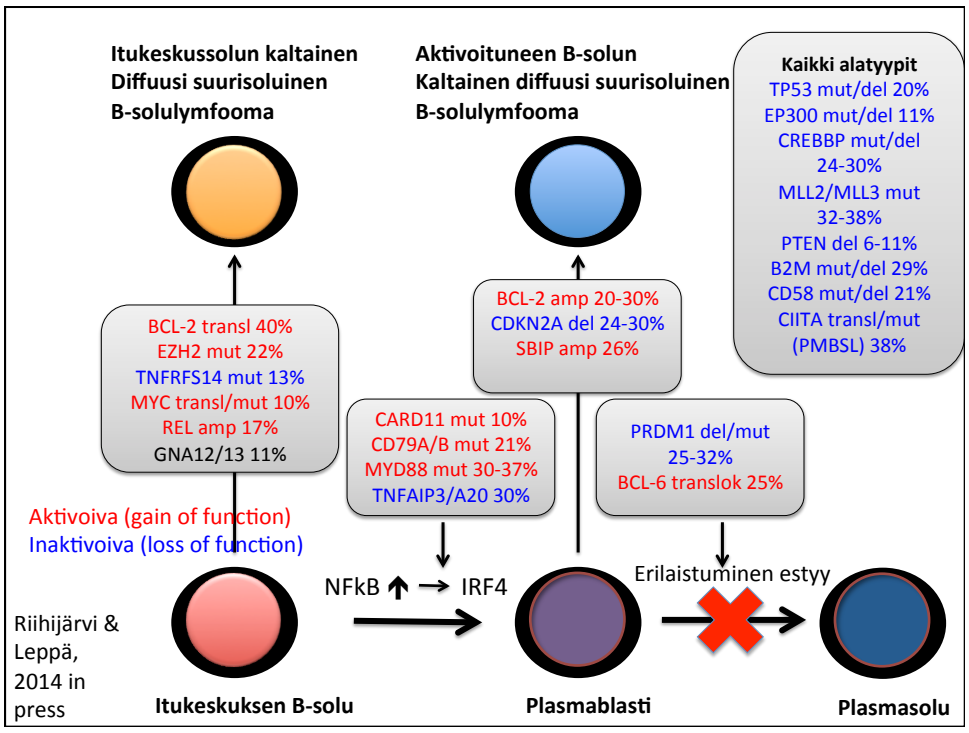
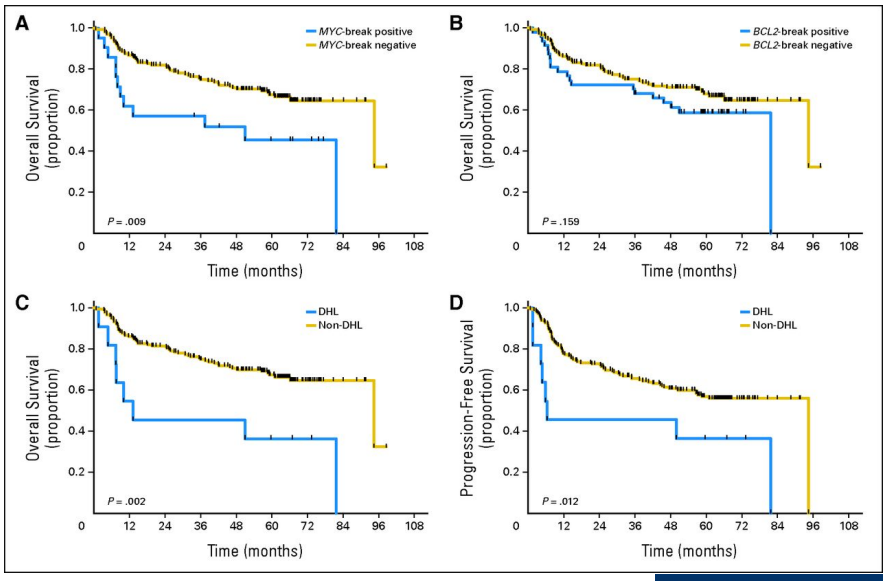


Biologiset riskitekijät-MYC/BCL2 Double hit



Green T M et al. JCO 2012;30:3460-3467

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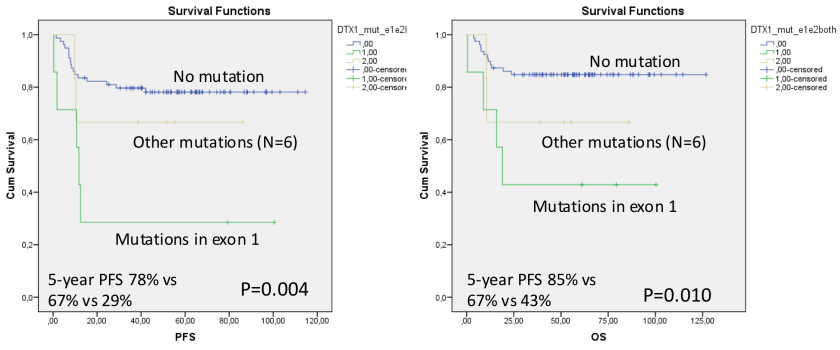
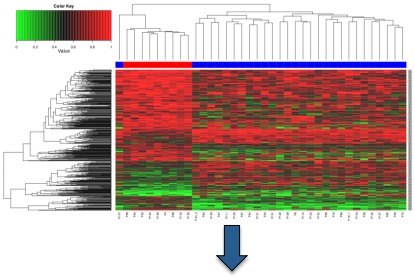
Survival-associated mutations in DLBCL

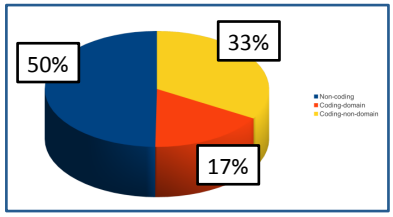


Taskinen, Meriranta, Pasanen et al., 2014. Novel Somatic Mutations in E3 Ubiquitin Ligase Deltex 1 Are Associated with Survival in Diffuse Large B-Cell Lymphoma

SL 29.8.2014

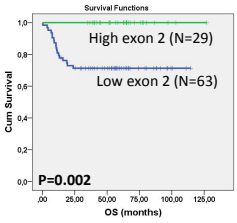
Global Profiling of Outcome Associated Alternative Splicing Events and Gene Expression In DLBCL



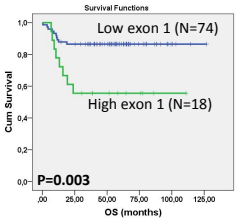


Survival and pathway analyses

ABC transporters
Phosphatidylinositol signaling
Regulation of actin cytoskeleton



ABCB1



BCAR1

Taskinen, Chen et al., 2014

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Miten hyödyntää molekyläaristä tietoa käytännössä?

- REMoDLB
  - A randomised evaluation of molecular guided therapy for diffuse large B-cell lymphoma with bortezomib
- Phoenix
  - A randomized study of the Bruton's tyrosine kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in combination with R-CHOP in subjects with newly diagnosed non-germinal center B-cell subtype of diffuse large B-cell lymphoma
- Nordic Bio-CHIC

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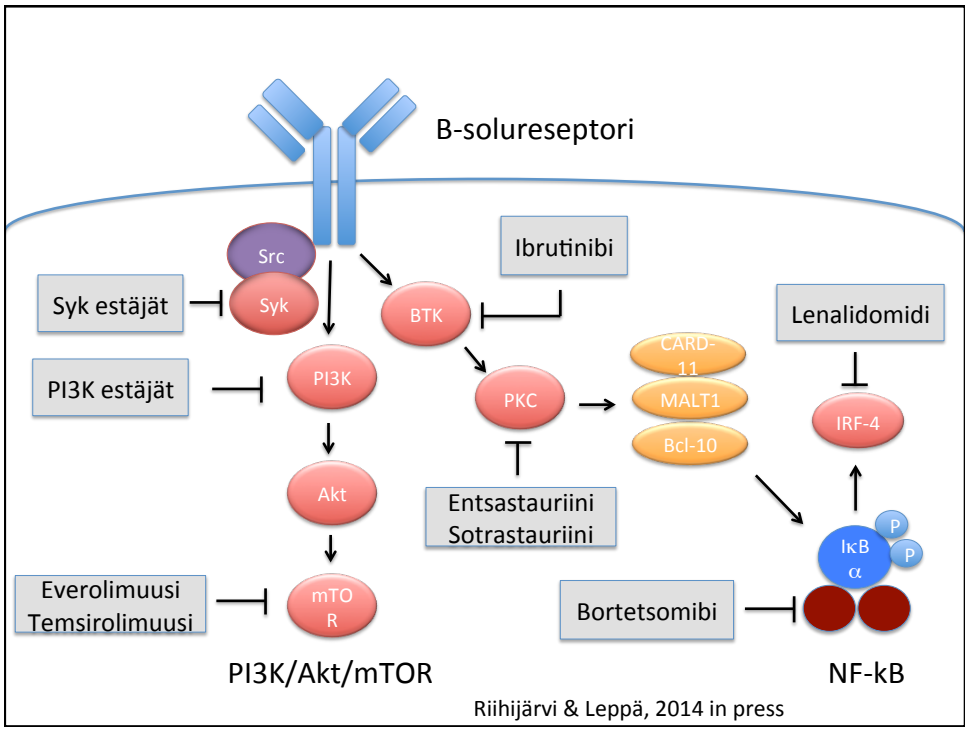

Riihijärvi & Leppä, 2014 in press

…Tulevaisuudessa…

- Alaryhmät tarkentuvat
- Biologisia ennustetekijöitä otetaan osaksi hoidon suunnittelua
- PET ohjaa hoidon valintaa
- Uusien biologisten lääkkeiden asema ja annostelu osana hoitoa selkiytyy
- Genomilaajuisen profiloinnin avulla löydetään potilaille tautispefisisiä hoitokohteita

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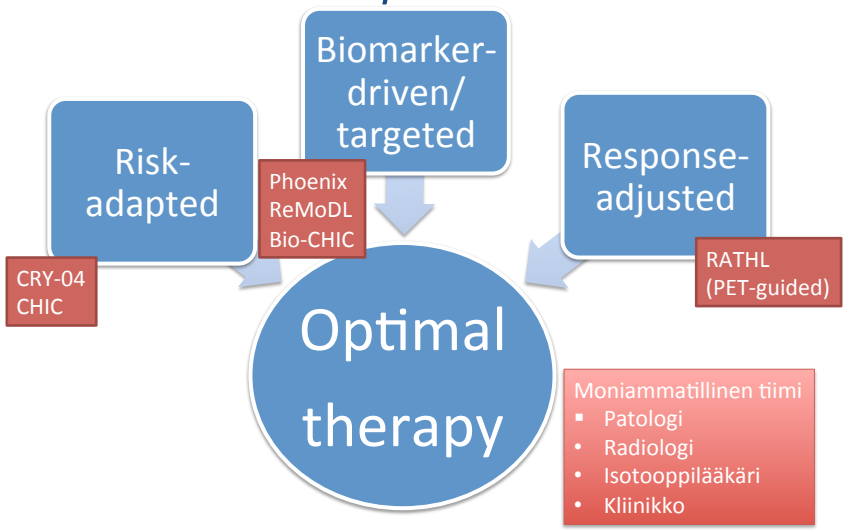
Miten lymfoomien hoitotuloksia voidaan parantaa?



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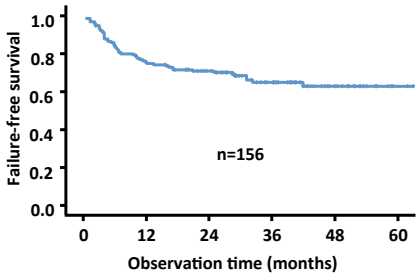
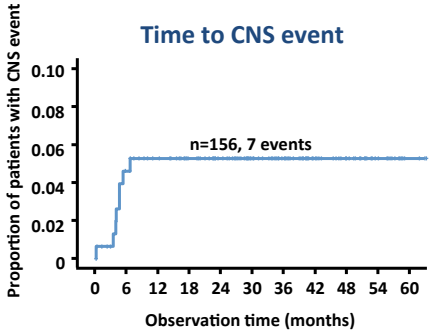
Nordic CRY-04 Study: Dose-dense chemoimmunotherary followed by systemic CNS prophylaxis for young high risk DLBCL

Failure free survival (FFS)



3-year FFS = 65.1%; OS = 81.2%

Time to CNS event



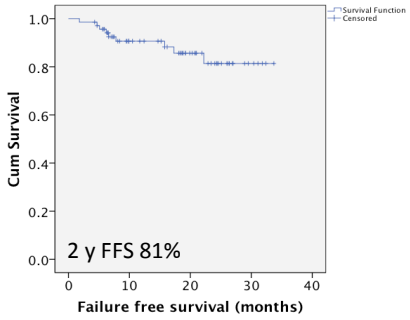
CNS relapse rate = 4.5%

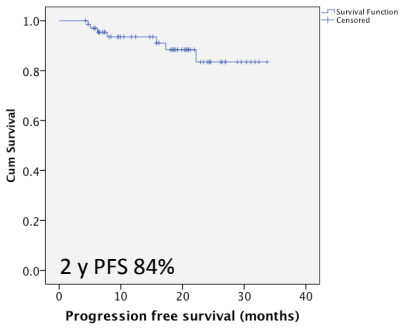
Holte, Leppä,Björkholm et al. Ann Onc 2013

10.12.2013 SL

Nordic CHIC-Study: Dose-Dense Chemoimmunotherapy and Early CNS Prophylaxis for Young High-Risk DLBCL

- Interim analysis, n=70, median f-up 19 months
- Nine events
- One toxic death, one withdrawal due to toxicity
- Two primary refractory
- Five relapses; two CNS recurrences, both isolated intracerebral and flow negative





Leppä, Thierens, Jorgensen et al., ASH2013

Next NLG LBC protocol (Bio-CHIC)

aaIPI > 1

Biologically high risk:
- Single MYC
- Double MYC/bcl2 hits
- P53 del (FISH)
- P53 + (IHC)
- MYC+/bcl+ (IHC)
- CD5 +

Prephase and
HD Mtx + R-CHOP x 2

Planned target size
N=150; of these 50 with biological risk factors

Staging: PR, CR

Mod dosing for pts>55 y

Biol markers +
R-EPOCH x 4
+R-HD-AraC

Biol markers –
R-CHOEP-14 x 4
+ R-HD Ara C

29.8.2014 SL

30.1.2015 10th Lasse Teerenhovi Symposium
7-8.5.2015 9th Helsinki Lymphoma Master Class
-Aiheena Hodgkinin lymfoomat