Il linfoma non-Hodgkin: inquadramento epidemiologico, fattori di rischio e presa in carico

Sistema Socio Sanitario
Regione Lombardia
ATS Brescia

Venerdì 30 novembre 2018

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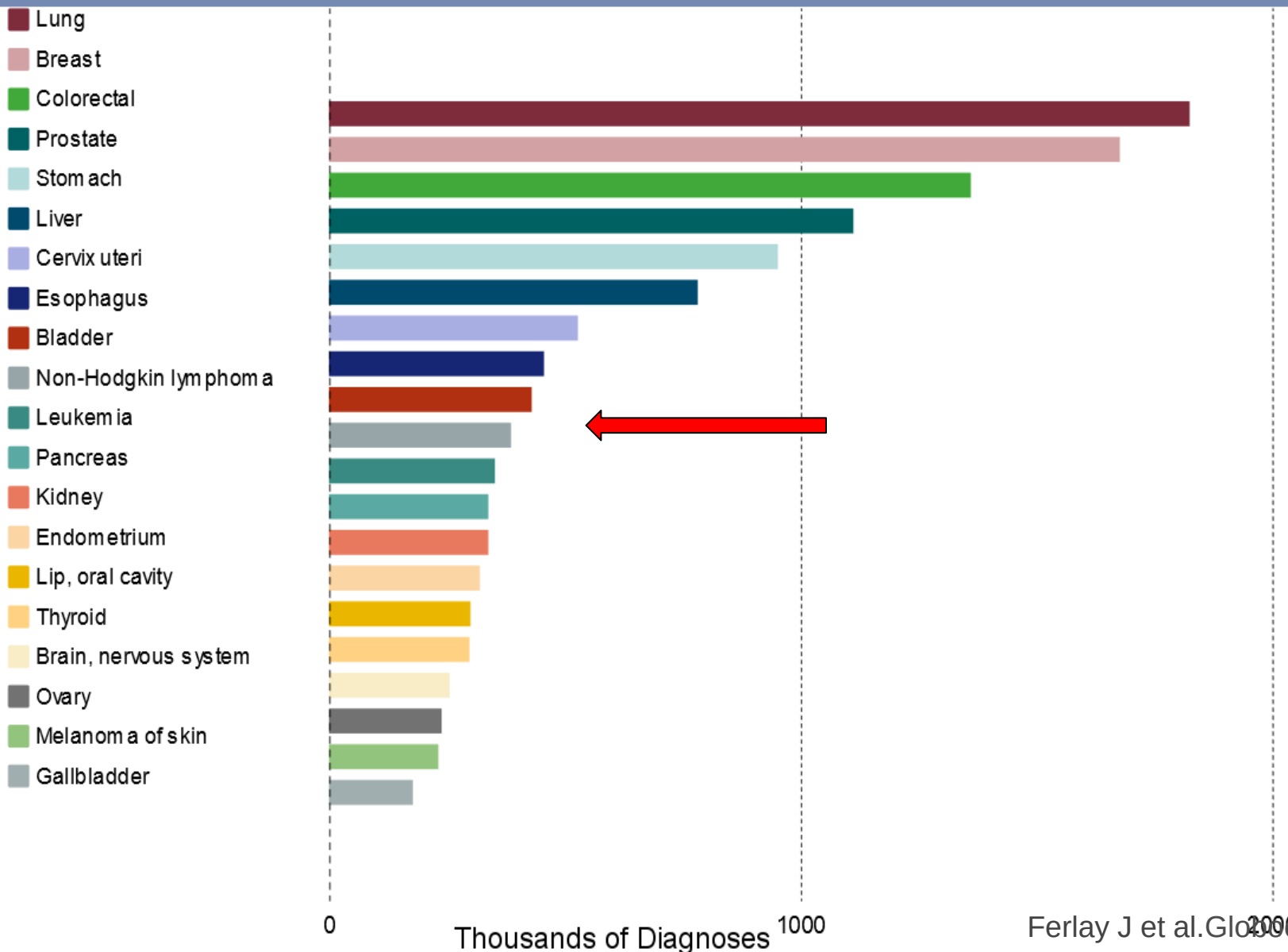
INQUADRAMENTO EPIDEMIOLOGICO

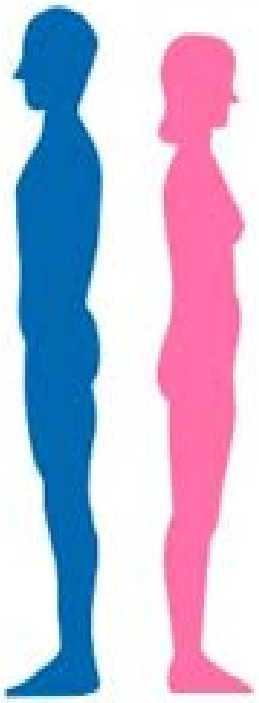
Incidence of top cancers worldwide 2012



Ferlay J et al.Globocan _2012

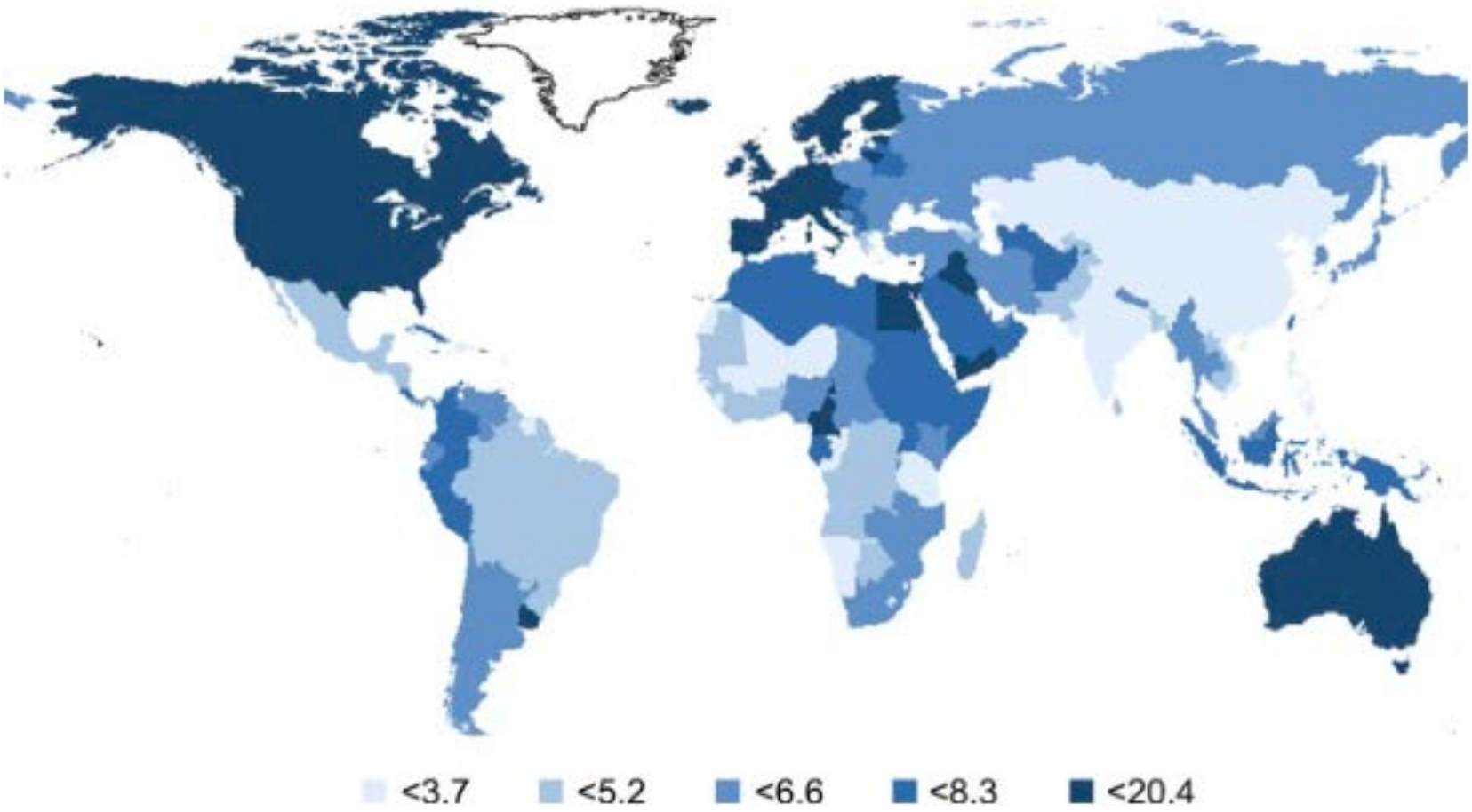
Estimated new cancer cases by sex, United States, 2014

Males			Females		
Prostate	233,000	27%	Breast	232,670	29%
Lung & bronchus	116,000	14%	Lung & bronchus	108,210	13%
Colorectum	71,830	8%	Colorectum	65,000	8%
Urinary bladder	56,390	7%	Uterine corpus	52,630	6%
Melanoma of the skin	43,890	5%	Thyroid	47,790	6%
Kidney & renal pelvis	39,140	5%	Non-Hodgkin lymphoma	32,530	4%
Non-Hodgkin lymphoma	38,270	4%	Melanoma of the skin	32,210	4%
Oral cavity & pharynx	30,220	4%	Kidney & renal pelvis	24,780	3%
Leukemia	30,100	4%	Pancreas	22,890	3%
Liver & intrahepatic bile duct	24,600	3%	Leukemia	22,280	3%
All Sites	**855,220**	**100%**	**All Sites**	**810,320**	**100%**



Siegel R, Ma J, Zou Z, Jemal A. *Cancer J Clin*. 2014; 64(1):9-29

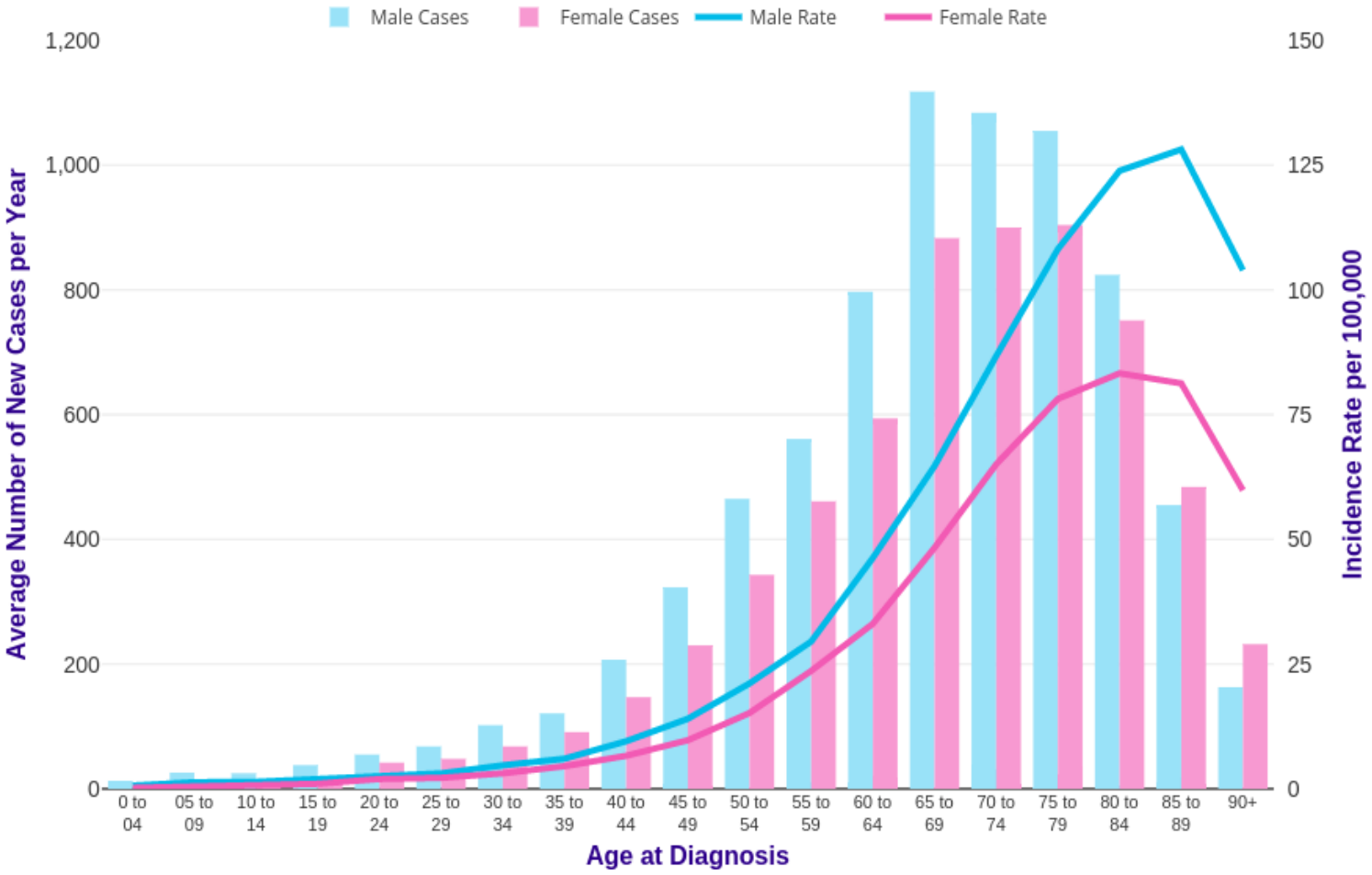
World map of the estimated age-standardized incidence rates (per 100,000 WHO world standard population) of non-Hodgkin and Hodgkin lymphoma



International Agency for Research on Cancer

World Health Organization

Numbers of New Cases and Age-Specific Incidence Rates by sex, NHL, UK 2013-2015



Distribuzione dei tipi di tumore più frequenti nei casi prevalenti in Italia nel 2018 per sesso

♂

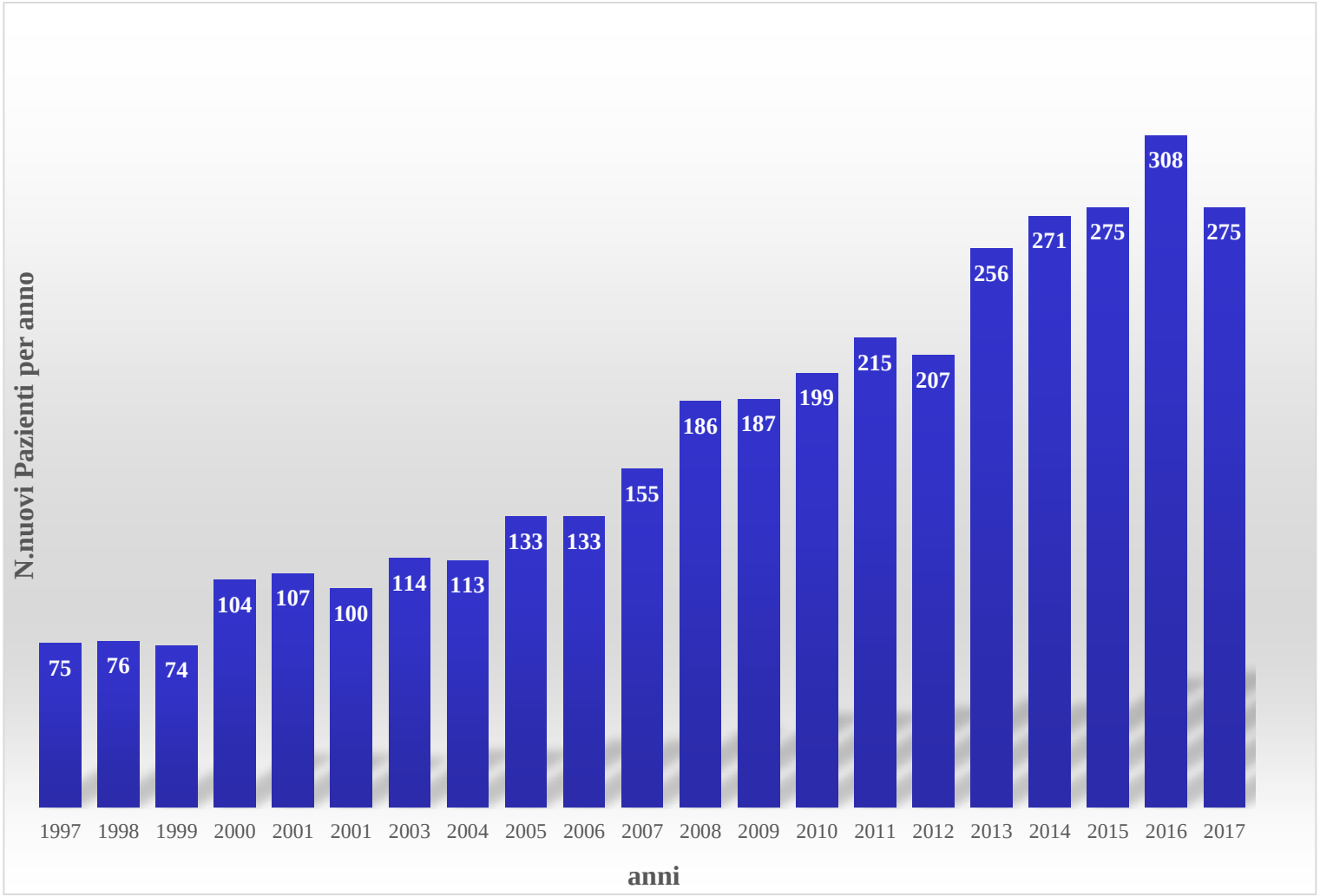
Tumore	N.	%
Prostata	457902	30
Colon-retto-ano	244046	16
Vescica	212326	14
Rene, vie urinarie	81603	5
Linfoma n. H.	73570	5
Cute (melanomi)	73076	5
Polmone	67405	4
Testicolo	51062	3
Leucemie	45198	3
Tiroide	44582	3
Altri	180388	12

♀

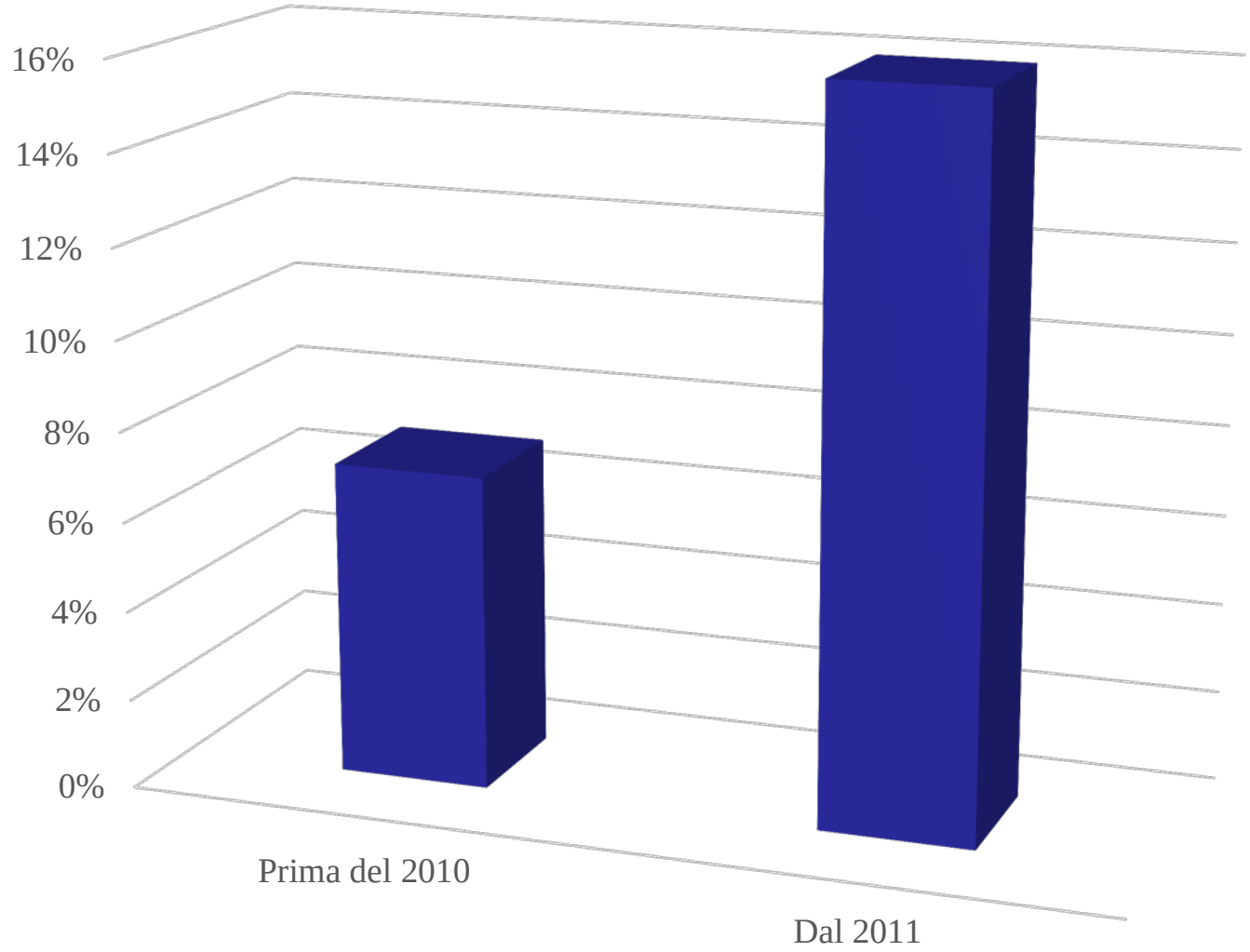
Tumore	N.	%
Mammella	799196	43
Colon-retto-ano	226652	12
Tiroide	155995	6
Utero corpo	114485	5
Cute (melanomi)	82066	4
Linfoma n. H.	67681	4
Vescica	57196	3
Utero cervice	56063	3
Ovaio	50032	3
Rene, vie urinarie	43858	2
Altri	184185	10

FONDAZIONE AIOM UNITI PER VINCERE IL CANCRO

Incidenza nella casistica Bresciana



PAZIENTI CON ETÀ > 80 ANNI
DLBCL NELLA CASISTICA BRESCIANA



WHO Classification of Lymphoid Neoplasms

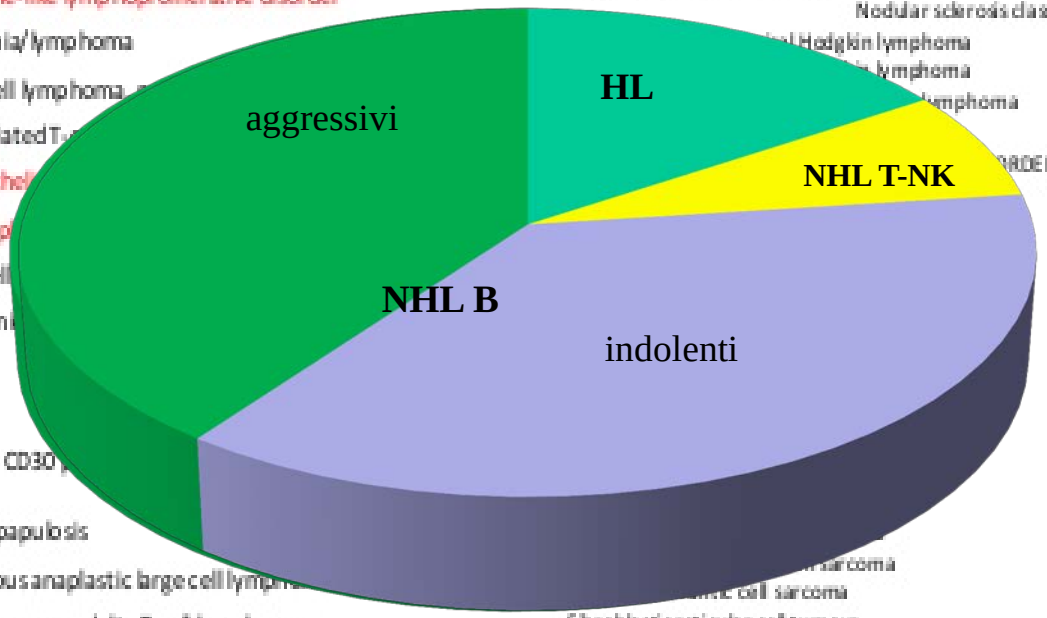
2016 WHO classification of Lymphoma

- MATURE B-CELL NEOPLASMS
- Chronic lymphocytic leukemia / small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis*
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic B-cell lymphoma/leukemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma
- Hairy cell leukemia-variant
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha heavy chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases*
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- Pediatric nodal marginal zone lymphoma
- Follicular lymphoma
- In situ follicular neoplasia*
- Duodenal-type follicular lymphoma*
- Pediatric-type follicular lymphoma*
- Large B-cell lymphoma with IRF4 rearrangement*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
- Germinal center B-cell type*
- Activated B-cell type*
- T cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL, NOS*
- EBV+ Mucocutaneous ulcer*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8 positive DLBCL, NOS*
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration*
- High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
- High grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

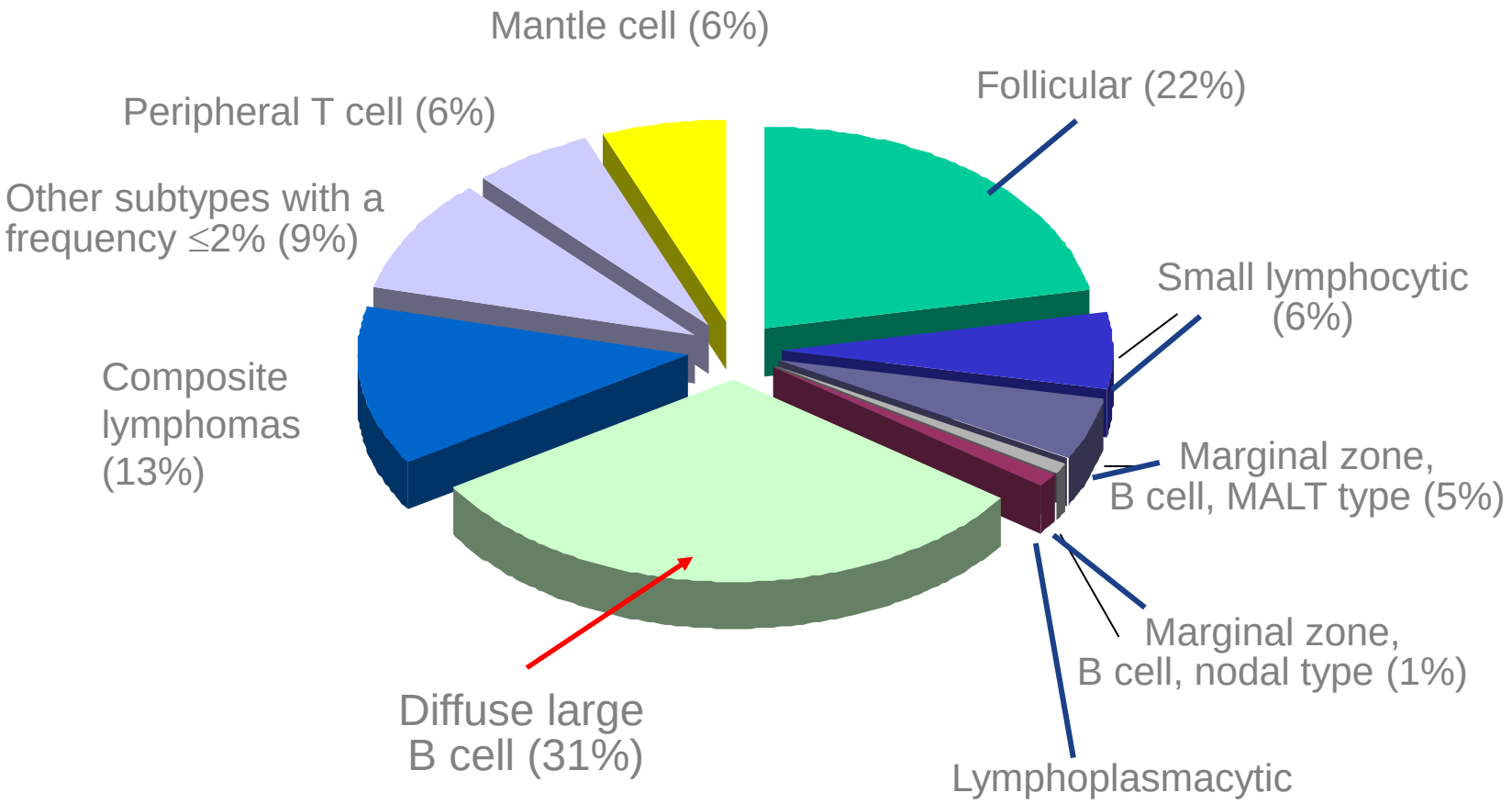
WHO Classification of Lymphoid Neoplasms

- MATURE T-AND NK-NEOPLASMS
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK cell leukemia
- Systemic EBV+ T-cell Lymphoma of childhood*
- Hydroa vacciniforme-like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma
- Enteropathy-associated T-
- Monomorphic epithel
- Indolent T-cell lymp
- Hepatosplenic T-cell
- Subcutaneous panni
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymph
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma*

Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder*
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma*
Nodal peripheral T-cell lymphoma with TFH phenotype*
Anaplastic large cell lymphoma, ALK positive
Anaplastic large cell lymphoma, ALK negative *
Breast implant-associated anaplastic large cell lymphoma
HODGKIN LYMPHOMA
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Hodgkin lymphoma
lymphoma
lymphoma
RDERS (PTLD)
sarcoma
cell sarcoma
Fibroblastic reticular cell tumour
Disseminated juvenile xanthogranuloma
Erdheim/Chester disease



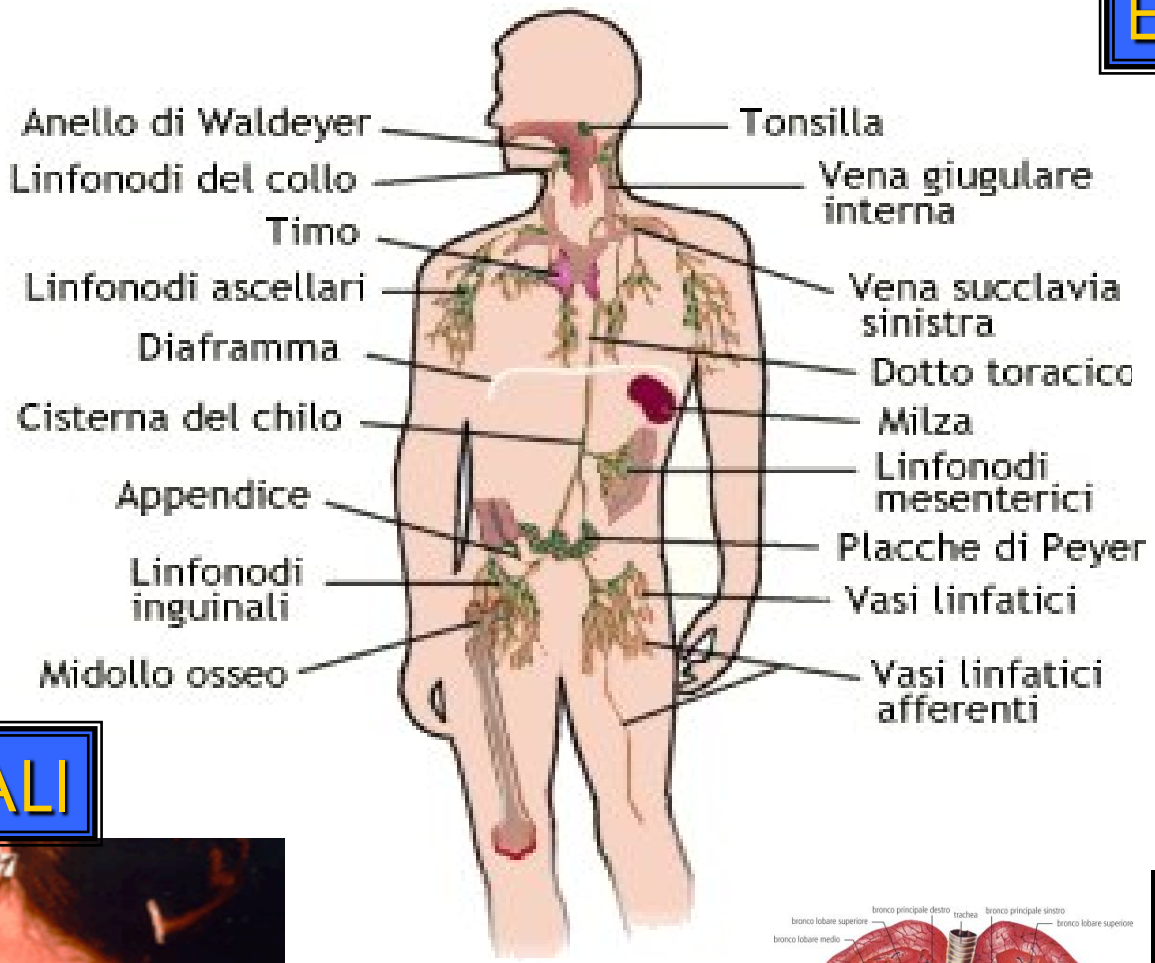
The Frequency of Various NHL Subtypes

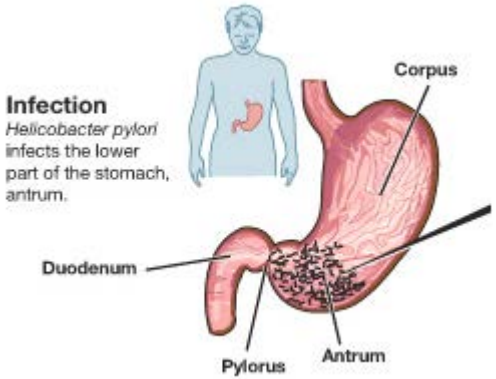


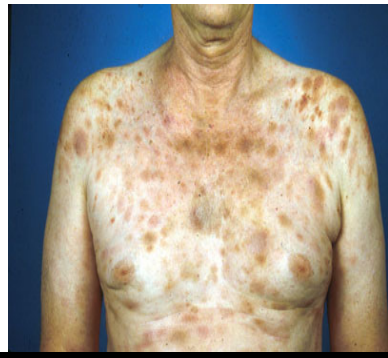
Armitage. J Clin Oncol. 1998;16:2780.

Neoplasie del sistema emolinfopoietico

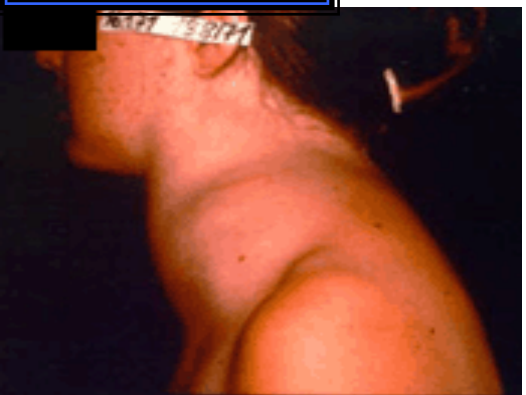
EXTRA NODALI

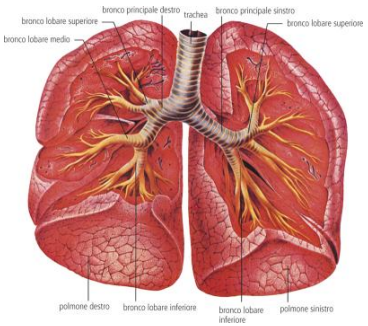


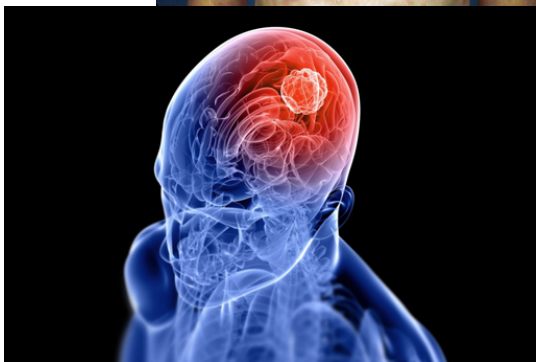




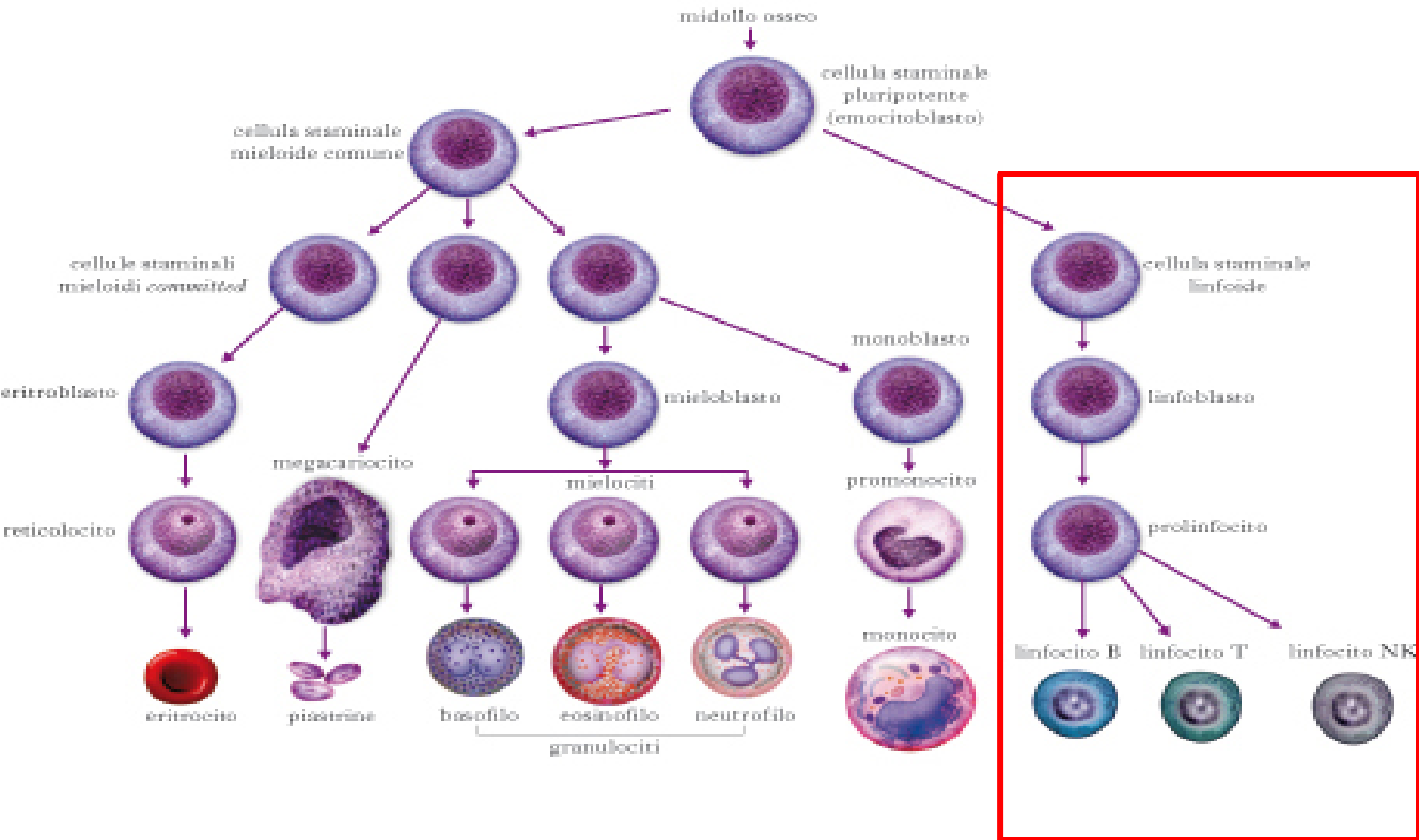
NODALI



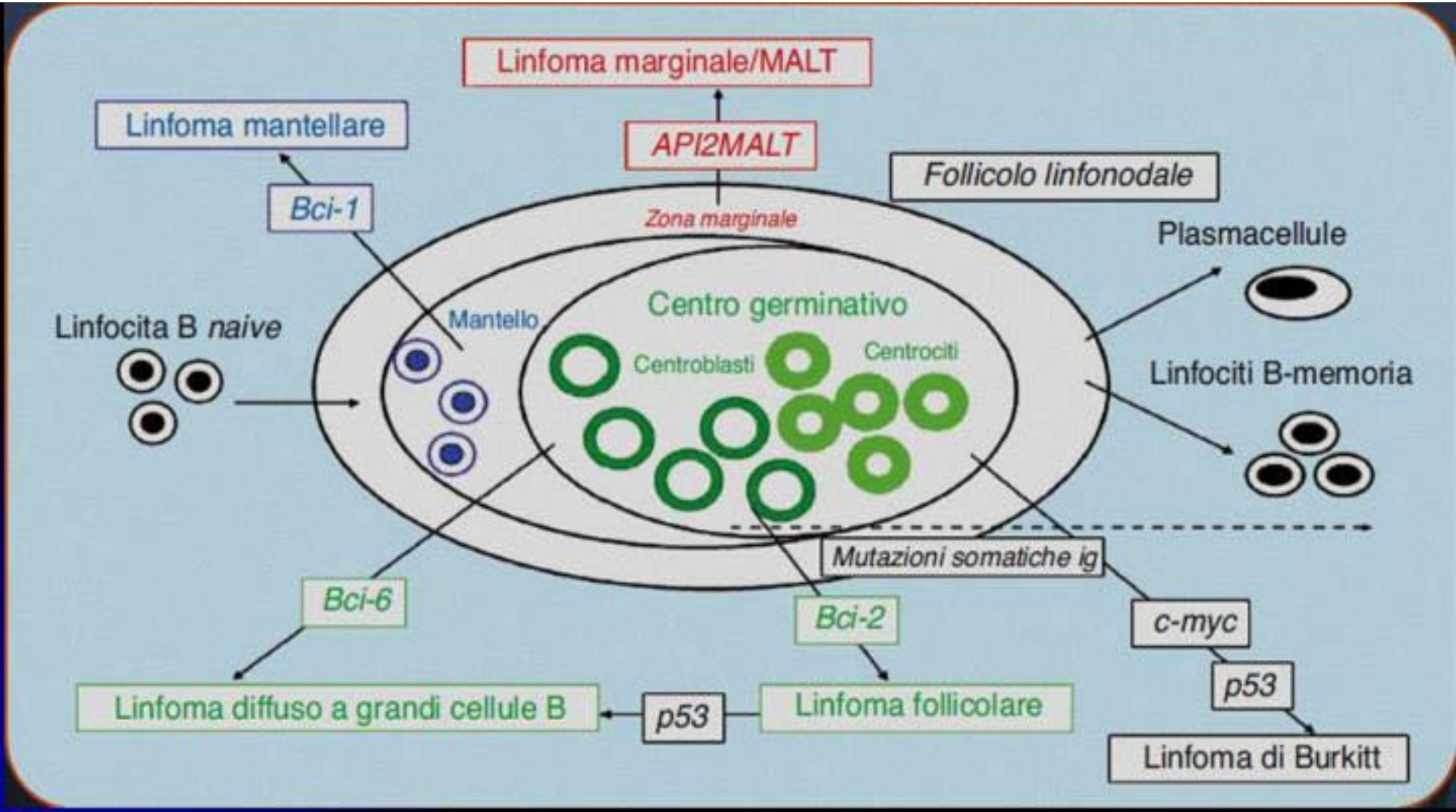




Emopoiesi


midollo osseo
cellula staminale pluripotente (emocitoblasto)
cellula staminale mieloide comune
cellule staminali mieloidi *committed*
eritroblasto
megacariocito
mielocita
monoblasto
mieloblasto
promonocito
reticolocito
piastrine
basofilo
eosinofilo
neutrofilo
granulociti
monocito
eritrocito
cellula staminale linfoide
linfoblasto
prolinfocito
linfocito B
linfocito T
linfocito NK

Struttura del linfonodo normale e zona di origine dei linfomi non Hodgkin a cellule B



FATTORI DI RISCHIO

Agenti infettivi:

- che causano un'immunostimolazione cronica: HP, campilobacter, clamidia psittaci, borrelia, HCV
- che indeboliscono il Sistema Immunitario: HIV, HTLV-1, EBV, HHV8

Malattie autoimmuni:

- flogosi cronica con reiterato stimolo del sistema immunitario
- riduzione dell'immunosorveglianza: secondaria alla patologia o iatrgena (DMARDS)

Immunodepressione:

- PTLD
- Linfomi HIV correlati
- Terapie immunosoppressive

Protesi mammarie

Farmaci chemioterapici, MTX-LPD, radioterapia

Regression of B-cell gastric lymphoma lymphoma after HP eradication

Lancet. 1993 Sep 4;342(8871):575-7.

Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori.

Wotherspoon AC[1], Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, Isaacson PG.

J Natl Cancer Inst. 1997;89(18):1350-1355

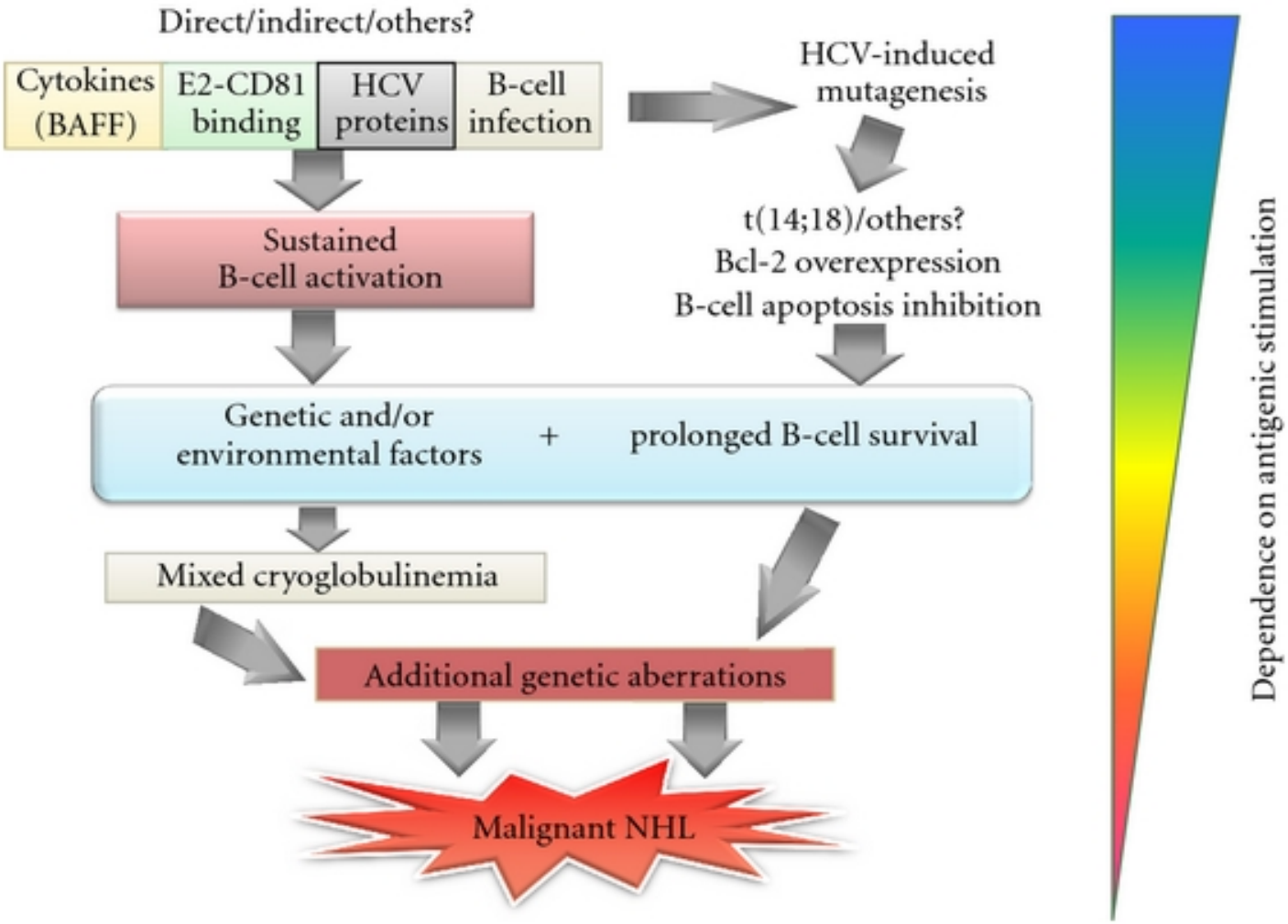
Cure of Helicobacter pylori Infection and Duration of Remission of Low-Grade Gastric Mucosa-Associated Lymphoid Tissue Lymphoma

Neuberger et al.

Table 1. Clinical, histologic, and demographic data on 50 patients with low-grade gastric MALT lymphomas who were treated to eradicate infection with *Helicobacter pylori**,†

	Complete remission (n = 40)			Partial remission (n = 4)			No change (n = 6)		
	Previous study	New	Total	Previous study	New	Total	Previous study	New	Total
No. (%)	24‡ (73)	16 (94)	40 (80)	3‡ (9)	1 (6)	4 (8)	6 (18)	0 (0)	6 (12)
Female/male	11/13	7/9	18/22	2/1	0/1	2/2	2/4	0	2/4
Median age, y (range)	57.5 (31–74)	67.5 (39–77)	61 (31–77)	37 (34–84)	60	48.5 (34–84)	47.5 (35–78)	0	47.5 (35–78)
Tumor stage (by histology)§									
EI	24	16	40	3	0	3	3	0	3
⩾EI	0	0	0	0	1	1	3	0	3
Endoscopic appearance									
Tumor	14	9	23	2	0	2	2	0	2
Ulcer	7	6	13	0	1	1	2	0	2
Mucosal erosion	1	0	1	0	0	0	0	0	0
Atypical mucosa	2	1	3	1	0	1	2	0	2
Tumor size, cm (range)	2.5 (1–10)	3 (1–8)	3 (1–10)	4 (2–5)	1	3 (1–5)	5 (2–8)	0	5 (2–8)

HCV and Lymphoproliferation



Zignego et al. Clin and Develop Immunology 2012

Associazione tra HCV e NHL
Studi epidemiologici

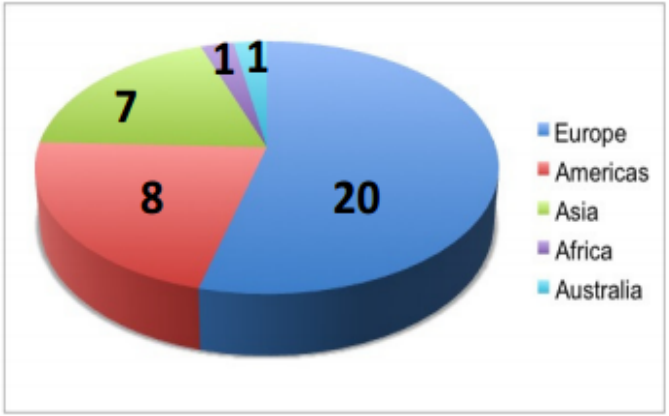
Studi di coorte, prospettici (8 studi):

- sviluppo di linfoma in coorti di soggetti HCV+ seguiti nel tempo
- eccesso di rischio di NHL ***x2*** in 3 studi

Ohsawa 1999, Waters 2005, Amin 2006, Franceschi 2006, Giordano et al. 2007

Studi caso-controllo (37 studi):

- confronto prevalenza HCV+ in pazienti NHL *vs* controlli sani
- Odds ratio (OR) ***x2*** nell'80% degli studi



- **Italia**: OR ***3.1*** (NHL indolenti 2.3 ; NHL aggressivi 3.5);

Mele et al, Blood 2003

Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi

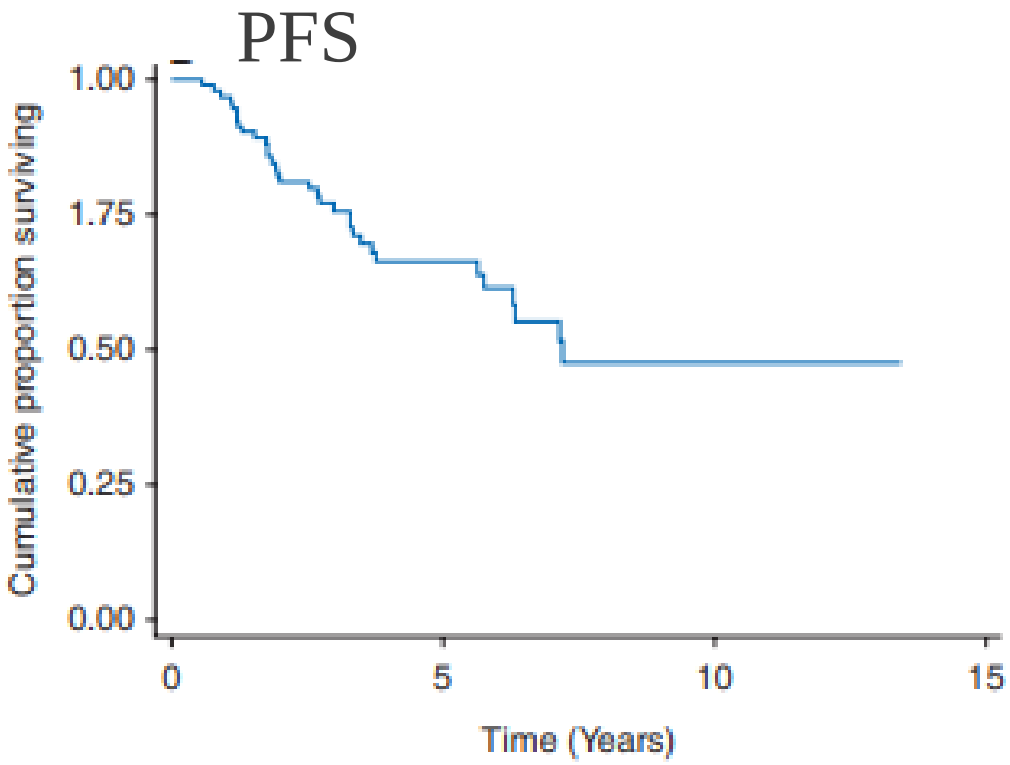
L. Arcaini[1,2], D. Vallisa[3], S. Rattotti[2], V. V. Ferretti[2], A. J. M. Ferreri[4], P. Bernuzzi[3], M. Merli[5], M. Varettoni[2], A. Chiappella[6], A. Ambrosetti[7], A. Tucci[8], C. Rusconi[9], C. Visco[10], M. Spina[11], G. Cabras[12], S. Luminari[13], M. Tucci[14], P. Musto[15], M. Ladetto[16], F. Merli[17], C. Stelitano[18], A. d'Arco[19], L. Rigacci[20], A. Levis[21], D. Rossi[22], P. Spedini[23], S. Mancuso[24], D. Marino[25], R. Bruno[26,27], L. Baldini[28] & A. Pulsoni[29]

Annals of Oncology 25: 1404–1410, 2014

100 pazienti
(prima linea)

44 RC

33 RP



Lymphoma response was related to achievement of HCV-RNA clearance (P 0.003)

Terapia antivirale nei linfomi indolenti HCV+
Linee guida

ESMO Consensus guidelines marginal zone lymphoma

Dreyling et al, Ann Onc 2013

1.11 *Consensus statement*

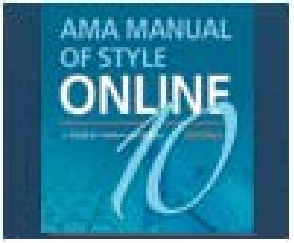
In patients with NMZL or SMZL and concurrent HCV-related chronic hepatitis who do not need immediately conventional treatment of lymphoma, antiviral treatment with pegylated interferon and ribavirin should be considered as first treatment

NCCN National Comprehensive Cancer Network®

According to the American Association for the Study of Liver Diseases, combined therapy with DAA should be considered in asymptomatic patients with HCV genotype 1 since this therapy can result in regression of lymphoma.

Terapia antivirale

terapia standard di 1ª linea nei pazienti affetti da iNHL HCV+ asintomatici (che non necessitano di terapia anti-linfoma convenzionale immediata)



Breast Implant–Associated Anaplastic Large Cell Lymphoma

A Systematic Review

Ashley N. Leberfinger, MD[1]; Brittany J. Behar, MD[1]; Nicole C. Williams, MD, MBA[2]; et al

From the first documented case in August 1997 through January 2017

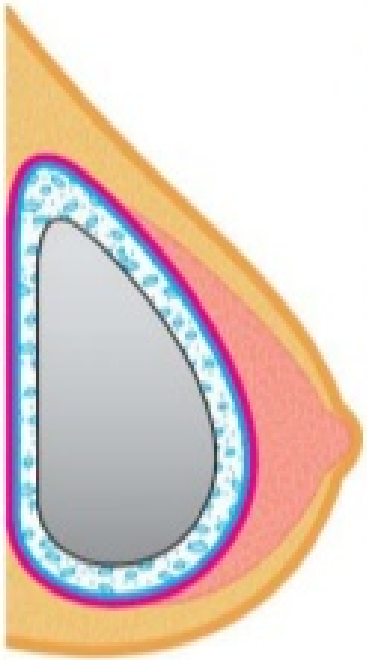
A total of **93** cases have been reported in the literature

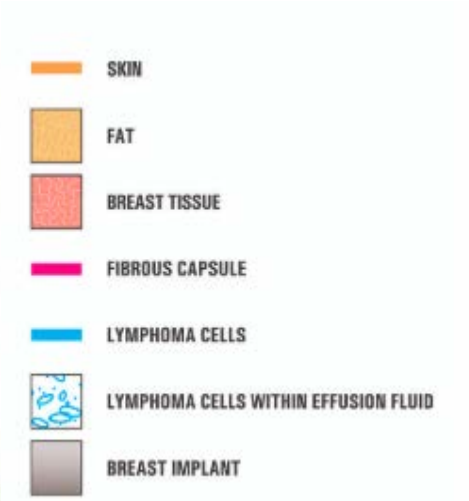
The underlying mechanism is thought to be due to **chronic inflammation** leading to malignant **transformation of T cells** that are anaplastic lymphoma kinase (ALK) negative and CD30 positive. Chronic bacterial biofilm infection is emerging as the likely culprit of lymphocyte activation.

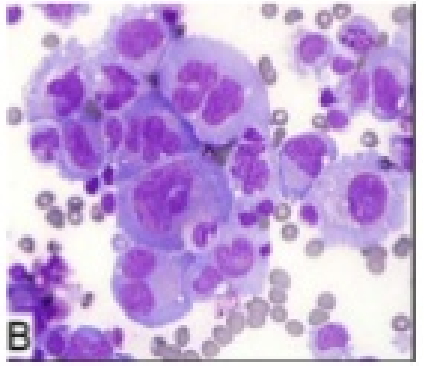
JAMA Surg. 2017;152(12):1161-1168

Breast implant associated ALCL

- Both saline and silicone filled implants
- Median interval from implant to the lymphoma 10 yr
- Trt: removal of the implant and capsule.
- If invasion through the capsule:systemic chemotherapy



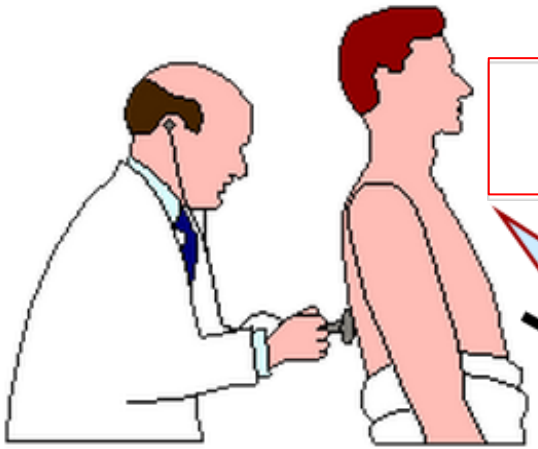




PRESA IN CARICO

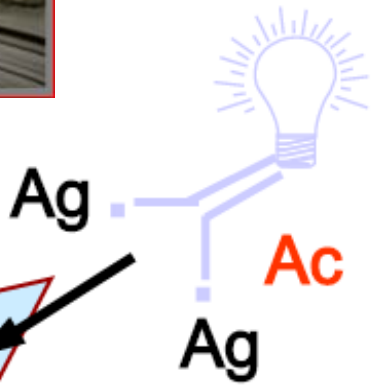
- Diagnosi
- Stadiazione
- Valutazione dei fattori prognostici
- Terapia

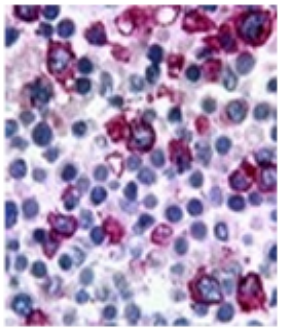
Esame clinico



Esami ematochimici

Analisi immunoistochimica

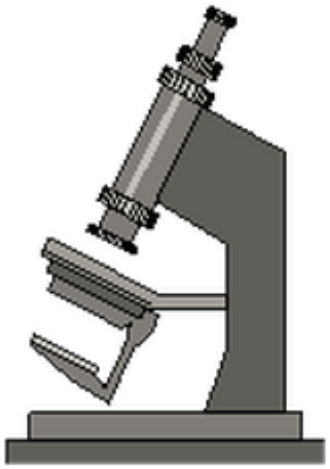




Diagnosi integrata dei linfomi

Biopsia

Esame microscopico morfologico



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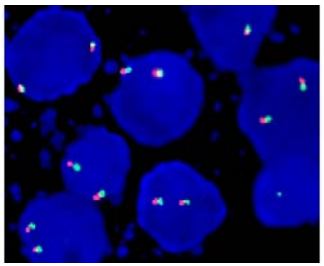
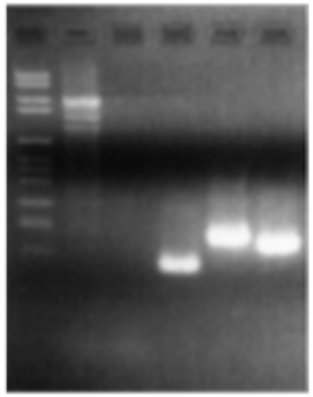


Biologia molecolare



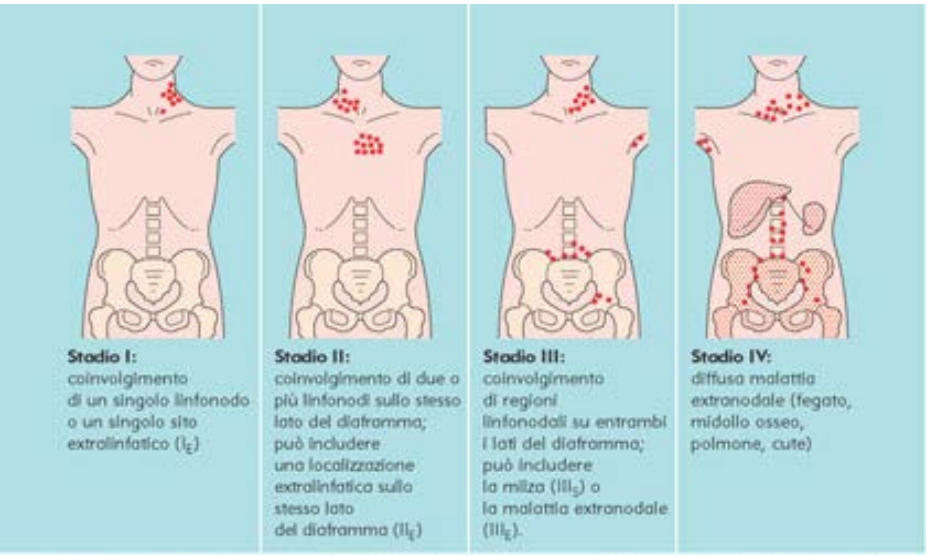
Clinical impact of recurrently mutated genes on lymphoma

Category	Gene mutations
1. Immediate impact on patient care	*TP53* mutations (exons 4-10) in CLL
2. Diagnostic impact	MYD88^{L265P} mutation in WM/LPL BRAF^{V600E} mutation in HCL *KLF2* mutations in SMZL *ID3* and *TCF3* mutations in BL *STAT3* mutations in LGLL *RHOA*, *TET2*, *IDH2* and DNMT3A mutations in AITL and other T_{FH}-derived PTCL
3. Prognostic impact	*CLL*: *TP53*, *ATM*, *BIRC3*, *NFKBIE*, *NOTCH1*, *SF3B1* MCL: *TP53*, *NOTCH1*, *NOTCH2* mutations SMZL: *NOTCH2*, *TP53* mutations DLBCL: *TP53* mutation & MYC translocation NKTCL: *DDX3X* mutations
4. Potential clinical impact in the near future	Therapy response to BcR inhibitors: WM: *MYD88*, *CXCR4* mutations DLBCL: *CD79B* mutations (responsive) *CARD11*, MYD88 mutations (non-responsive) Resistance to BcR inhibitors: BTK^{C481S}, PCLG2 mutations New inhibitors under development: *EZH2*, *SF3B1* & *NOTCH1*

Rosenquist et al. Haematologica 2016 Volume 101(9):1002-1009

Stadiazione

TAC tap, PET, BOM, ORL



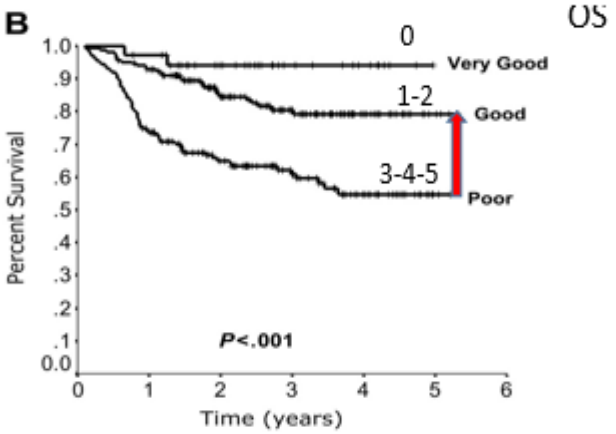
Fattori prognostici

IPI SCORE

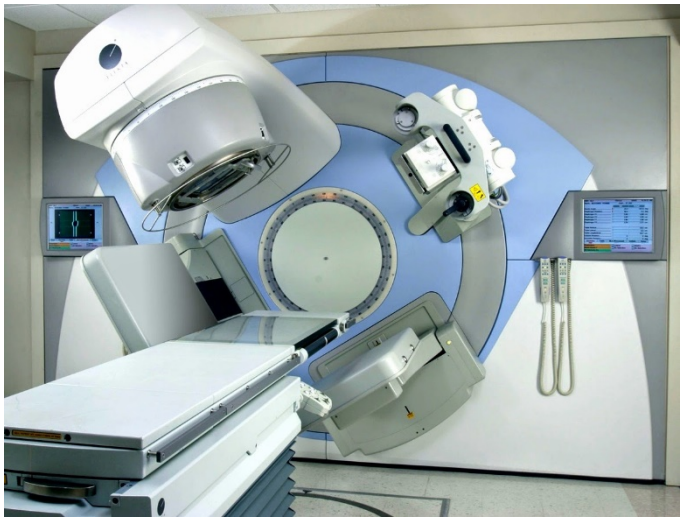
- Età > 60 anni
- LDH superiore alla norma
- Performance status ≥ 2
- Stadio Ann Arbor III-IV
- >1 sede extranodale

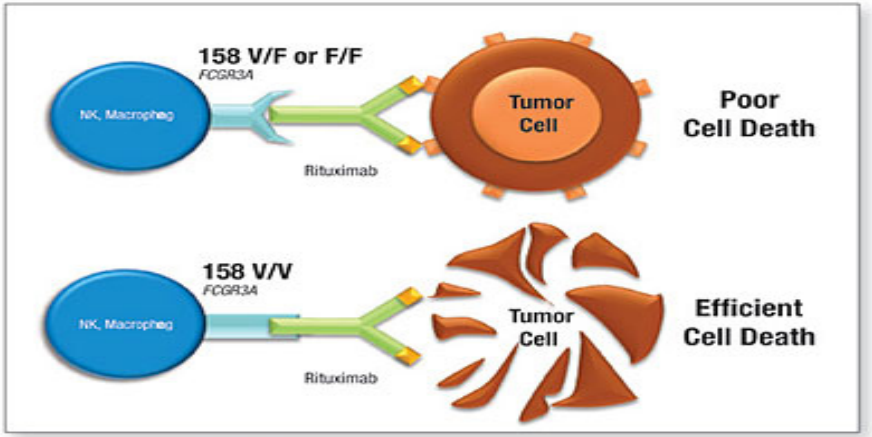
VGM

ADL
IADL
CIRS-G

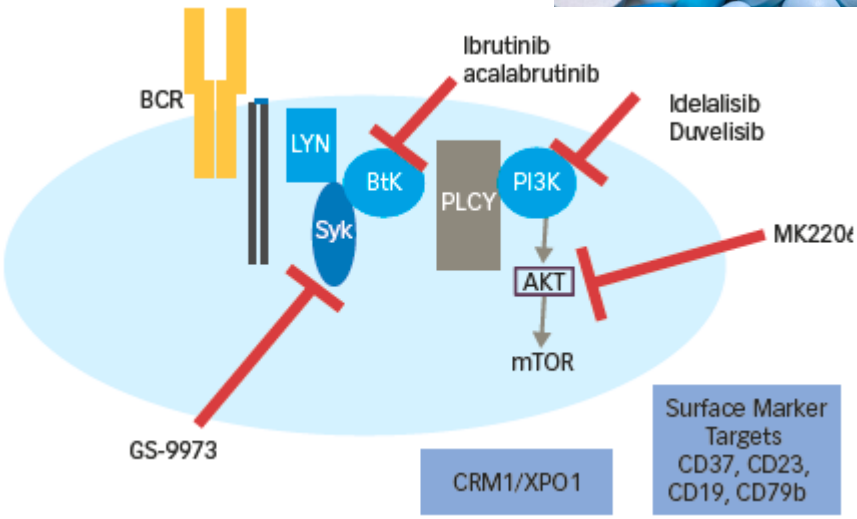


Terapia



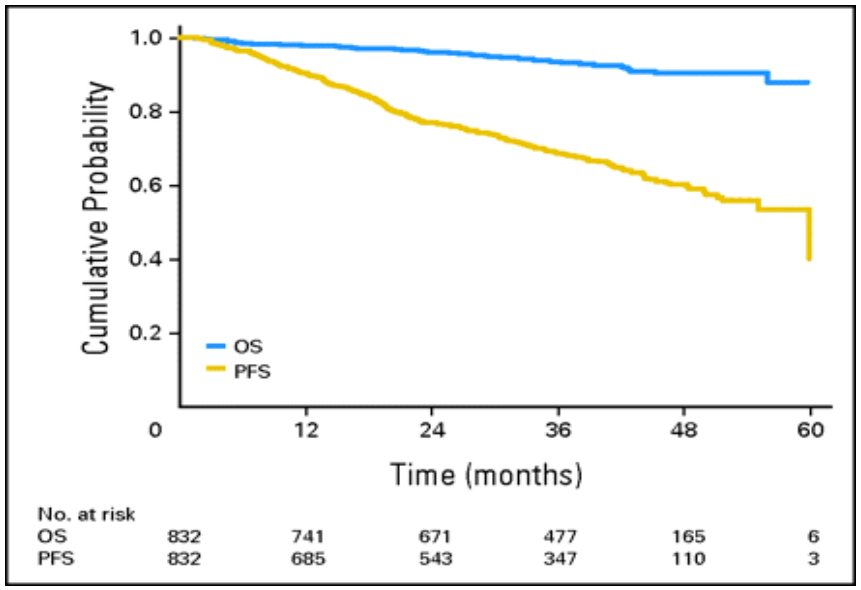


Dall'Ozzo S, et al. Cancer Research, 2004; 64:4664-4669.



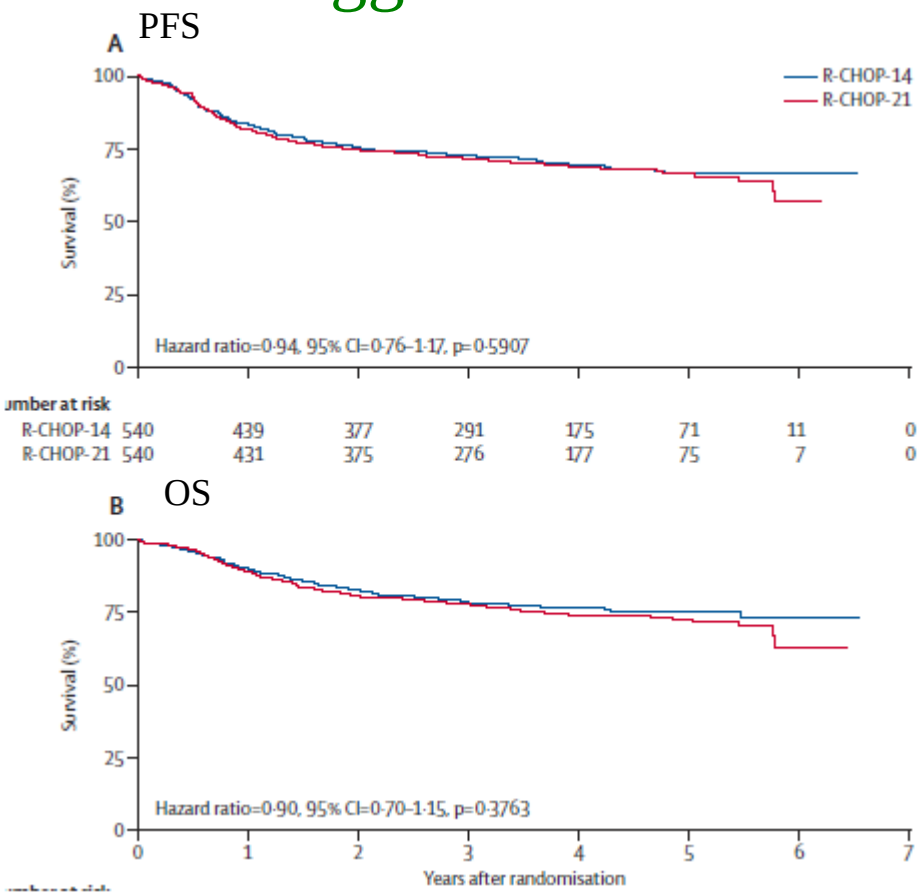
Outcome of indolent and aggressive lymphoma

Indolent



Federico et al. *J Clin Oncol 2009; 27:4555-62*

Aggressive



Cunningham et al. Lancet 2013; 381: 1817–26

FONDAZIONE ITALIANA LINFOMI

Grazie Per L'attenzione !