IV Congresso Nazionale
III Assemblea Associativa GIIMA

GIIMA
Gruppo Italiano Infermieristico Mobilizzazione ed Aferesi

Classificazione WHO linfomi

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2017 Update

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

“There were only three things certain in life:

death, taxes…and a new classification of lymphomas”

БРОНЕНОСЕЦ КОТЕМКИН

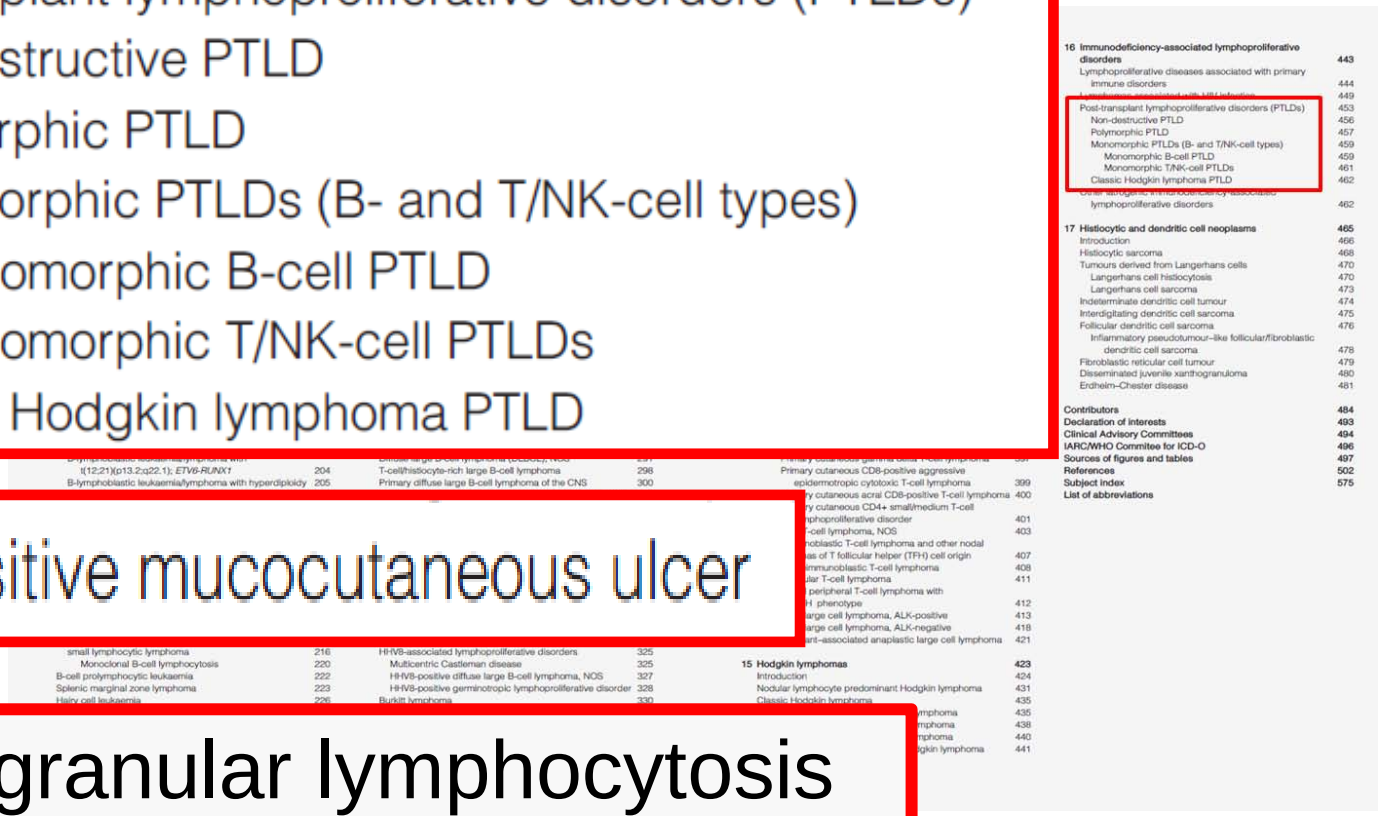
La Corazzata Potëmkin

Classificazione WHO: disordini linfoproliferativi post-trapianto

Post-transplant lymphoproliferative disorders (PTLDs)
- Non-destructive PTLD
- Polymorphic PTLD
- Monomorphic PTLDs (B- and T/NK-cell types)
  - Monomorphic B-cell PTLD
  - Monomorphic T/NK-cell PTLDs
- Classic Hodgkin lymphoma PTLD

EBV-positive mucocutaneous ulcer

Large granular lymphocytosis



Post-transplant lymphoproliferative disorders (PTLD)

Definition

Post-transplant lymphoproliferative disorders (PTLDs) are lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in a recipient of a solid organ or stem cell allograft. They constitute a spectrum ranging from usually EBV-driven polyclonal proliferations to EBV-positive or EBV-negative proliferations indistinguishable from a subset of B-cell or (less often) T/NK-cell lymphomas that occur in immunocompetent individuals.

1. Proliferazioni linfoidi/pc

2. Immunosoppressione post trapianto

3. Spettro morfologico

4. EBV

PTLD dopo SCT
Epidemiologia

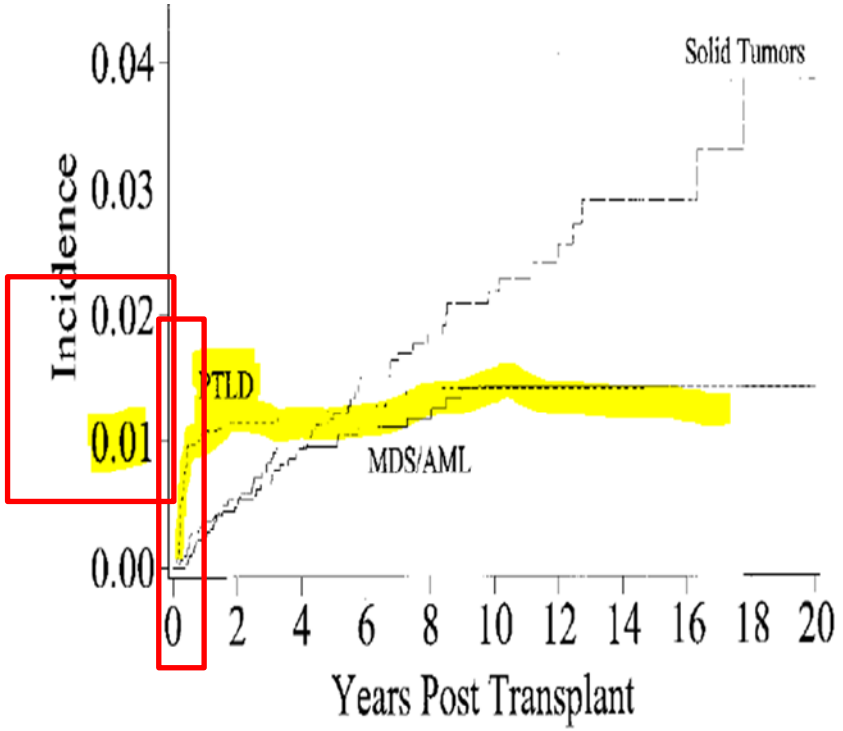


Fig 2. Cumulative incidence of solid tumors, myelodysplastic syndrome or acute myeloid leukemia, and posttransplant lymphoproliferative disorder occurring after stem-cell transplant.

Baker et al, JCO 2003

- Incidenza bassa (1-2%)

- Insorgenza precoce

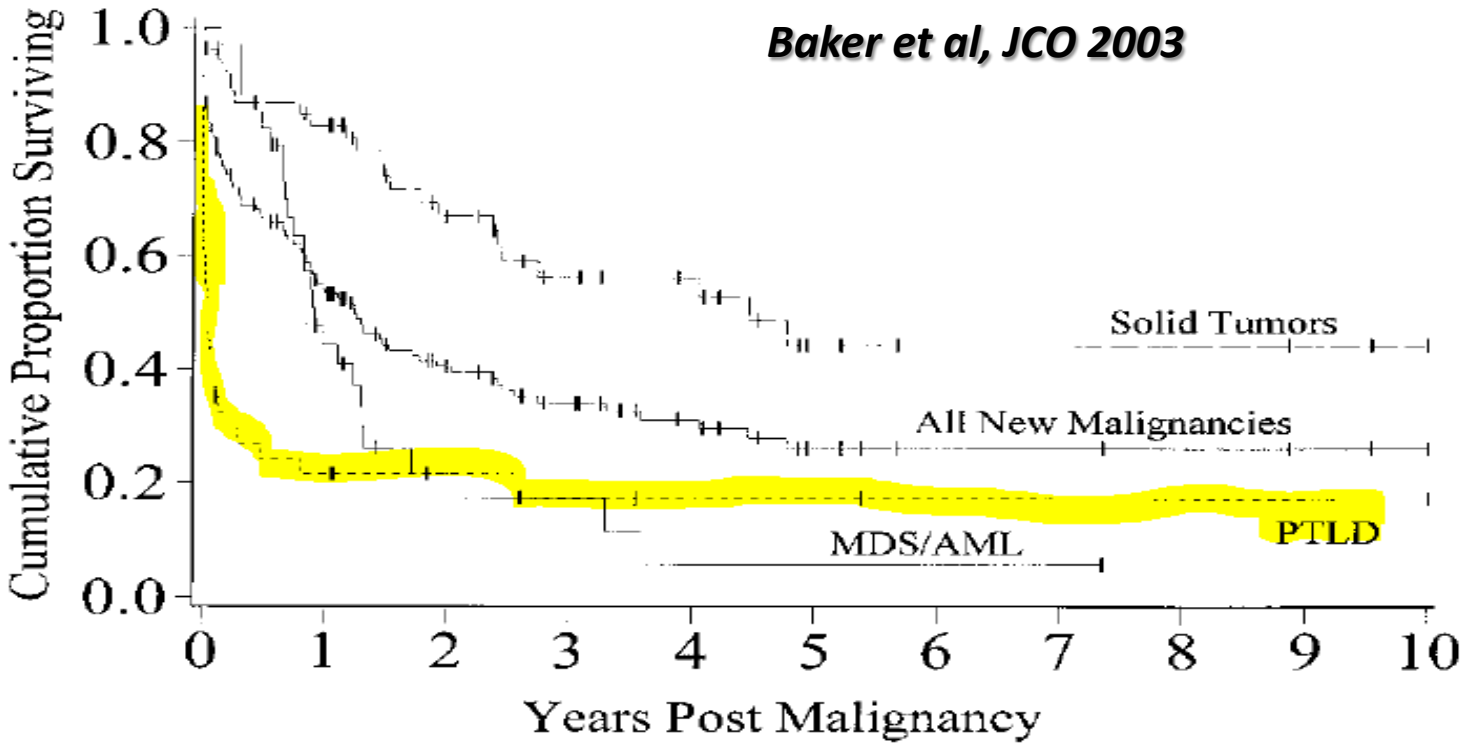
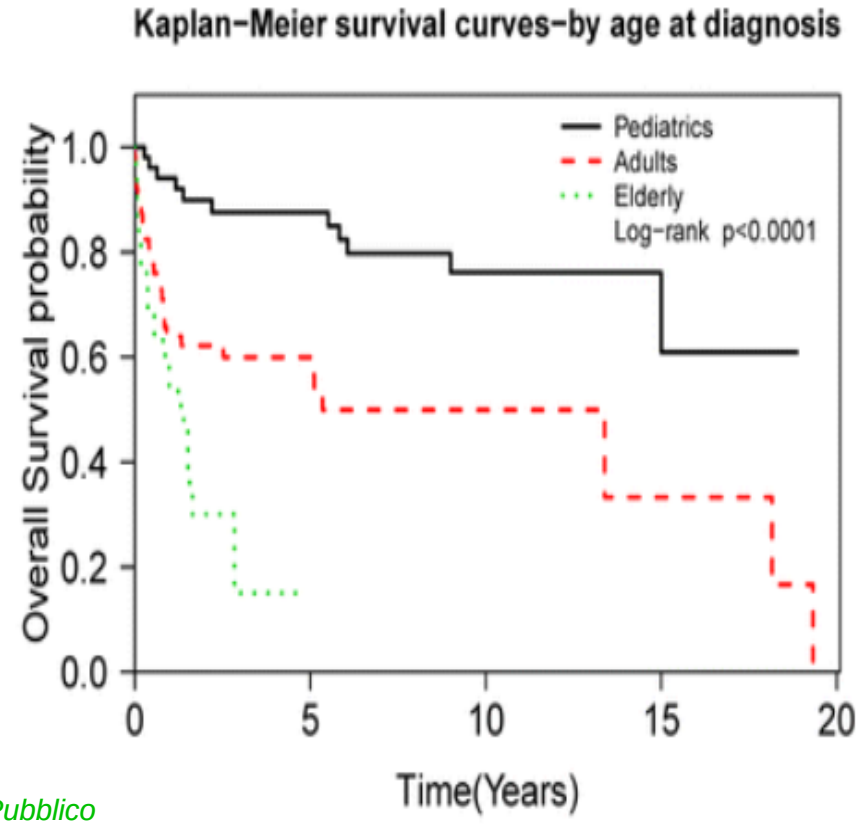


Fig 3. Kaplan-Meier survival for patients diagnosed with solid tumors, post-transplant lymphoproliferative disorder, myelodysplastic syndrome or acute myeloid leukemia and for all posttransplant malignancies combined.

- Elevata mortalità (40-60%)

I pazienti pediatrici

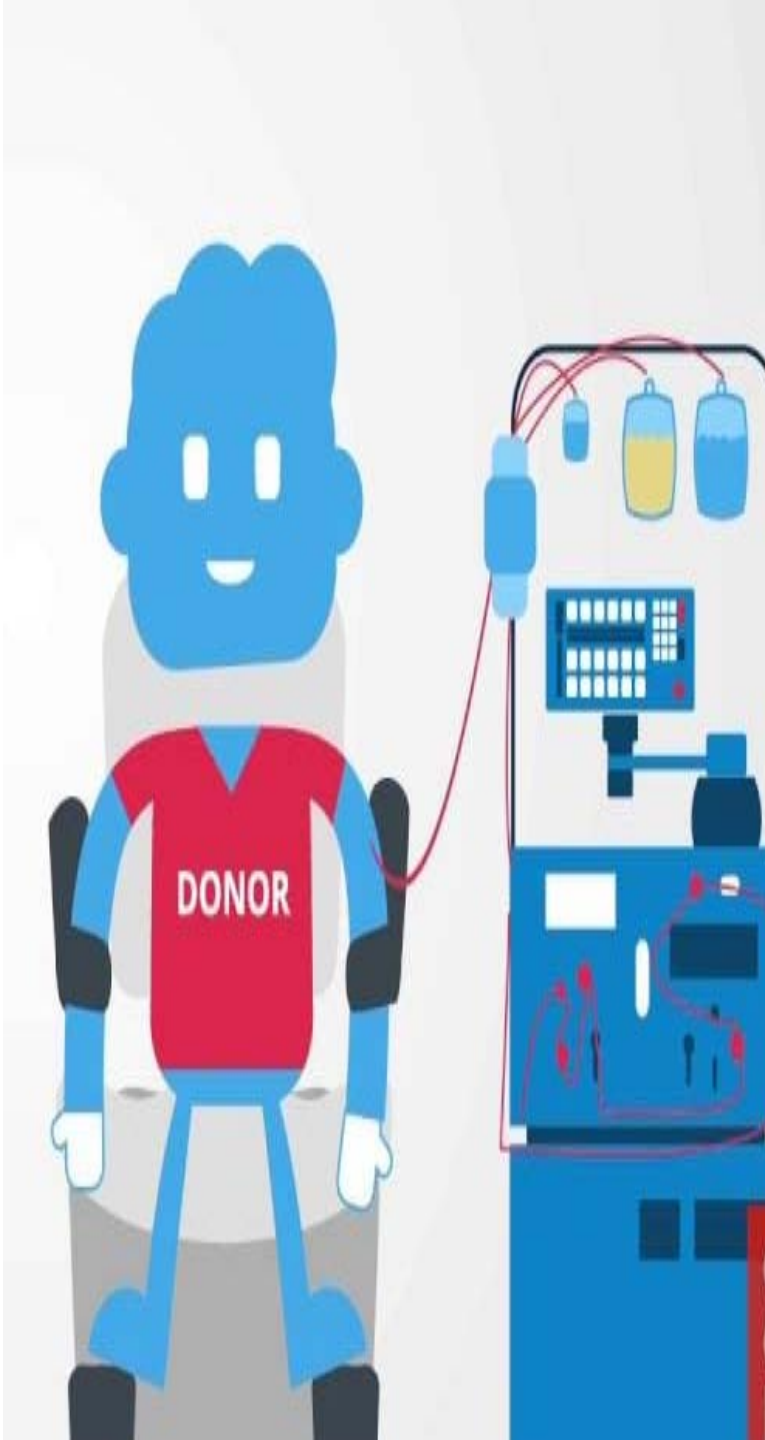
Factor	Total Cohort No.	%	PTM No.	%	PTLD No.	%
No. of patients	3,372		137		43	
No. of cancers			147		44	
Age, years						
< 10	932	28			19	44
10-19	582	17			7	16
20-29	412	12			4	9
30-39	560	17			5	12
40-49	551	16			6	14
50+	335	10			2	5



Baker et al, JCO 2003

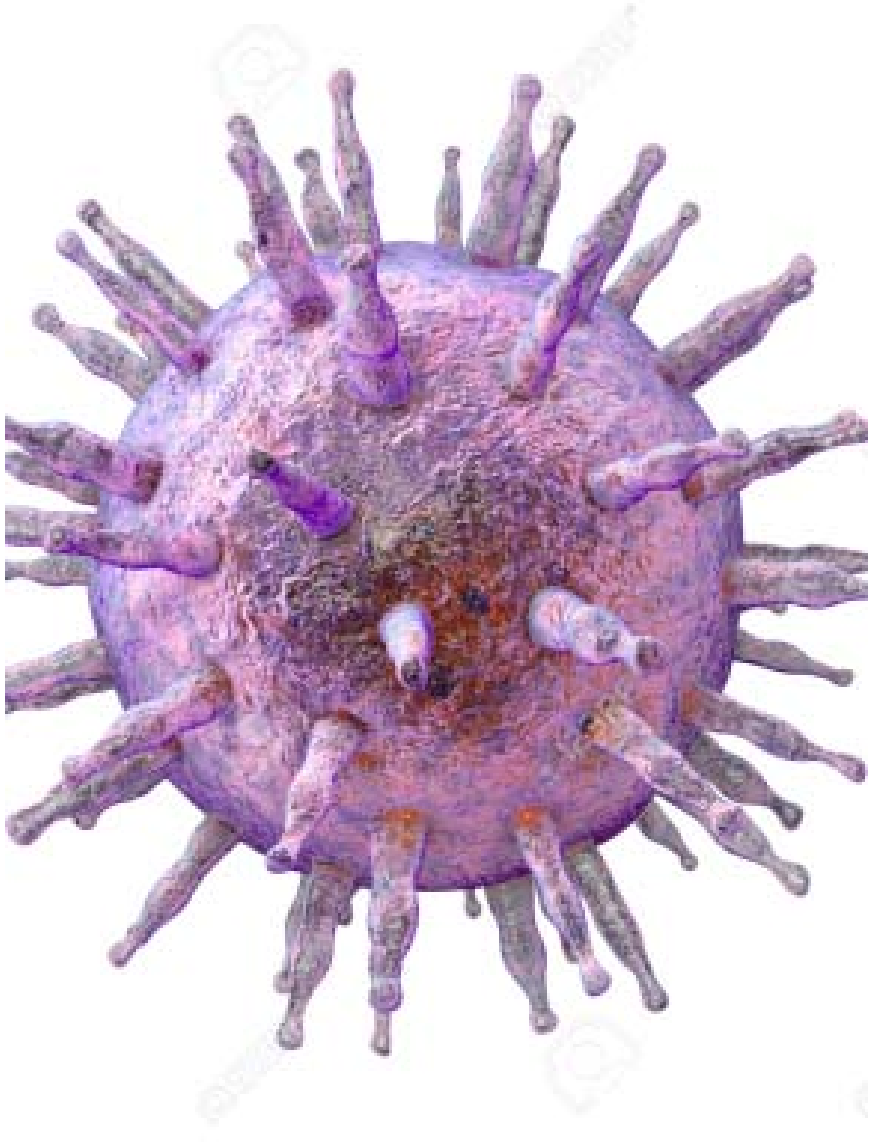
Bishnoi et al, Exp Hematol Oncol 2017

- **SCT allogenico**
- Origine dal **donatore**
- Rarissimi dopo SCT autologo



Correlazione con EBV

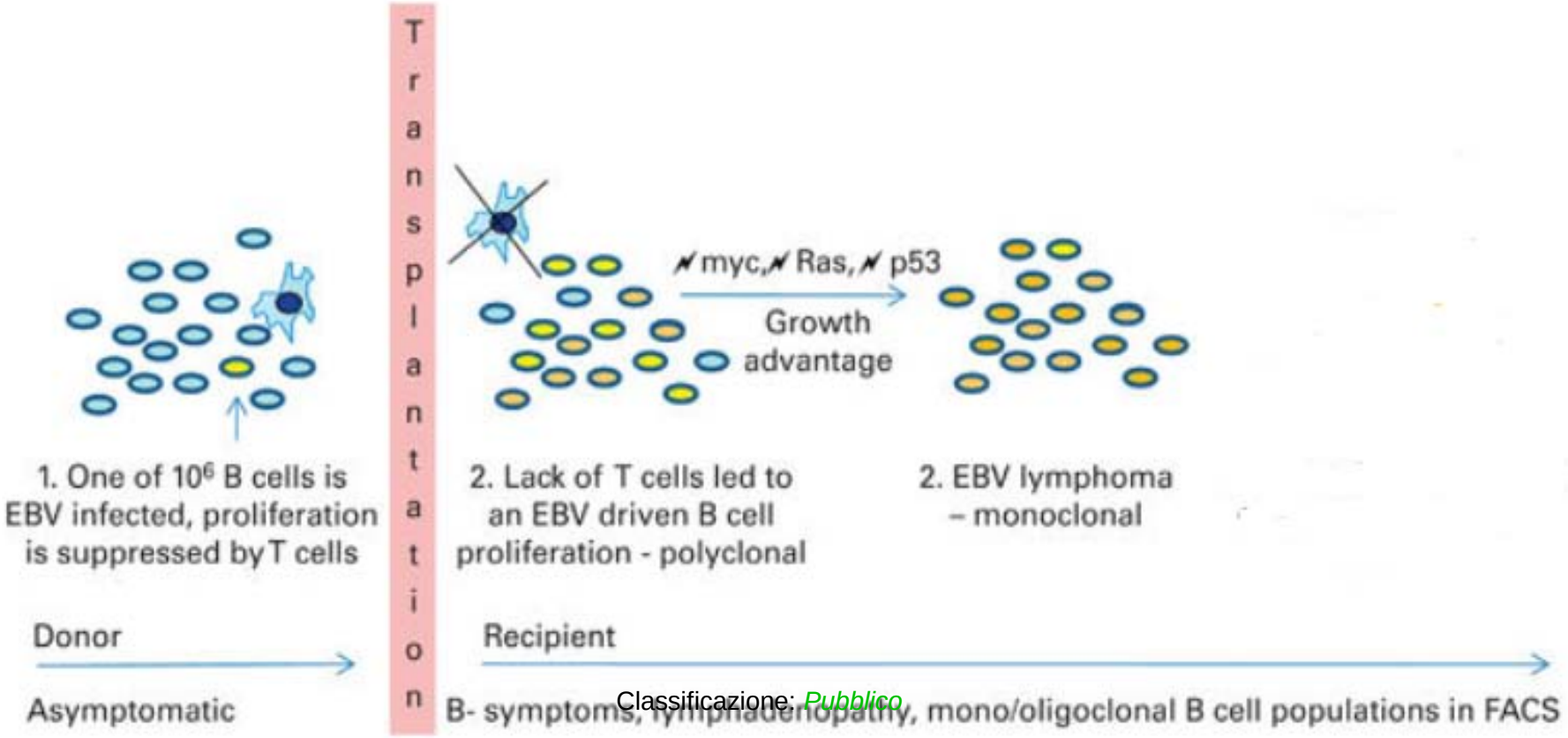
I PTLD dopo HSCT sono quasi sempre EBV+



- Le forme EBV negative sono molto rare
- Spesso sono tardive

Correlazione con EBV

I PTLD sono proliferazioni linfoidi indotte dal virus in un contesto di ridotta sorveglianza T-linfocitaria



Fattori di rischio

Table 3. Risk factors for EBV-PTLD after HSCT.

ECIL-6 guidelines for EBV-PTLD after HSCT

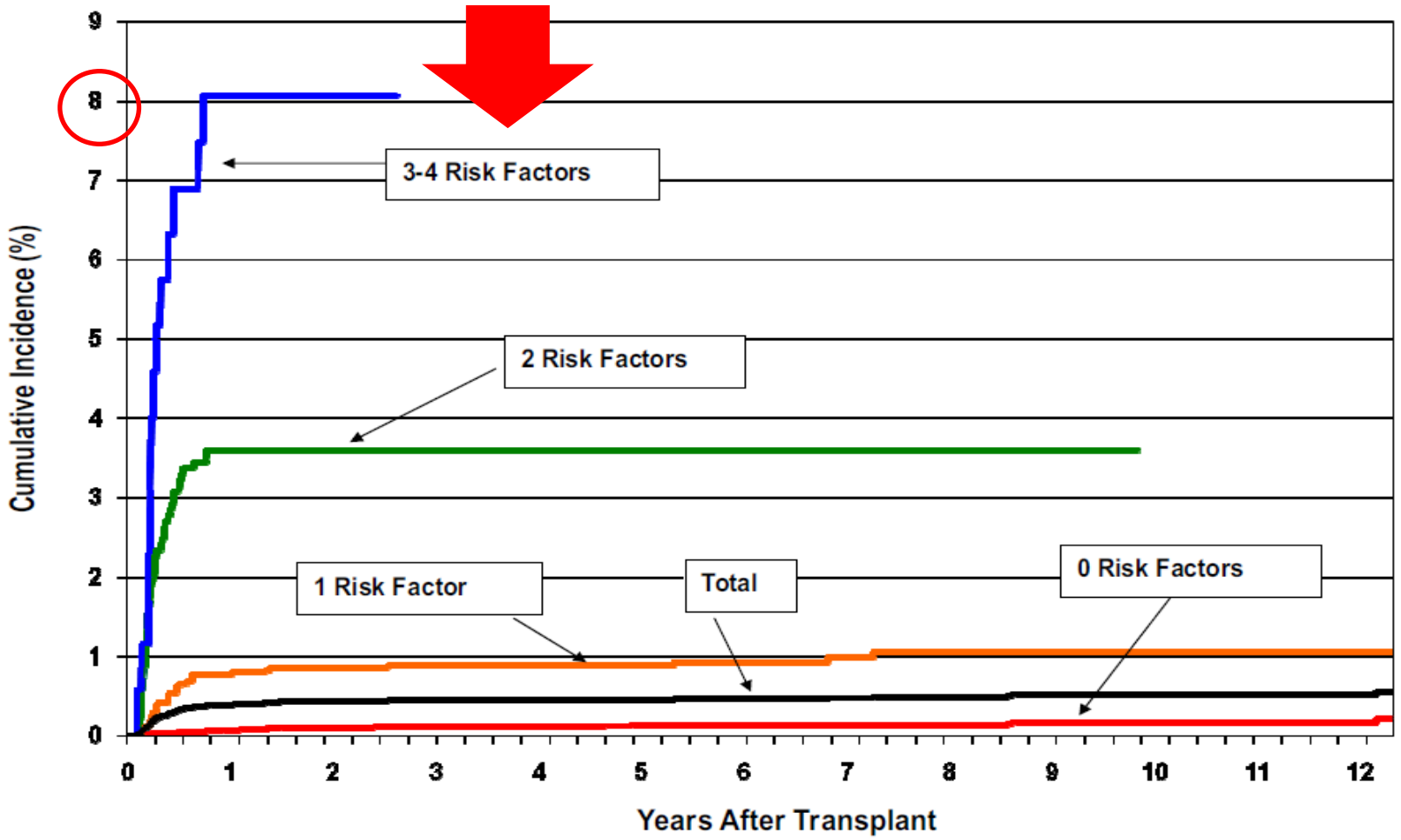
Pre-transplant risk factors

- T-cell depletion (either *in vivo* or *ex vivo*)
- EBV serology donor/recipient mismatch
- Cord blood transplantation (CBT)
- HLA mismatch
- Splenectomy
- Second HSCT

Post-transplant risk factors

- Severe acute (especially steroid-refractory) or chronic GvHD requiring intensive immunosuppressive therapy
- High or rising EBV viral load
- Treatment with mesenchymal stem cells

Fattori di rischio e incidenza: è una complicanza rara per *tutti* i pazienti?



Landgren et al, Blood 2009

Quali pazienti sono più a rischio?

Table 4. Recommendations for prevention of EBV disease after HSCT.

Allo-HSCT patients
• Patients at high risk for EBV-PTLD after allo-HSCT should be closely monitored for symptoms or signs attributable to PTLD or other end-organ EBV disease (AIIu).
• After high-risk allo-HSCT, prospective monitoring of EBV DNA-emia is recommended (AIIu).

Chi è "*high risk*"?

- MFD with at least one risk factor
- MUD/MMUD
- alternative donors including CBT

ECIL-6 guidelines for EBV-PTLD after HSCT

Come eseguire la sorveglianza?

- **EBV DNA** by **quantitative PCR** (whole blood, plasma or serum)
- Screening should start **within the first month** and continue **for at least 4 months** after HSCT
- Frequency: **at least once a week**

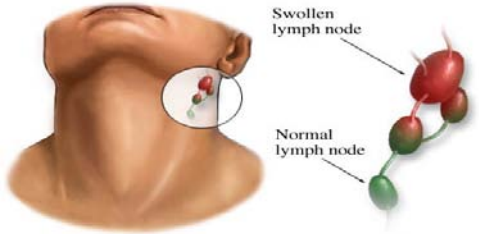
ECIL-6 guidelines for EBV-PTLD after HSCT

Clinica

- Molto variabile, in parte dipende dal sottotipo istologico

- Febbre, malessere
- Sintomi simil-mononucleosi infettiva

- Tumefazione delle tonsille e/o delle adenoidi
- Adenopatie o masse extranodali



- Disfunzione d'organo

Table 16.02 Categories of post-transplant lymphoproliferative disorder (PTLD)

Non-destructive PTLD
- Plasmacytic hyperplasia
- Infectious mononucleosis
- Florid follicular hyperplasia

Polymorphic PTLD

Monomorphic PTLD[a]
(classify according to lymphoma they resemble)
- B-cell neoplasms
  - Diffuse large B-cell lymphoma
  - Burkitt lymphoma
  - Plasma cell myeloma
  - Plasmacytoma
  - Other[b]
- T-cell neoplasms[a]
  - Peripheral T-cell lymphoma, NOS
  - Hepatosplenic T-cell lymphoma
  - Other

Classic Hodgkin lymphoma PTLD[a]

↓ immunosoppressione
Migliore prognosi

↓ immunosoppressione
+
Anti CD20 / CHT

Maggiore mortalità

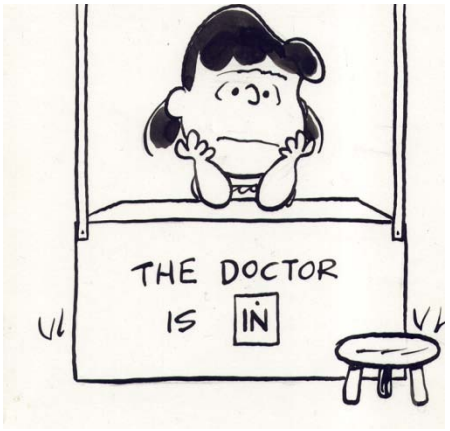
Non-destructive PTLDs (per patologi)

Pathological type of PTLD	Histopathology		Immunophenotype/ in-situ hybridization	Genetics	
	Architectural effacement	Major findings		IGH/TR clonal rearrangements	Cytogenetic/oncogene abnormalities
Plasmacytic hyperplasia	Absent	Predominantly small lymphocytes and plasma cells	PcI B cells and admixed T cells; EBV+	PcI or very small mcl B-cell population(s)	None
Infectious mononucleosis	Absent	Admixed small lymphs, plasma cells, and immunoblasts	PcI B cells and admixed T cells; EBV+	PcI or very small mcl B-cell population(s); may have clonal/ oligoclonal TR genes	Simple cytogenetic abnormalities rarely present
Florid follicular hyperplasia	Absent	Prominent hyperplastic germinal centres	PcI B cells and admixed T cells; EBV±	PcI or very small mcl B-cell population(s)	Non-specific simple cytogenetic abnormalities rarely present

- Struttura **conservata**!!!!
- **EBV+**

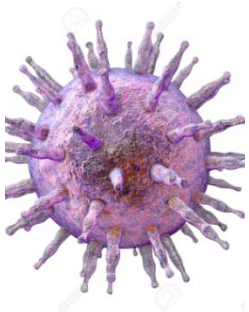
- Biologia molecolare: **cellule B policlonali**

Non-destructive PTLDs (per i clinici)

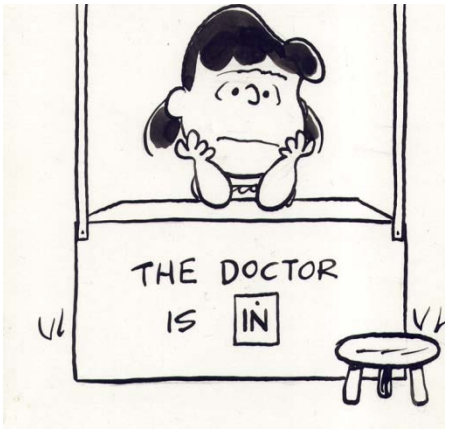


- Pazienti più giovani rispetto agli altri istotipi
- Bambini e giovani adulti

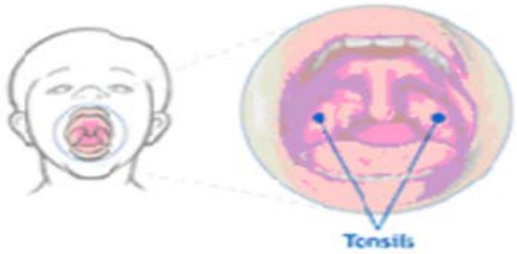
- Infezione primaria da EBV



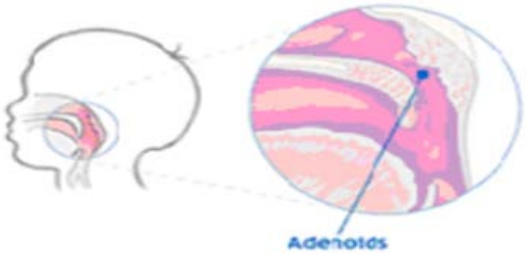
Non-destructive PTLDs (per i clinici)



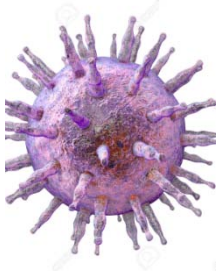
- Tonsille, adenoidi e linfonodi



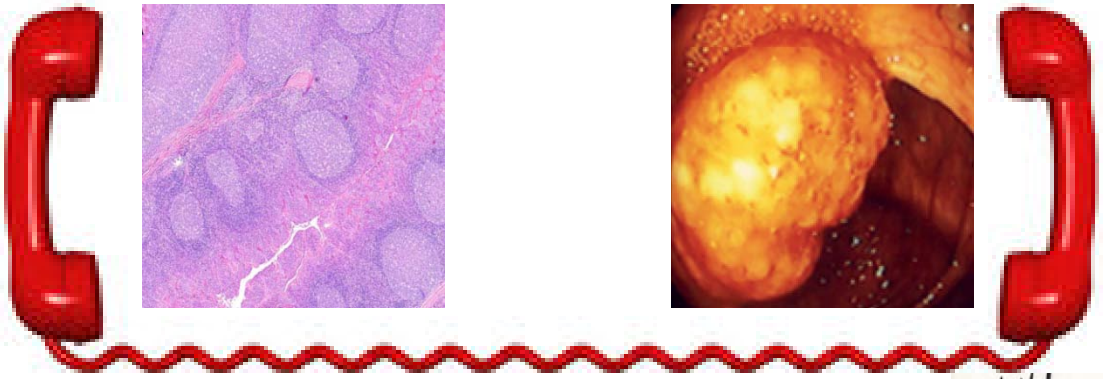
- Lesioni formanti **massa**

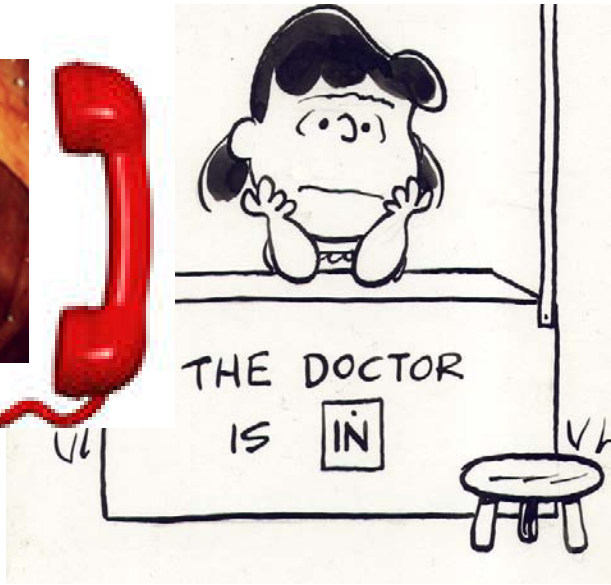


- Sintomi da mononucleosi infettiva



Non-destructive PTLDs



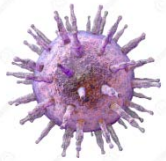


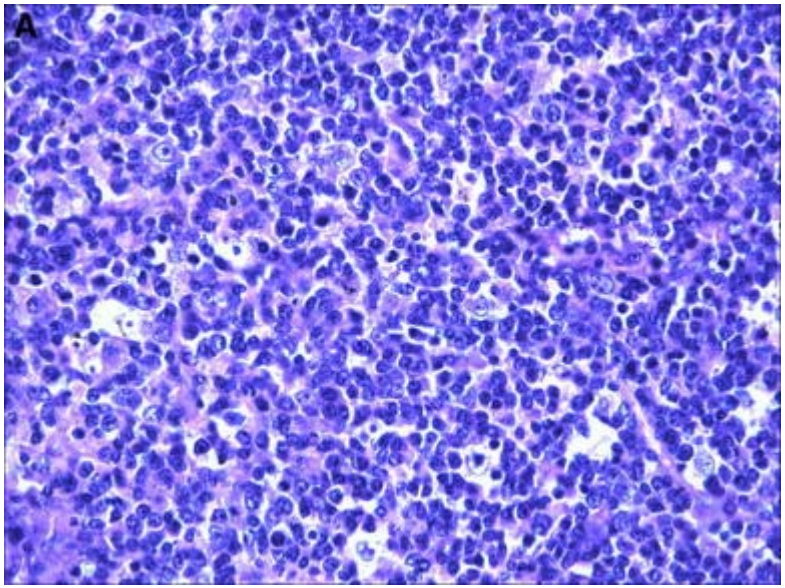
Quadro istologico **identico** a una condizione reattiva

E’ necessario sapere che c’è la formazione di una **massa**

Polymorphic PTLDs (per patologi)

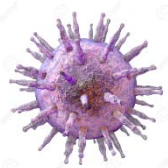
Pathological type of PTLD	Histopathology		Immunophenotype/ in-situ hybridization	Genetics	
	Architectural effacement	Major findings		IGH/TR clonal rearrangements	Cytogenetic/oncogene abnormalities
Polymorphic	Present	Full spectrum of lymphoid maturation seen, not fulfilling criteria for NHL	Pcl ± mcl B cells and admixed T cells; most EBV+	Mcl B cells, non-clonal T cells	Some have *BCL6* somatic hypermutations

- Struttura **<u>alterata</u>**
- **EBV+** 
- Biologia molecolare: **cellule B monoclonali**

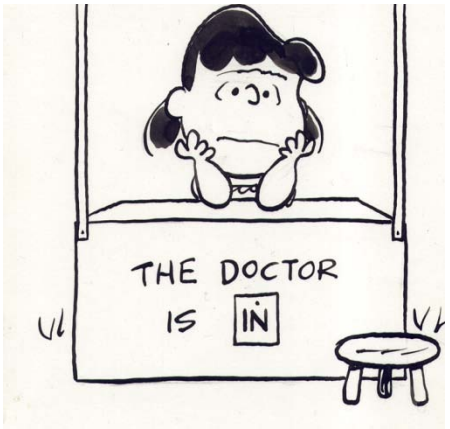


Monomorphic PTLDs (per patologi)

Pathological type of PTLD	Histopathology		Immunophenotype/ in-situ hybridization	Genetics	
	Architectural effacement	Major findings		IGH/TR clonal rearrangements	Cytogenetic/oncogene abnormalities
Monomorphic	Usually present	Fulfils criteria for an NHL (other than one of the indolent B-cell neoplasms[a]) or plasma cell neoplasm	Varies based on type of neoplasm they resemble; EBV more variable than in other categories	Clonal B cells and/or T cells (except for rare NK-cell cases)	Variably present (see text)

- Struttura **alterata**: istologicamente identici a DLBCL / BL /neoplasia plasmacellulare / T -NHL
- **EBV+**  nella maggioranza dei casi
- Biologia molecolare: **cellule B o T monoclonali**

Monomorphic PTLDs (per i clinici)



- Istotipo più frequente
- Presentazione clinica non specifica: legata al tipo di linfoma
- Frequente localizzazione extranodale

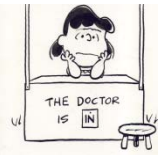
Cosa è richiesto per la diagnosi?

- Presenza di segni e sintomi 

- Biopsia di un linfonodo patologico o di un'altra sede coinvolta 

- Ricerca EBV su tessuto con ibridazione *in situ* (EBER) 

- Se la biopsia NON è possibile, si possono usare metodi non invasivi (EBV DNA-emia, PET/TC)

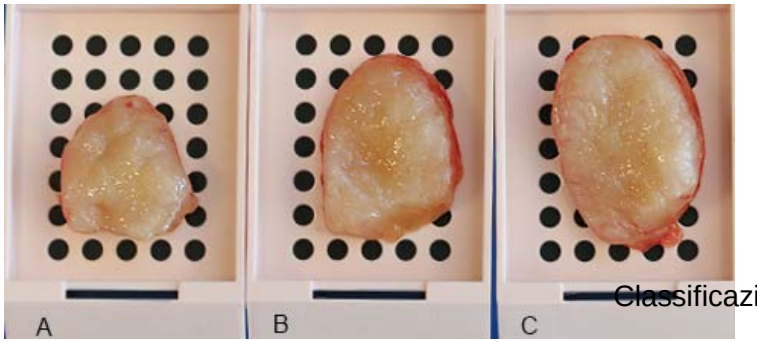


“Patients may have **more than one** type of PTLD in a single site or at separate sites”

«Given the intralesional heterogeneity of many PTLDs, the importance of architectural features in their categorization,

excisional biopsy is preferred

over fine-needle aspiration or core needle biopsies whenever feasible»



Strategie terapeutiche

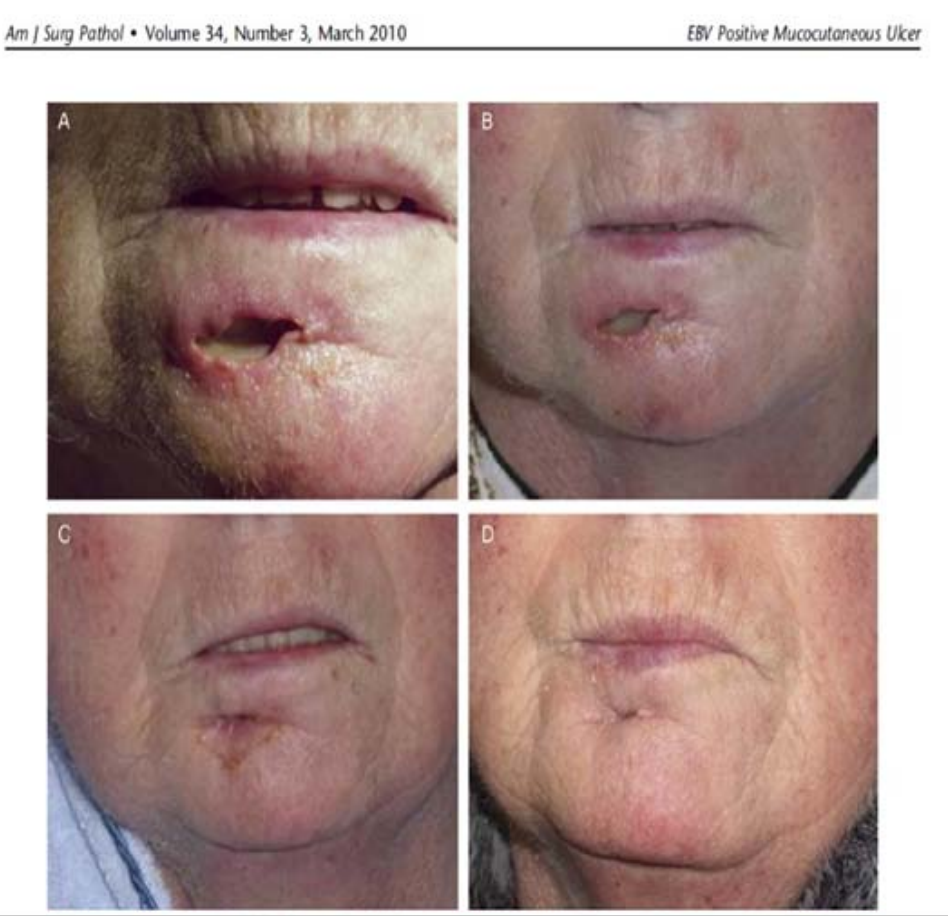
- Ripristinare la ridotta immunità T contro EBV

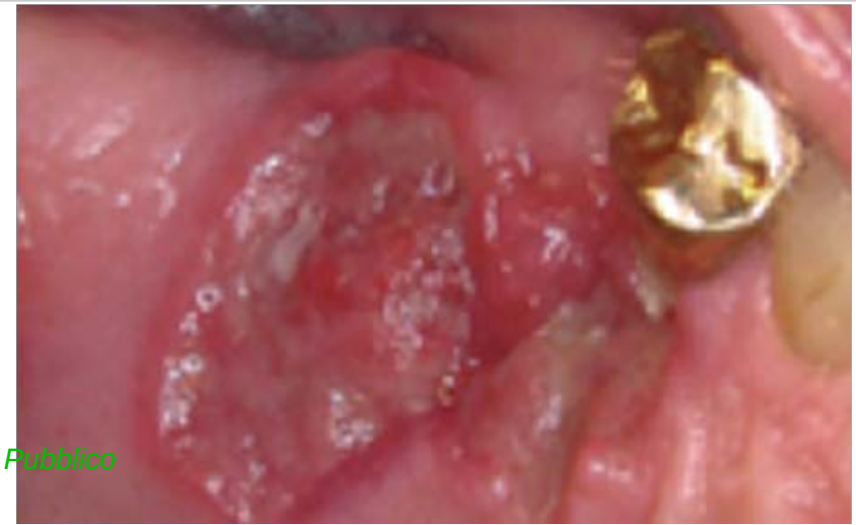
- Colpire direttamente la proliferazione B linfocitaria EBV+

anti CD20 e/o CHT

EBV-positive mucocutaneous ulcer

- Nuova entità clinicopatologica
- Anziani o immunosoppressi
- Cavità orale (gengiva!)
- Cute o altre mucose



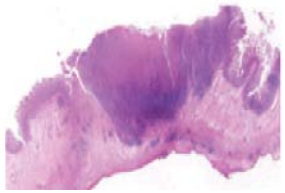
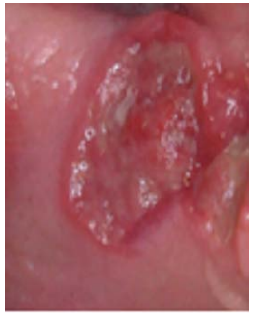


Bone Marrow Transplantation (2016) **51,** 300–302

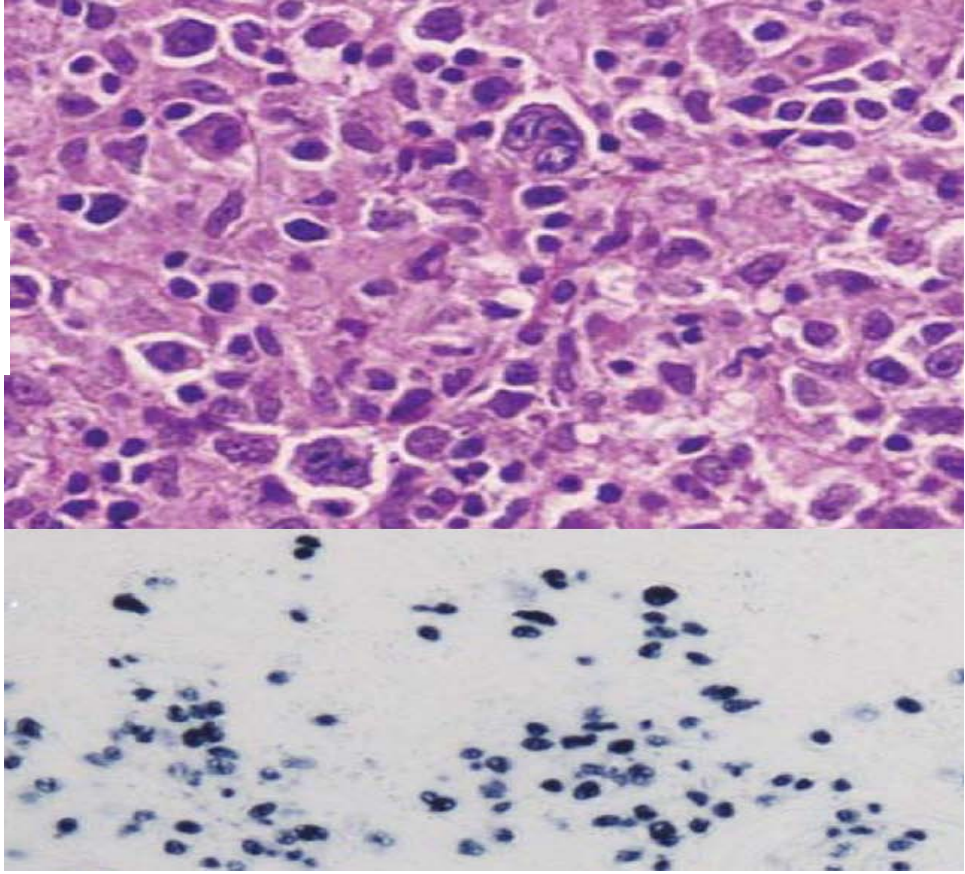
www.nature.com/bmt

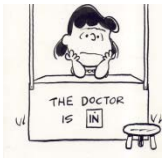
LETTER TO THE EDITOR

Presentation and management of post-allogeneic transplantation EBV-positive mucocutaneous ulcer

	HCT	Clinical history	Source of immunosuppression (IS)	Site	Treatment	Outcome
64/F	Reduced intensity sibling HSCT (2007 and 2009) for secondary MDS	Four months post transplant-diarrhoea suspicious of GVHD. Small shallow ulcer at rectosigmoid junction suspicious of IBD	Cyclosporin A	Colon 	↓IS	CR
65/M	Autologous HCT for mantle cell lymphoma. Therapy-related MDS treated with HLA-identical sibling allogeneic HCT.	At day +60 the patient reported otalgia associated with a right sided oral ulceration (2 × 2 cm right buccal mucosal ulcer covered with a white exudate). The mucosal ulcer did not respond to empiric antibiotics.	Tacrolimus	Oral cavity 	↓IS	CR

- Morfologia Hodgkin like
- CD30+/CD20+/CD15-
- EBER+





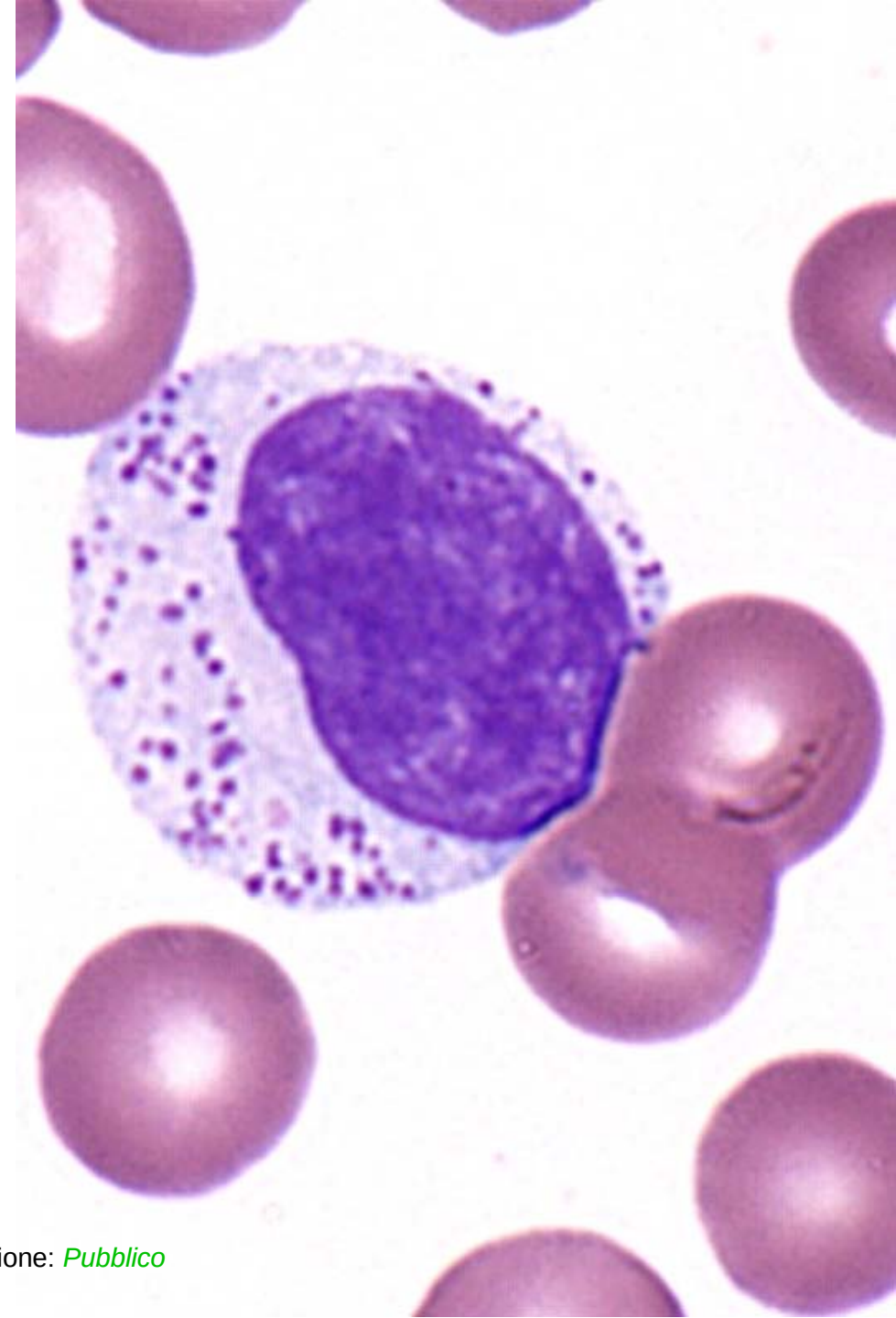
Decorso indolente, talora con regressione spontanea (≠ PTLD!!!)

Large granular lymphocytosis

Cellule T CD3+ o NK CD3-

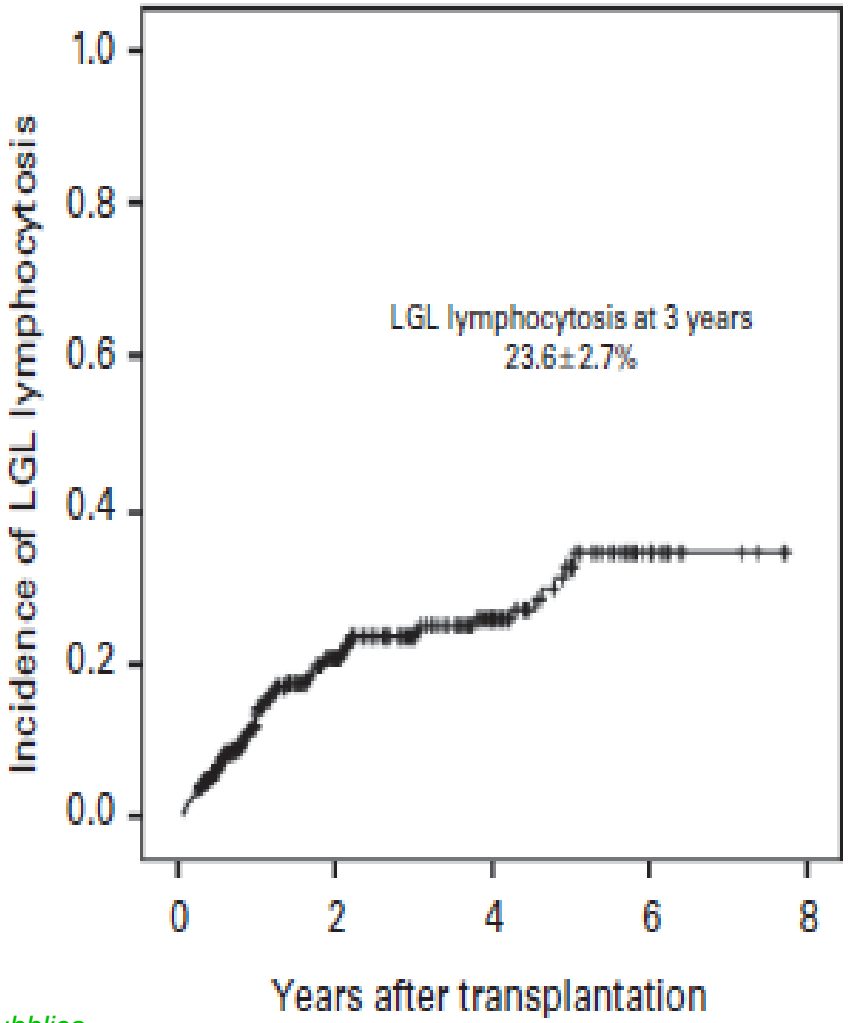
Ampio citoplasma e granuli azzurofili

CD8+/CD57+

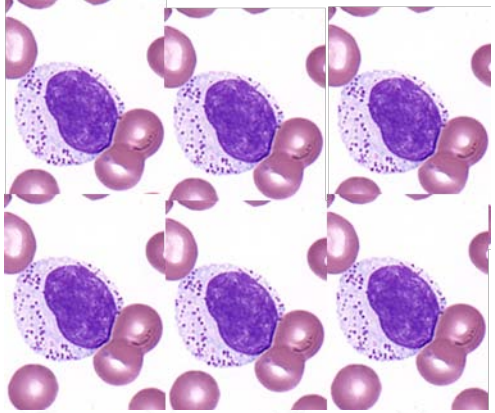


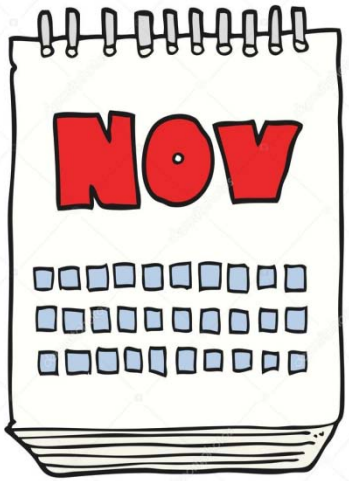
Kim et al, Bone Marrow Transplantation 2013
Le Bris et al, Bone Marrow Transplantation 2017

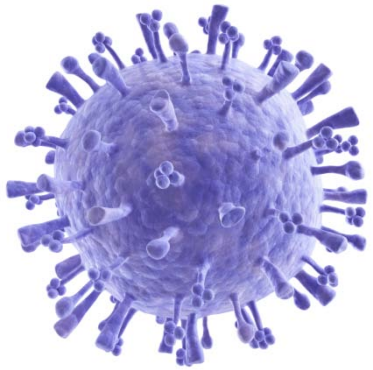
- Espansione in corso di stimolazione antigenica cronica
- Si osserva nel 20% degli allo-SCT
- Immunofenotipo: soprattutto T CD3+/CD8+/CD57+



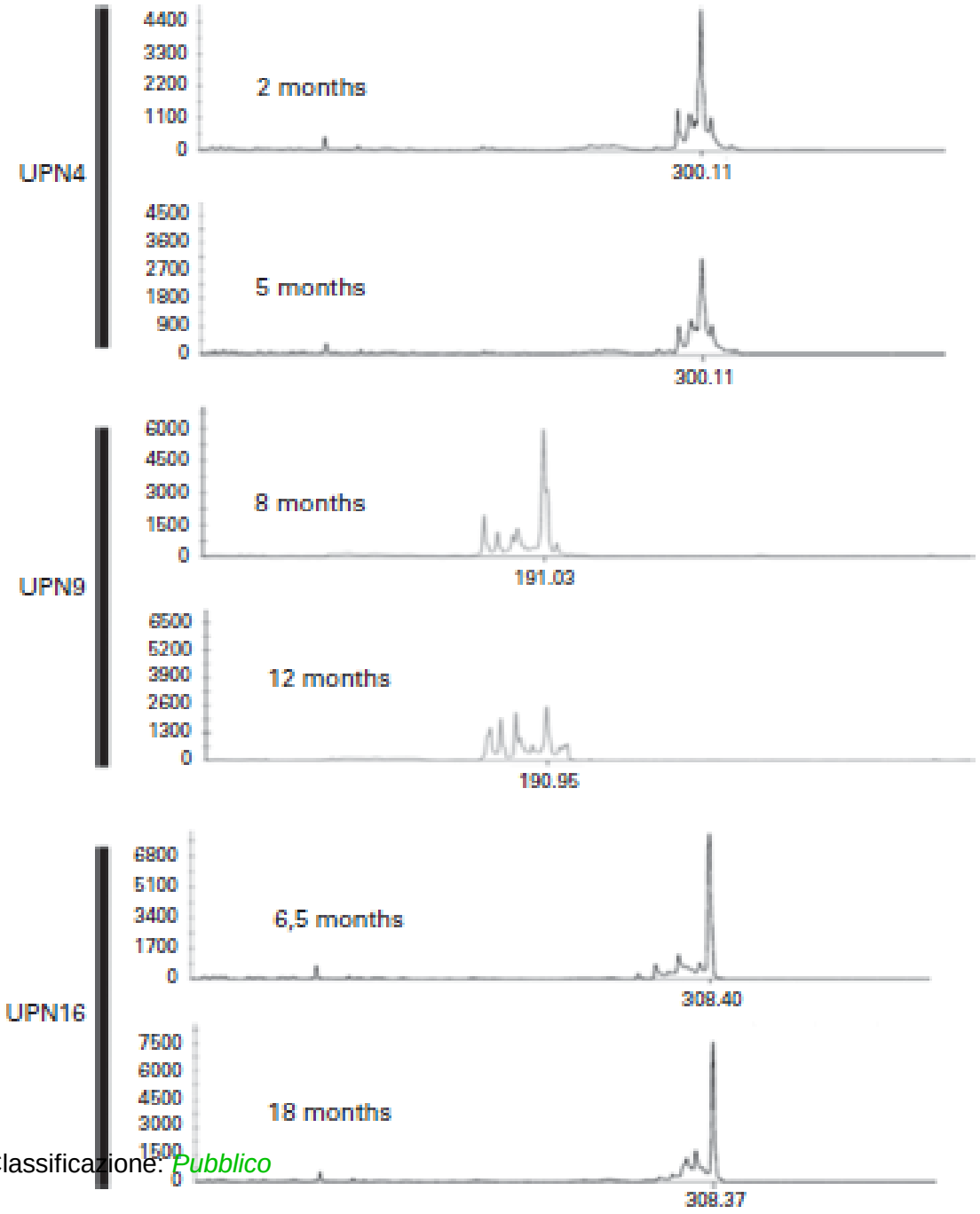
- Linfocitosi (> 3000/mmc) con 30% LGL
- Insorge in media a 12 mesi dal trapianto
- Durata prolungata ma transitoria (persiste in media per 400 giorni)
- Correlazione con GVHD e CMV







- **TGR spesso monoclonale**
- **NON** è sinonimo di *leucemia a linfociti ampi e granulari*
- Se il trapianto era stato fatto per un linfoma T, *attenzione a non scambiare il clone per una recidiva!*
- Associazione con un miglior outcame



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