Prevalent lymphomas in Africa

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Disclaimer

I declare that I have no conflict of interest

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A "TUMOUR SAFARI" IN EAST AND CENTRAL AFRICA

DENIS BURKITT

From the Department of Surgery, Makerere College Medical School, and Mulago Hospital, Kampala, Uganda

Received for publication May 4, 1962

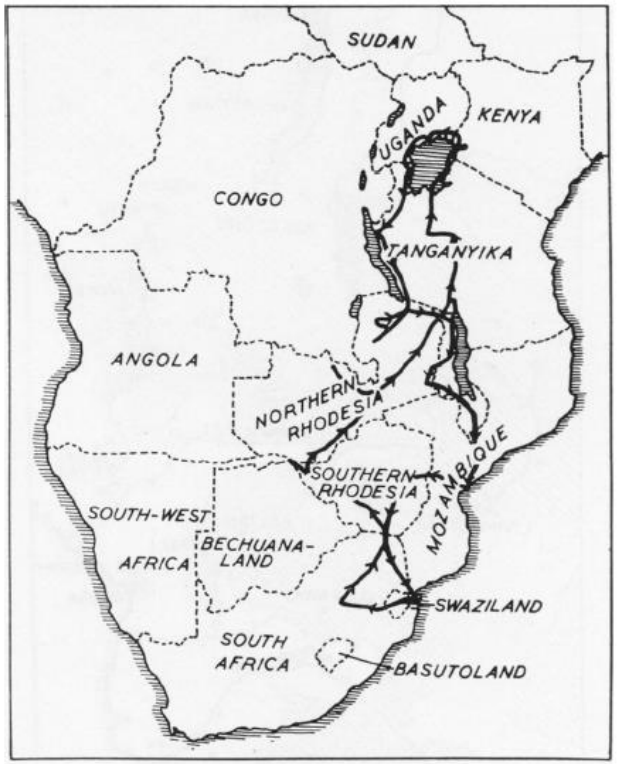


FIG. 2.—The safari route.

Denis Burkitt 1911-1993

- Surgeon and humanitarian
- 1958 Burkitt's lymphoma: African curiosity
- 1964 Ebstein, Barr and Achong: EBV 1st human cancer virus
- Subsequently >10000 publications
- Advanced knowledge of immunology, molecular genetics, viral oncology, chemotherapy

D.Esau. Denis Burkitt: a legacy of global health. Journal of Medical biography 2016

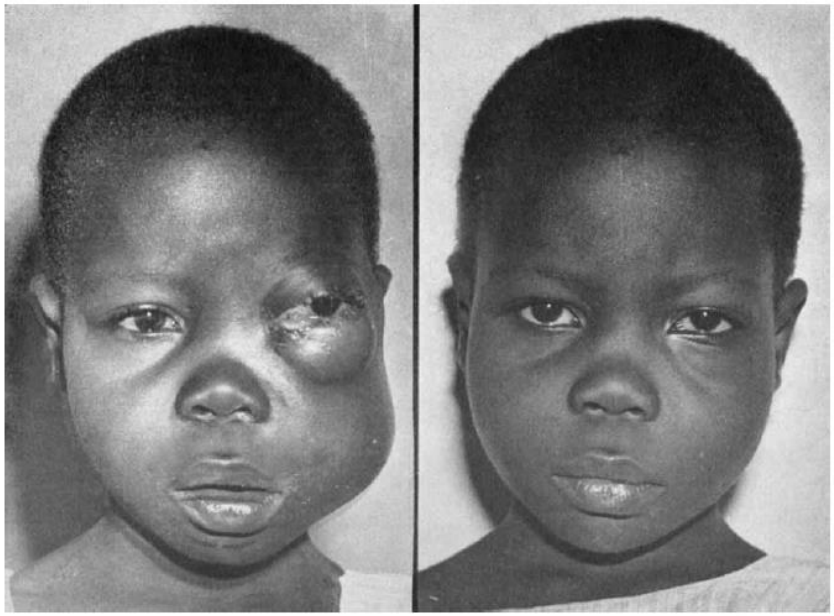


FIG. 7. J 231. A girl aged 5 years with tumors in all 4 jaw quadrants and invasion of left orbit.
FIG. 8. J 231. The same patient 10 days later.

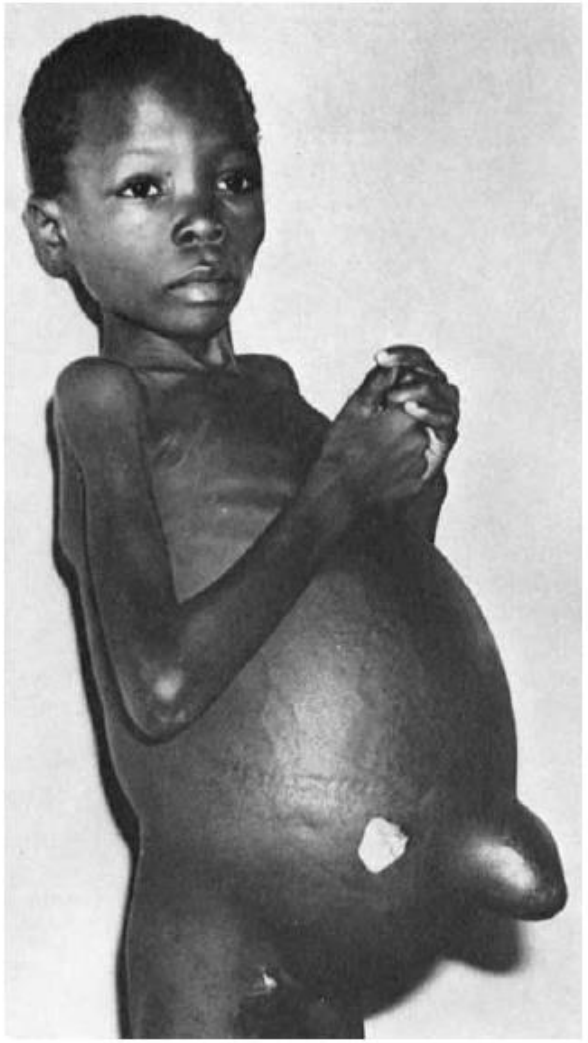


FIG. 9. J 231. The same patient more than a year later with massive ascites due to extensive peritoneal invasion with tumor. Clinically and radiologically the jaws were tumor free.

D Burkitt. African Lymphoma. Cancer 1966

THE GEOGRAPHICAL DISTRIBUTION OF BURKITT'S TUMOUR COMPARED WITH THE GEOGRAPHICAL DISTRIBUTION OF OTHER TYPES OF MALIGNANT LYMPHOMA IN UGANDA

D. H. WRIGHT AND M. ROBERTS

From the Department of Pathology, Makerere University College Medical School, Kampala, Uganda

Received for publication, April 25, 1966

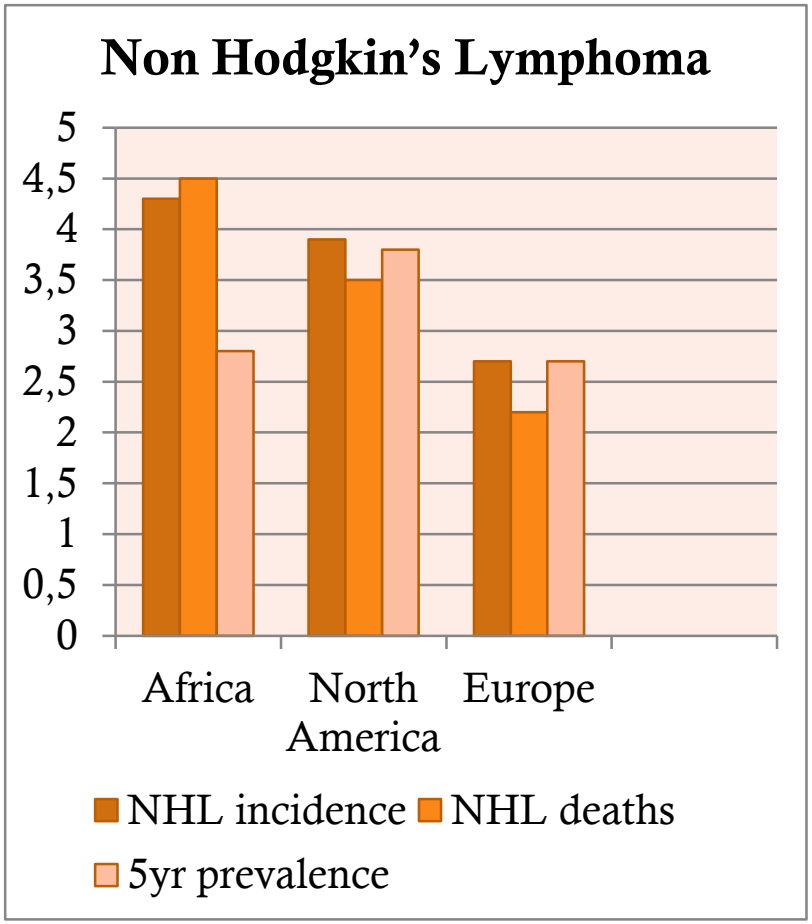
DISTRIBUTION OF BURKITT'S TUMOUR

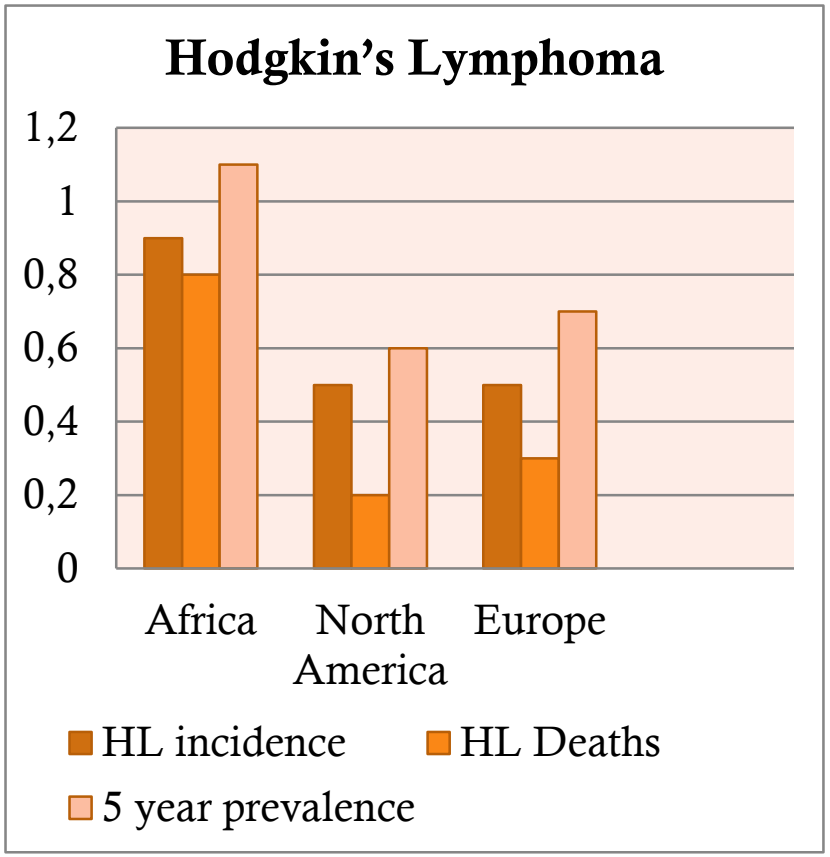
TABLE I.—*Histological Classification of 749 Cases of Malignant Lymphoma Seen in Uganda from 1959 to 1964 Inclusive*

Histiocytic—lymphoma Stem cell lymphoma	Reticulum cell sarcoma	191
Hodgkin's disease (paragranuloma, granuloma and sarcoma)		106
Lymphocytic lymphoma (lymphosarcoma)		128
Burkitt's tumour		324
Total		749

WHO/IARC factsheet 2012

Incidence % per 100000 population





Cancer in Indigenous Africans

- African cancer registries cover 11% of population
- Genetically-diverse, heterogeneous
- NHL 5th commonest cancer

Non Hodgkin's Lymphoma incidence per 100000

	East Africa	Central Africa	North Africa	Southern Africa	West Africa	All Africa
Males	7.1	4.5	4.4	4.8	5.7	5.6
Female	4.4	6.9	2.4	3	3.5	3.9

Parkin et al. Cancer in indigenous Africans. Lancet Oncol 2008;9:683-92

>1.2 billion Africans

UNAIDs: HIV prevalence 2015

Adults aged 15-49 years

	East and Southern Africa	West and Central Africa	Middle East and North Africa
HIV prevalence	7.1%	2.2%	0.1%
ART coverage	54%	28%	17%
Pregnant women	90%	48%	12%

Lymphoma Subtypes

- 2008 WHO Classification of Lymphoid Neoplasms
- 2016 edition: advances in genetic and molecular knowledge
  - Targeted therapy
  - Prognosticate

Swerdlow et al. The 2016 revision of the World Health Organisation classification of lymphoid neoplasms. Blood 2016

African Challenges

- Basing diagnosis on FNAC
- Poor quality histology
- Minimal immunohistochemistry
- Lack of cytogenetics and molecular tools
- Dearth of expertise
- Using outdated Classification systems

Research cannot be conducted without accurate diagnosis

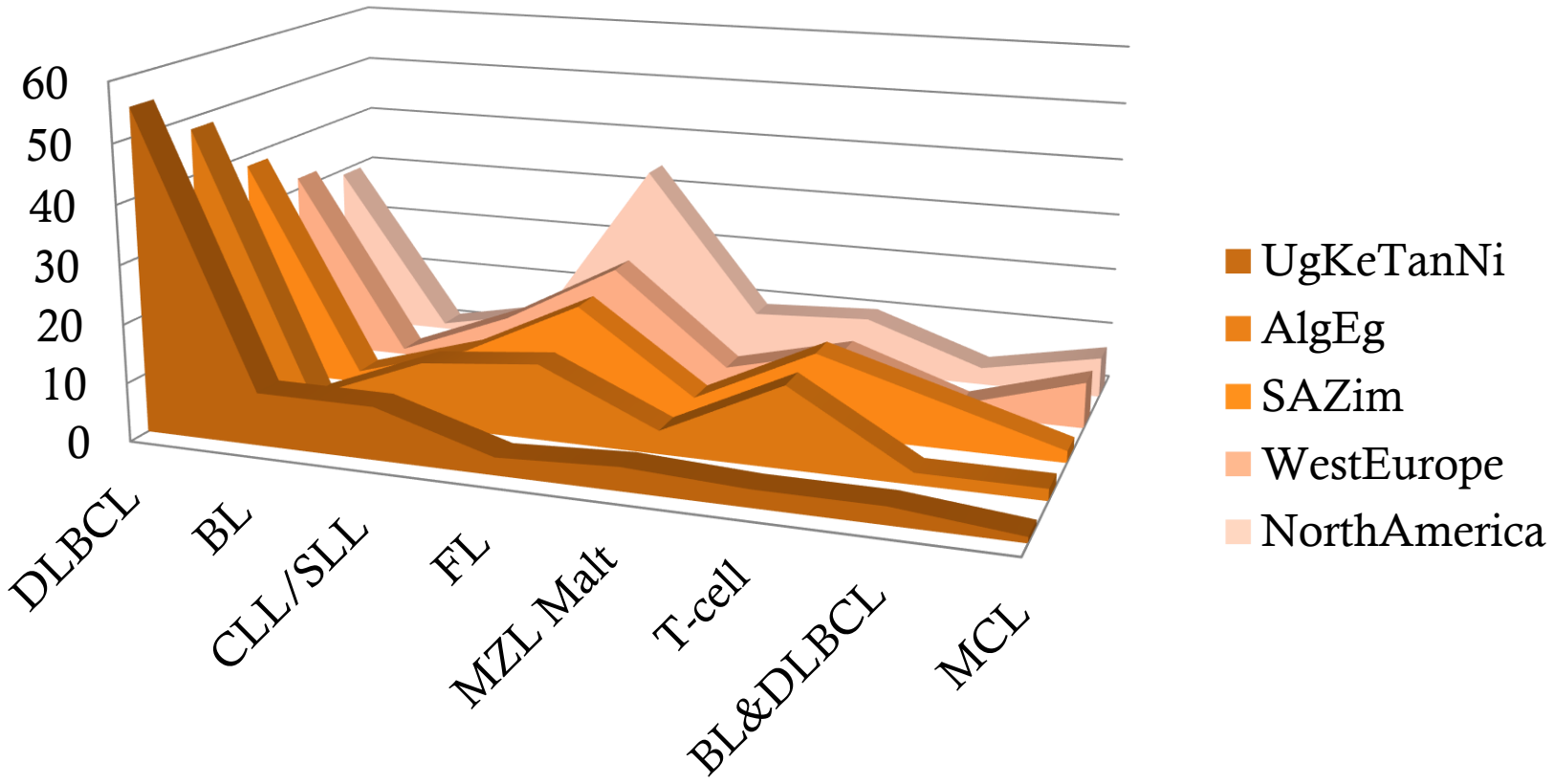
Naresh et al: Lymphomas in sub-Saharan Africa – what can we learn and how can we help in improving diagnosis, managing patients and fostering translational research? Br J Haematol 2011

African Lymphoma classification studies

- Naresh et al: expert review of samples from 4 African countries using 2008 WHO classification
  - 159 FNAs: 76% BL
  - 467 biopsies, 393 (85%) assessable: 73% confirmed as lymphoma
- Mkwakigonja et al: 2001 WHO classification of lymphomas in Tanzania
  - 158/174 biopsies confirmed to be lymphoma (91%)
- International Non-Hodgkin's Lymphoma Classification project: 2001 WHO classification

NHL	Naresh et al. 2011	Perry et al 2016	Perry et al 2016	Anderson et al 1998	
Regions	Ugan, Ken, Tanz, Nigeria	SA, Zim	Algeria, Egypt	Western Europe	North America
Year		1985-1999	1989-2012	1988-1990	
Specimens	172	487	327	580	399
DLBCL	55%	38.2%	48%	32.2%	29.3%
BL	9%	1.6%	3%	0.9%	0.8%
CLL/SLL	9.4%	8.4%	10.7%	8.6%	4.8%
PBL	3.6%				
FL	3%	18.1%	13%	20%	33.6%
Malt & MZ	3.6%	4.3%	3.9%	14.3%	8.5%
T-cell	3%	14.2%	11%	9.1%	9.5%
Intermed BL&DLBCL	3%	8.2%	1.5%	2.4%	2.5%
MCL	0.6%	1.8%	1.8%	8.3%	7%

NHL prevalence



Naresh et al 2011; Perry et al. Non Hodgkin Lymphoma in Southern Africa: review of 487 cases from The International Non-Hodgkin Lymphoma Classification project Br J Haematol 2016; Perry et al. Relative frequency of Non Hodgkin lymphoma subtypes in North Africa, the middle east and India: a review of 971 cases. Br J Haematol 2016

HL prevalence

- Naresh et al: Uganda, Tanzania, Kenya, Nigeria
  - HL 13.2% (52/393)
    - <18yrs 11.8% (19/160)
    - Adults 14.3% (32/223)
- Mwakigonja et al: Tanzania
  - HL 15.2% (24/158)
- Oluwasola et al: Nigeria
  - HL 12.5% (80/638)

Naresh et al; Mwakigonja et al. Tanzanian malignant lymphomas: WHO classification, presentation, ploidy, proliferation and HIV/EBV association. BMC Cancer 2010; Oluwasola et al. A Fifteen year review of lymphomas in a Nigerian tertiary healthcare centre. J Health Popul Nutr 2011

Impact of HIV on lymphoma subtypes

Johannesburg, SA: Comparison of 2225 cases of LPD (2007-2009) to 1897 cases (2004-2006)

	2004-2006	2007-2009
HIV prevalence	44.3%	62%
DLBCL	16%	21%
Plasmablastic	5%	8%
BLPD high grade	8%	5%
BL	6%	7%
BLPD low grade	15%	7%
SLL/CLL	16%	10%
HL	7%	12%

Wiggell et al. Changing pattern of lymphoma subgroups at a tertiary academic complex in a high prevalence HIV setting: A South African perspective. JAIDS 2011

Lymphoma types by HIV status

Cape Town, SA

- 1076 cases seen 2002-2009
- 20% HIV positive

	HIV negative	HIV positive
DLBCL	34%	24%
FL	9%	0
BL	0	31%
PBL	0	16%
HL	20%	7%

Abayomi et al. Impact of the HIV epidemic and anti-retroviral treatment policy on lymphoma incidence and subtypes seen in the Western Cape of South Africa, 2002-2009. Transfus Apher Sci 2011

Prevalent Lymphomas in Africa

1. DLBCL
2. HL
3. CLL/SLL
4. Burkitt
5. Plasmablastic

EBV

- DLBCL nos without immunodeficiency 10% EBV+
- Naresh et al: EBV+ in 78% of BL, 14% of DLBCL, 100% of PBL and 86% of cHL
- Meta-analysis of EBV in cHL
  - Africa 74.4%
  - Europe 35% and North America 31.9%
- MD Anderson: EBV status in PBL in 61 patients
  - HIV positive: 100% EBV (19 cases)
  - HIV negative 52%

Naresh et al; Ju-Han Lee et al. Prevalence and Prognostic significance of EBV in cHL: A meta-analysis. Arch of Med Res 2014; Loghavi et al. Stage, age and EBV status impact outcomes of plasmablastic lymphoma patients: a clinicopathologic analysis of 61 patients. J Hematol and Oncol 2015

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7] Michele Ghielmini,[8] Gilles A. Salles,[9] Andrew D. Zelenetz,[10] and Elaine S. Jaffe[11]

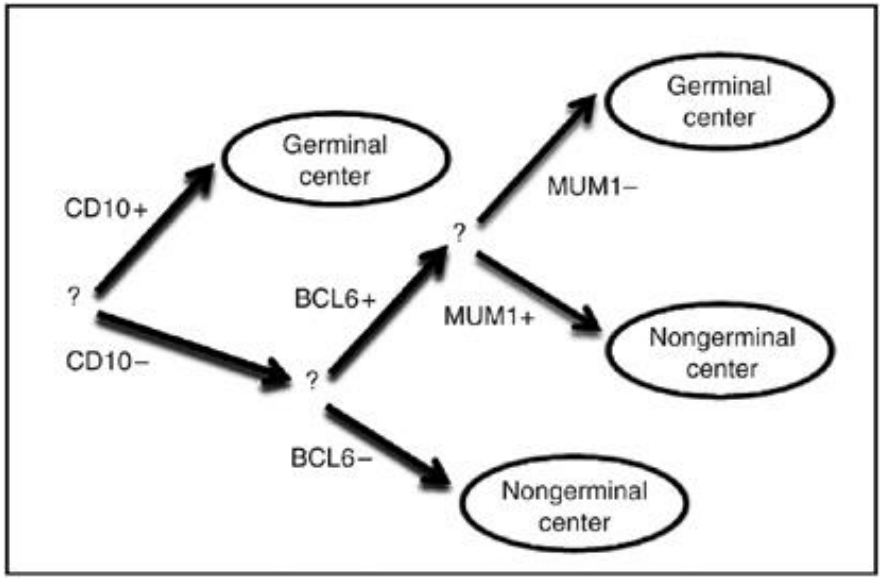
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV$^+$ DLBCL, NOS*
*EBV$^+$ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*HHV8$^+$ 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

Diffuse large B-cell lymphoma

- Excision biopsy
- Immunohistochemistry:
  - Pan-B markers +ve (CD19, CD20, CD22, CD79a)
  - 30-60% CD10+
  - 60-90% BCL6+
  - 35-65% IRF4/MUM1+
  - Ki67>40%
  - 20-30% BCL2+
- Cell of origin (COO): germinal centre B (GCB) vs activated B-cell (ABC)

GCB vs ABC

- Require Gene Expression Profiling to differentiate
- Immunohisto algorithms
- Pre-Ritux era 5 year OS
  - GCB 50-60%
  - ABC 15-30%
- ESMO does not recommend COO determination outside of clinical trials
- Revised WHO classification requires COO



Tilly et al. Diffuse Large B-cell lymphoma: ESMO Clinical practise guidelines for diagnosis, treatment and follow up. Annals of Oncology 2015; Ladetto et al. ESMO consensus conference 2016

High Grade B-cell Lymphomas

- *MYC* gene rearranged in 5-15% DLBCL
- When associated with *BCL2* and *BCL6* results in "double" or "triple-hit" lymphomas
- *MYC* protein expression detected in 30-50% of DLBCL nos and associated with *BCL2* in 20-35% of cases and is called "double or "triple expressor" lymphomas

Significance of c-*Myc*

- Oncogene on chromosome 8
- Overexpressed in 70% of human cancers
- *Myc* has > 600 gene targets
  - Cell proliferation
  - Apoptosis
- Translocated in >90% of Burkitt lymphoma (t8;14)
- *MYC* mediated activity:
  - activation of *p19(ARF)-MDM2-TP53* pathway
  - Repression of the apoptosis inhibitor *BCL2*

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High-grade B-cell lymphoma, NOS*
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High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations

- Present with poor prognostic indicators eg high LDH, high IPI, BM and CNS involvement
- Inferior outcomes with standard R-CHOP
- Suggested treatment regimens:
  - DA-EPOCH-R
  - RHyperCVAD
  - R-CODOX-RM-IVAC

Burkitt lymphoma

- Typical immunophenotype:
  - CD10+
  - CD20+
  - Ki 67≥95%
  - BCL2-
  - BCL6+
- Cytogenetics: t(8;14), *MYC*
- Can there be Burkitt without *MYC* translocation?
  - WHO 2016 *Burkitt-like lymphoma with 11q aberration*

Plasmablastic Lymphoma

- Immunophenotype
  - Positive: CD 138, CD 38, IRF4/MUM1, Ki 67>90%
  - Negative: CD20, CD45, PAX5
- How to treat?
  - Review of stage 1 and 2: Doxyrubicin-based chemo and ISRT resulted in 90% 2yr PFS and 100% 2yr OS
  - Analysis of 61 patients: patients who received CHOP had better OS than hyperCVAD (p=0.078)
    - Age, stage and EBV positivity are sig prognostic factors

Pinnix et al. Doxorubicin-based chemotherapy and RT produces favorable outcomes in limited-stage PBL: a single institution review; Loghavi et al

Lymphoma in Africa

- Socioeconomic factors and inequality
- Access to good diagnostics and treatment
- Adequate ART coverage

- Require randomized controlled trials
- Require “Africa-specific” treatment protocols for the resource-constrained masses