Lymphomas presenting in the head and neck

R3 陳贈成
**Introduction:**

- Hodgkin’s lymphoma (HL) and non-Hodgkin’s lymphoma (NHL)
- NHL five times more than HL
- HL:
  - Bimodal distribution; 15~34 and >50
  - Male predominant, especially pediatric
  - Nodular sclerosis is the most common subtype
  - Lymphocyte depleted is the least common

**Table 1-1. World Health Organization (WHO) Classification of Lymphoid Tumors**

<table>
<thead>
<tr>
<th>B-CELL NEOPLASMS</th>
<th>Precursor B-cell neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
<td></td>
</tr>
<tr>
<td>B-cell prolymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
<td></td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td></td>
</tr>
<tr>
<td>Plasma cell neoplasms: plasma cell myeloma, plasmacytoma, monoclonal immunoglobulin deposition diseases, heavy-chain diseases</td>
<td></td>
</tr>
<tr>
<td>Extranodal marginal zone B-cell lymphoma (MALT lymphoma)</td>
<td></td>
</tr>
<tr>
<td>Nodal marginal zone B-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td></td>
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<tr>
<td>Mantle cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Large B-cell lymphoma subtypes: mediastinal (thymic), intravascular, primary effusion lymphoma; plasmablastic, ALK+ large B-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Burkitt’s lymphoma/leukemia</td>
<td></td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T-CELL NEOPLASMS</th>
<th>Precursor T-cell neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor T-lymphoblastic leukemia/lymphoma</td>
<td></td>
</tr>
<tr>
<td>Mature T-cell and NK-cell neoplasms</td>
<td></td>
</tr>
<tr>
<td>T-cell prolymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>T-cell large granular lymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Aggressive NK-cell leukemia</td>
<td></td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td></td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td></td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Blastic NK-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides/Sézary syndrome</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD30-positive T-cell lymphoproliferative disorders: primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, borderline lesions</td>
<td></td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, unspecified</td>
<td></td>
</tr>
<tr>
<td>Systemic anaplastic large cell lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

**HODGKIN’S LYMPHOMA (HODGKIN’S DISEASE)**

- Nodular Lymphocyte Predominant Hodgkin’s Lymphoma
- Classic Hodgkin’s Lymphoma
- Nodular sclerosis Hodgkin’s lymphoma
- Mixed cellularity Hodgkin’s lymphoma
- Lymphocyte-rich classic Hodgkin’s lymphoma
- Lymphocyte depleted Hodgkin’s lymphoma
Epidemiology of HL:

- **Risk factors**
  - EBV: IM show a threefold increase in risk
  - Genetic: HLA Class II antigens (DRB1*1501-DQA1; ...)
  - HHV-6
  - HIV-1
  - Woodworking and Chemical exposure

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogenesis/Co-factor</th>
<th>Epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt’s lymphoma</td>
<td>EBV, malaria, immunodeficiency, c-Myc</td>
<td>Endemic vs. sporadic in North America</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td>HTLV-1</td>
<td>SW Japan, Caribbean</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>KSHV/HHV-8</td>
<td>HIV, Mediterranean</td>
</tr>
<tr>
<td>MALT lymphomas</td>
<td><em>Helicobacter, MALT1/MLT</em></td>
<td>Feltre, Italy</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td>EBV, genetics</td>
<td>Asia, Central and South America</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td><em>Bcl-2</em></td>
<td>United States, Western Europe</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td><em>Cyclin D1</em></td>
<td>Southern Europe</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td><em>ALK</em></td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Epidemiology of NHL:

- Risk factors
  - **Immunodeficiency:**
    a. transplantation, autoimmune disorder
  - **Occupational exposures**
  - **Genetics**
  - **Infectious agents**
    a. HIV
    b. EBV (endemic Burkitt’s lymphoma)
    c. Chronic antigen stimulation, as H.P (MALT lymphoma)
Immunophenotype:

- **B-cell lymphoma marker**
  - Heavy chain gene rearrangement, CD19, CD79a
  - Light chain gene rearrangement, CD20
  - B-cell specific transcription factor. Pax-5
  - Inhibitory receptor for B cell receptor (BCR) signaling : CD22

- **T-cell lymphoma marker**
  - No Specific immunophenotypic profiles

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<table>
<thead>
<tr>
<th>Disease</th>
<th>CD5</th>
<th>CD10</th>
<th>CD23</th>
<th>CD43</th>
<th>Cyclin D1</th>
<th>Ig class</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>IgM, IgG</td>
</tr>
<tr>
<td>MCL</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>IgM/IgD</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>IgM/IgD</td>
</tr>
<tr>
<td>LPL</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/−</td>
<td>-</td>
<td>IgM (c)</td>
</tr>
<tr>
<td>MALT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/−</td>
<td>-</td>
<td>IgM (c, s)</td>
</tr>
<tr>
<td>SMZL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>−/+</td>
<td>IgM/IgD</td>
</tr>
<tr>
<td>HCL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>−/+</td>
<td>IgG</td>
</tr>
</tbody>
</table>

Fl, follicular lymphoma; MCL, mantle cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; LPL, lymphoplasmacytic lymphoma; MALT, marginal zone lymphoma of MALT type; SMZL, splenic marginal zone lymphoma; HCL, hairy cell leukemia; Ig class, most commonly expressed heavy chain classes; c, cytoplasmic Ig; s, surface Ig.
Differential diagnosis:

- Infections
  - Toxoplasmosis
  - Tuberculosis
  - EBV-induced infections, IM
  - Human immunodeficiency virus (HIV)
- Autoimmune lymphadenopathy
  - Rheumatoid arthritis, affect up to 75%
  - Felty's syndrome (splenomegaly, neutropenia, recurrent infections), NHL risk ↑
  - Systemic lupus erythematosus (SLE)
  - Sjogren's syndrome
Differential diagnosis:

- Hypersensitivity lymphadenopathy
- Silicone-associated lymphadenopathy
- Benign lymphoproliferative disorders
- Histiocytic necrotizing lymphadenitis (Kikuchi’s lymphadenitis)
- Sinus Histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
Staging of lymphomas:

- Originally developed for Hodgkin’s lymphoma
- For non-Hodgkin’s lymphoma as well

### Ann Arbor staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single nodal region or single extranodal site (IE) involved</td>
</tr>
<tr>
<td>II</td>
<td>Two or more nodal regions or one nodal region and one extranodal site (IIE) involved; disease limited to one site of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Nodal disease on both sides of the diaphragm with no extranodal sites (III), one extranodal site (IIE), or splenic involvement (IIS)</td>
</tr>
<tr>
<td>IV</td>
<td>Liver, bone marrow, or multiple extranodal sites involved</td>
</tr>
</tbody>
</table>

**Modifiers**

- A: Constitutional (B) symptoms absent
- B: Fever $>38^\circ$C, Weight loss $>10\%$ in 6 months, night sweats

Classification of NHL:

- Rappaport classification, Luke and Collins classification
- Working formulation system
  - most widely accepted classification
  - correlate well with untreated mean survival times
  - not incorporate new disease entities, such as MALToma

<table>
<thead>
<tr>
<th>Working formulation</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Subtypes</td>
</tr>
<tr>
<td>Low</td>
<td>A. Small lymphocytic</td>
</tr>
<tr>
<td></td>
<td>B. Follicular small cleaved cell</td>
</tr>
<tr>
<td></td>
<td>C. Follicular mixed cell</td>
</tr>
<tr>
<td>Intermediate</td>
<td>D. Follicular large cell</td>
</tr>
<tr>
<td></td>
<td>E. Diffuse small cleaved cell</td>
</tr>
<tr>
<td></td>
<td>F. Diffuse mixed cell</td>
</tr>
<tr>
<td></td>
<td>G. Diffuse large cell (clinically high-grade)</td>
</tr>
<tr>
<td>High</td>
<td>H. Immunoblastic</td>
</tr>
<tr>
<td></td>
<td>I. Lymphoblastic</td>
</tr>
<tr>
<td></td>
<td>J. Small noncleaved cell</td>
</tr>
</tbody>
</table>

Classification of NHL:

- High grade lymphomas:
  - More frequently in children and young adults

- Intermediate-grade lymphomas:
  - Most common
  - Diffuse large B-cell lymphomas, 30%
  - 10 years free survival rate: Stage I 80%, Stage II 60%, Stage III 40%

- Low-grade lymphomas:
  - Some with indolent clinical course, not requiring treatment
  - One third of all NHL, mainly in older populations
  - 4% of localized (Stage I, II) patients with B symptoms
  - Richter’s transformation into more aggressive grade
Classification of NHL:

- Kiel classification
- Revised European American lymphoma and WHO classification
  - morphology, immunophenotype, genotype, normal cell counterpart, clinical features
  - not reflect prognosis
- All head and neck NHL
  - Low grade, 15%
  - Intermediate grade, 80%
  - High grade, 5%
Non-Hodgkin's lymphoma

- **International Prognostic Index (IPI):**
  - Localized (Stage I-II) or Advanced (Stage III-IV)
  - Age (<60y/o or >60y/o)
  - performance status (ECOG 2-4)
  - number of extranodal sites (>1)
  - LDH (>1x normal)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Risk Factors</th>
<th>Distribution of Cases (%)</th>
<th>CR Rate (%)</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0,1</td>
<td>35</td>
<td>87</td>
<td>84/73</td>
</tr>
<tr>
<td>Low-Intermediate</td>
<td>2</td>
<td>27</td>
<td>67</td>
<td>66/51</td>
</tr>
<tr>
<td>High-Intermediate</td>
<td>3</td>
<td>22</td>
<td>55</td>
<td>54/43</td>
</tr>
<tr>
<td>High</td>
<td>4,5</td>
<td>16</td>
<td>44</td>
<td>34/26</td>
</tr>
</tbody>
</table>

Notes: Factors include age >60, LDH > normal, performance status >1, Stage III/IV, extranodal involvement >1 site.

Score 0 or 1 for each factor: 0 = absent, 1 = present.
Clinical presentation:

- Persistent painless cervical lymphadenopathy, most common
- Constitutional symptoms, weight loss, night sweats, and fever
- One quarter of systemic NHL case: ENT field involved
Pretreatment assessment

- **CT of the head and neck, chest, abdomen and pelvis**
  - homogenous, slightly hyperintense on CT
  - enhance with CT and MRI contrast agents
  - Tend to push, compress, or surround rather than direct invade
  - Central necrosis in node: high grade or immunocompromised patient

- **CBC/DC**

- **HIV screening**, especially aggressive NHL or HL

- **Lumbar puncture**: only in patients with CNS disease
Pretreatment assessment

- Waldeyer’s ring, thyroid, and salivary gland MALToma:
  - *upper GI series*, *barium enema*, *endoscopy*, or *colonoscopy* may be indicated

- **Bone marrow biopsy**
  - unilateral bone marrow specimen at least 2cm in length
  - PET should not as a substitute
  - molecular and cytogenic studies of bone marrow

- **PET study**: FDG or $^{111}$In-DTPA-D-Phe(1)-octreotide
  - monitor response to therapy
  - false positive: infection, inflammation, or thymic hyperplasia
Therapy:

- **Complete remission**
  - complete disappearance of all detectable disease
  - complete disappearance of all disease-related symptoms
  - all lymph node must <1.5cm or <1cm
  - enlarged spleen prior therapy must regressed
  - bone marrow infiltration must be cleared

- **Complete remission/Unconfirmed**
  - fulfill criteria 1,2
  - residual LN >1.5cm, but regressed more than 75%
  - Indeterminate bone marrow finding
Therapy:

- **Partial remission**
  - LN diameter decrease > 50%
  - No increase in the size of liver, spleen
  - No new sites of disease

- **Stable disease**
  - Less than PR, but not progressive disease

- **Relapsed disease**
  - Appearance of any new lesion
  - Increase more than 50% in size
Therapy:

- **Early-Stage disease (Stage I, II nonbulky)**
  - 3 cycles of CHOP C/T plus involved-field R/T
  - Integration of rituximab: SWOG Phase II clinical trial
  - 30~30Gy for complete response patient
  - 40~50Gy for uncertain complete responses

- **Advanced-Stage disease (Stage II bulky, III and IV)**
  - CR rate of aggressive histologies: 44% to 61%
  - Projected DFS rate: 43%
  - 6~8 cycles of CHOP-based C/T with rituximab: standard treatment
  - Overexpressed bcl-2: limited benefit of rituximab Tx
  
  ➔ All stages treated with C/T primarily; R/T for bulky disease…..
Monoclonal Antibodies:

- Both normal and tumor cells are targeted
- Constant generation of nonmalignant new B and T cells
- Anti-CD20 antibody: IF5, tositumomab, and rituximab

**Rituximab:**
- Antibody-dependent cellular cytotoxicity
- Complement-dependent cytotoxicity
- Apoptosis
Non-Hodgkin’s lymphoma

- **Waldeyer’s Ring**
  - 70% of primary head and neck NHL cases
  - tonsils, adenoid, tongue base, nasopharynx
  - 50~60% Stage I and II NHLs
  - 20~30% with synchronous or metachronous GI involvement
  - Histology: Diffuse large B cell lymphoma > follicular lymphoma > MALT type > Burkitt’s lymphoma
  - mucosal ulceration is not common
  - Most common presentation: dysphagia, airway obstruction, E tube block, neck mass
# Non-Hodgkin’s lymphoma

## Table 18-8. Overview of Series in Literature Outlining Demographics, Histology, Therapy, and Outcome for Patients with Localized Waldeyer’s Ring Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Reference Study Type</th>
<th>Number</th>
<th>Median Age (y)</th>
<th>% Male</th>
<th>Histology</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aviles (1996)(^5) Randomized trial</td>
<td>316</td>
<td>55</td>
<td>50</td>
<td>DLCL</td>
<td>97%</td>
<td>1. IRRRT</td>
<td>5-y FFS 30% relapses occurred in GI tract</td>
</tr>
<tr>
<td>Krol (2001)(^1) Retrospective series</td>
<td>77</td>
<td>66</td>
<td>48</td>
<td>DLBCL</td>
<td>66%</td>
<td>None</td>
<td>7% Not reported separately for localized subgroup</td>
</tr>
<tr>
<td></td>
<td>(74% localized)</td>
<td>FL</td>
<td>14%</td>
<td>CMT</td>
<td>6%</td>
<td>2. CHOP-type</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCL</td>
<td>4%</td>
<td>IRRRT</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SLL</td>
<td>3%</td>
<td>ChemoRx</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DLBCL</td>
<td>84%</td>
<td>ChemoRx</td>
<td>45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezzat (2001)(^2) Retrospective review</td>
<td>130</td>
<td>55</td>
<td>67</td>
<td>DLBCL</td>
<td>84%</td>
<td>3. IRRRT → CHOP-type</td>
<td></td>
</tr>
<tr>
<td>Harabuchi (1997)(^3) Retrospective review</td>
<td>71</td>
<td>45</td>
<td>50</td>
<td>DLCL</td>
<td>94%</td>
<td>3. IRRRT</td>
<td>5-y DFS 68%</td>
</tr>
<tr>
<td></td>
<td>(72% localized)</td>
<td>5-y OS 58%</td>
<td>49</td>
<td>CMT</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liang (1997)(^4) Retrospective review</td>
<td>47</td>
<td>63</td>
<td>49</td>
<td>DLCL</td>
<td>58%</td>
<td>5-y DFS 58%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>indolent</td>
<td></td>
<td>18%</td>
<td>IRRT</td>
<td>49%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-y OS 72%</td>
<td>CMT</td>
<td>62%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aggressive Indolent 71%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-y OS 75%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

ChemoRx, chemotherapy, usually with an anthracycline; CHOP-type, cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin; CMT, combined modality therapy (surgery, chemotherapy, plus/minus irradiation); DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FFP, freedom from progression; FL, follicular lymphoma; IPI, International Prognostic Index; IRRRT, involved region radiotherapy; MALT, mucosa associated lymphoid tissue lymphoma; OS, overall survival; y, years.
Non-Hodgkin’s lymphoma

- **Salivary gland**
  - 2 ~5 % of all salivary neoplasms
  - Lymphoepithelial sialoadenitis of Sjogren’s syndrome (LESA): 44-fold increased risk
  - Salivary gland nodal: follicular type most common
  - Extranodal salivary gland: MALT type most common
  - Others: diffuse large B cell, mantle cell, lymphoplasmocytic, small lymphocytic
  - Primary T cell lymphoma is very rare
  - Painless swelling of the involved salivary gland
Non-Hodgkin’s lymphoma

**Orbit**
- Half of all orbital tumors
- Vast majority B-cell NKL, T-cell only 1~3%
- Histology type: MALToma > diffuse large B cell
- Diffuse large B cell: posterior orbit > anterior tissue
- Painless unilateral orbital swelling, proptosis, ptosis, blurred vision, diplopia, 10~20% bilateral
- Conjunctival involved (+): bilateral, 45%
Non-Hodgkin’s lymphoma

- **Thyroid**
  - Hashimoto’s autoimmune thyroiditis are risk
  - MALT lymphoma are most common
- **MALT lymphoma**
  - from post-germinal center memory B cell
  - clinically low grade, course indolent
  - 50% t(11,18) translocation
**NK/T cell lymphoma, nasal type**

- **Sinonasal lymphoma**
  - Extranodal NK/T-cell lymphoma, nasal type
  - Highly associated with EBV
  - Most common presentation: destructive nasal or midline facial tumor, palatal destruction, orbital swelling and edema
  - Chemotherapy outcome poor; Radiation for localized disease effective
  - EBV-encoded small nuclear RNA (EBER ½): positive
  - CD2 (+), CD3(-)
  - R/T field: significant prognostic factor of LCR, DFS, OAS
  - R/T dose: >= 50Gy
NK/T cell lymphoma, nasal type

**FIGURE 2.** This graph illustrates the local control probability as a function of radiotherapy (RT) field. Solid line: an RT field that encompassed all sinuses, the nasopharynx, and macroscopic lesions; dashed line: an RT field that included macroscopic lesions with a margin.

**FIGURE 3.** This graph illustrates the local control probability as a function of radiotherapy dose. Solid line: doses ≥ 50 grays (Gy); dashed line: doses < 50 Gy.
Thanks for your attention