Malignant Lymphomas Introduction

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Lymphoproliferative neoplasms are mainly divided into two major categories: Hodgkin lymphoma (HL) with an annual incidence of ~2,5–3/100000 and non-Hodgkin lymphomas (NHL), which are approximately seven to eight-fold more common. NHL constitute a heterogeneous group of disorders: 85% are of B-cell and 15% of T-cell origin. The 2008 World Health Organization scheme was recently modified, so that the lymphomas are currently classified according to the 2016 WHO classification scheme (Table 92.1) [1, 2]. Among NHL, diffuse large B-cell lymphomas (DLBCL) are the most common subtype (31% of the total), followed by follicular lymphomas (~25%), extranodal marginal (MALT) lymphomas (8%), mantle cell lymphoma (6%), and primary mediastinal large B-cell lymphoma (PMLBCL) (2–3%). Altogether, the common "nodal" T-cell lymphomas (peripheral T-cell NOS, angioimmunoblastic and anaplastic large-cell lymphoma) comprise ~8% of the total cases of NHL. It should be noted that small lymphocytic lymphoma and B-chronic lymphocytic leukemia (B-CLL) are reported to account for ~10% of NHL cases. However, this figure is based on histologic data, whereas many cases of B-CLL are diagnosed by blood flow cytometry without a lymph node and frequently without bone marrow biopsy. Thus, B-CLL is a separate entity with an annual incidence of 4,5–5,5/100000 [1, 2].

In contrast to solid tumors, which are generally staged based on TNM classification schemes, lymphoma staging is based on the Ann Arbor system (described in the next chapter, Table 93.1) and its recent Lugano modification . The Ann Arbor staging system was primarily developed for HL and reflects the tendency of this disease to affect lymph nodes in an anatomically contiguous manner [3, 4]. Its use was extended to NHL as well, although its performance may be inferior in this setting. The same general principles are applicable to the Lugano staging system as well [5]. Specific NHL subtypes cannot be practically staged by these systems. Thus, specific staging systems have been reported for gastric MALT lymphomas, Burkitt lymphoma, primary CNS diffuse large B-cell lymphomas, cutaneous T-cell lymphomas, etc.

Before the introduction of computed tomography (CT), "pathological" staging was routinely used in order to assess disease extent in a more accurate way, especially in patients with "seemingly" localized or limited HL, who could be treated with radiotherapy alone. Pathological staging included staging laparotomy with splenectomy, nodal sampling, and liver and bone marrow biopsy. The introduction of CT in the everyday practice facilitated the evaluation of

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Table 92.1 The 2016 World Health Organization (WHO) classification of mature and precursor lymphoid neoplasms

Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Waldenstrom macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM
μ heavy chain disease
γ heavy chain disease
α heavy chain disease
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia variant
Splenic marginal zone lymphoma
Extranodal marginal zone lymphoma (MALT)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia
Follicular lymphoma
In situ follicular neoplasia
Follicular lymphoma, duodenal type
Follicular lymphoma, pediatric type
Follicle center cell lymphoma, primary cutaneous
Large B-cell lymphoma with IRF4 rearrangement
Diffuse large B-cell lymphoma, 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-positive DLBCL, NOS
EBV -positive mucocutaneous ulcer
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
HHV8-positive DLBCL, NOS
ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
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
Burkitt lymphoma

Table 92.1 (continued)

Burkitt-like lymphoma with 11q aberration
Monoclonal gammopathy of undetermined significance (MGUS), IgG/IgA
Plasma cell myeloma
Solitary plasmacytoma of the bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases
Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorders of NK cells
Aggressive NK-cell leukemia
Adult T-cell leukemia/lymphoma
Extranodal NK−/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sezary syndrome
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large-cell lymphoma
Lymphomatoid papulosis
Primary cutaneous $\gamma\delta$ T-cell lymphoma
Primary cutaneous CD8-positive, aggressive, epidermotropic, cytotoxic T-cell lymphoma
Primary cutaneous acral CD8-positive 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
Systemic EBV-positive T-cell lymphoma of childhood
Hydroa vacciniforme-like lymphoproliferative disorder
Precursor lymphoid neoplasms
B-cell lymphoblastic leukemia/lymphoma (either NOS or seven subtypes with recurrent cytogenetic abnormalities)
T-cell lymphoblastic leukemia/lymphoma

NOTE: This table includes only the mature and precursor lymphoid neoplasms. Posttransplant lymphoproliferative disorders and histiocytic and dendritic cell neoplasms are not included in this table for reasons of simplicity
NOTE: The provisional entities are shown in italics
*NOS = not otherwise specified

abdominal disease, and pathological staging was gradually substituted by clinical staging. However, there were still normal-sized nodes on CT, which were involved by the disease. Bipedal lymphangiography could provide a qualitative means to identify infradiaphragmatic disease at that time. Despite false negatives by CT scanning, technical difficulties and the more common use of systemic chemotherapy led to the abandonment of lymphangiography.

CT remained the gold standard for staging of malignant lymphomas for many years. MRI and

ultrasonography (US) could be used for further evaluation of certain CT findings, and bone scanning was used for the evaluation of osseous disease in patients with relevant symptoms. However, CT cannot reliably assess the significance of residual masses after the end of therapy, which are very common in HL, PMLBCL, and DLBCL and may occur in almost every disease subtype. Gallium scanning has been traditionally used for the evaluation of the presence of viable lymphoma in residual masses, although its accuracy was relatively limited. The introduction of positron emission tomography (PET scan and PET/CT scan) during the recent years provided a much more reliable tool for response assessment and evaluation of residual masses. PET/CT also provided a very sensitive means for accurate baseline staging, due to its unique ability to detect sites of extranodal disease as well as involved lymph nodes of normal size [5–8].

In everyday practice, "clinical staging" according to the Ann Arbor or Lugano system is based on clinical examination, chest X-rays, whole-body CTs (except the brain), and bone marrow biopsy. Specific studies, including MRI, US, brain imaging (CT and/or MRI), bone scanning, upper and lower GI endoscopy, etc., are performed in the appropriate clinical setting. Recently, 18-fluoro-deoxy-glucose (18-FDG) positron emission tomography combined with CT (PET/CT) has been strongly recommended for staging and evaluation of response to therapy in various lymphoma subtypes, mainly HL and aggressive B-cell lymphomas, but also in all 18-FDG avid lymphoma subtypes (see relevant chapter) [6–8].

This chapter aims to review the contribution of each of these methods in lymphoma imaging, acknowledge their limitations, and summarize recent clinical results related to the application of novel imaging methods, mainly PET/CT.

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