Opinion statement

We are increasingly successful in the treatment of Hodgkin lymphoma. Current risk adapted trials seek to maintain the excellent efficacy of older therapies, while simultaneously limiting their late toxicities. Current management of early stage/favorable disease involves the use of two to four cycles of tailored chemotherapy, often followed by low-dose, involved field radiation. Those with intermediate and advanced stage disease require more intense chemotherapy and radiation regimens. Functional imaging using $[\text{^{18}F}]$-2 fluoro-D-2-deoxyglucose is increasingly used to determine complete vs. partial response and to detect relapse. Given the success of primary therapy, retrieval of patients remains a highly individualized challenge. The majority of children failing combined-modality treatment undergo high-dose chemotherapy followed by autologous hematopoietic stem cell rescue, oftentimes with consolidative radiotherapy.

Evolution of treatment for pediatric Hodgkin lymphoma

The story of pediatric Hodgkin lymphoma has been one of continual success. Originally a uniformly fatal disease, the use of radiotherapy provided the first successful treatment. By the 1960s, high-dose, extended field irradiation was standard for pediatric and adult patients. This treatment, while largely successful, was associated with growth abnormalities in children. The subsequent development of MOPP [mechlorethamine, oncovin (vincristine), procarbazine, prednisone] chemotherapy and recognition of the late sequellae of radiotherapy prompted the first combined-modality trials which sought to determine if chemotherapy could replace a portion of the requisite radiotherapy. By the 1980s, treatment strategies had evolved to include several cycles of multi-agent chemotherapy with low-dose radiotherapy given only to sites of initial disease (i.e., involved field radiotherapy). With increasing emphasis on systemic therapy, advances in diagnostic imaging and recognition of the complications of surgical staging with splenectomy, the staging laparotomy was abandoned and clinical staging adopted. ABVD [Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine] chemotherapy was developed as an alternative to MOPP, whose toxicities of male infertility and often fatal secondary leukemia were being realized. The first trials of hybrid MOPP/ABVD chemotherapy and involved field radiation therapy were devised, with exposure to any individual agent minimized, in an effort to lessen toxicity while preserving efficacy.

From the 1990s through today, the main focus of clinical research in pediatric Hodgkin lymphoma has
been to minimize toxicity while preserving the excellent event-free (EFS) and overall survival (OS) seen with older therapies. In general, this has required the use of multi-agent chemotherapy with radiotherapy, in a risk- or response-adapted approach. Patients with “favorable” or low-risk disease are generally given 2–4 cycles of combination chemotherapy with a limited exposure to alkylating agents and cardiopulmonary toxins, and a minimum of radiotherapy. For those “unfavorable” patients with more advanced disease, dose-intense, combination chemotherapies are utilized, with radiotherapy given to involved sites, or those of initial disease.

### Staging

- The most widely utilized staging system for pediatric Hodgkin lymphoma is the Ann Arbor Staging system. This staging system divides lymph node regions into nodal sites (i.e., neck, axilla, mediastinum, etc.) and stage is then determined by the number of involved sites. Stage I disease involves only a single nodal site, whereas Stage II involves several sites which lie together on one side of the diaphragm. Stage III disease spans the diaphragm and stage IV is disseminated systemic disease. Additional modifiers include: A or B, to describe the absence or presence of systemic symptoms; and E, the involvement of extra-nodal extension of Hodgkin lymphoma. The presence of bulky mediastinal disease, described as greater than 1/3 the intra-thoracic diameter, is also considered.

- Following the abandonment of the staging laparotomy, clinical staging has become standard. Routine clinical staging includes a complete history and physical examination, with attention to all nodal sites. Laboratory assessment includes complete blood count with differential, serum chemistry including albumin, lactate dehydrogenase and alkaline phosphatase, erythrocyte sedimentation rate, or C-reactive protein (CRP). Radiographic studies include chest X-ray, computed tomography (CT) of the neck, chest, abdomen, and pelvis. Bone marrow biopsy is reserved for those patients with systemic (B) symptoms or stage III–IV disease. Functional imaging is being used increasingly in the staging and follow-up of patients, with the older gallium-67 scan is being replaced by $[^{18}F]_2$ fluoro-D-2-deoxyglucose positron emission tomography (PET). PET has been especially helpful in assessing response to treatment, where persistent metabolic activity may indicate persistent disease. Bone scan and MRI are used selectively.

### Histology

- The World Health Organization classification system separates Hodgkin lymphoma into two broad categories: “Classical,” comprising lymphocyte depleted, nodular sclerosing, mixed cellularity, and classical lymphocyte rich; and “Lymphocyte predominant” Hodgkin lymphoma. Ninety percent of new cases of Hodgkin lymphoma are of the “Classical” type, characterized by the presence of CD15 and CD30-positive Reed-Sternberg cells. Although there are immunohistological differences between subtypes of classical Hodgkin lymphoma, response to treatment is similar.

- By contrast, Lymphocyte-predominant Hodgkin lymphoma (LPHD), previously known as paragranuloma, is a subtype of CD20-positive Hodgkin lymphoma in which the predominant lymphocytic and histiocytic (L&H) cells express markers not typically seen in “classical” Hodgkin lymphoma (B-cell: CD20, CD79a, CD75, Epithelial membrane antigen, Lymphocyte: CD45). This difference in pathology is