ABOUT THE AUTHOR

Shruthi Kodad, DNB, FHO
Dr. Shruthi Kodad completed her Internal Medicine residency and Fellowship in Hematology at Narayana Health, Bangalore, India before joining the Leukemia/BMT Program of British Columbia as a Clinical Fellow in 2016. After two years of Fellowship, she worked as a Clinical Associate at the Saskatoon Cancer Centre until 2021. She is now working as a Transplant Hematologist at the Saskatoon Cancer Centre. She has clinical and research interests in lymphoid malignancies, chronic lymphocytic leukemia, autologous and allogeneic stem cell transplants and long-term complications of stem cell transplantation

Affiliations:
University of Saskatchewan
Saskatchewan Cancer Agency

MANAGEMENT OF LIMITED STAGE HODGKIN LYMPHOMA

Introduction

Hodgkin lymphoma (HL) is a lymphoid neoplasm characterized by malignant lymphocytes, known as Reed-Sternberg cells, on a background of non-neoplastic inflammatory cells. Lugano staging[1] (**Table 1**) determines the stage of Hodgkin lymphoma, which, in turn, determines the treatment and prognosis. Limited-stage disease is defined as Stage I and Stage II, which is diagnosed in more than 50% of patients.[2] Pre-treatment risk stratification, PET-adapted therapy, and combined modality treatment have significantly improved cure rates, making limited-stage HL one of the most curable malignancies.[3] In this article, we discuss the current approach to managing limited-stage HL.

Staging and Risk Stratification

Accurate staging and risk assessment are crucial for proper assignment to a risk group and making informed treatment decisions in HL. Lugano classification for the staging of lymphomas includes Stage I to Stage IV (**Table 1**). Patients with Stage I and Stage II are classified as limited or early-stage disease. PET/CT is recommended for initial staging in the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) HL guidelines,[4] and Lugano classification.[1] In a retrospective analysis, PET, in addition to a contrast-enhanced computed tomography (CT) scan, upstaged the disease in up to 25% of patients.[5] The improved sensitivity and specificity of PET/CT enable the elimination of the initial bone marrow biopsy for patients with normal [18F]FDG uptake in the bone marrow.[6]

Stage I – Involvement of a single lymph node region (I) or a single extra lymphatic organ or site (IE)
Stage II – Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extra lymphatic organ or tissue (IIE)
Stage III - Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm; nodes above the diaphragm with spleen involvement
Stage IV - Diffuse or disseminated involvement of 1 or more extranodal organs or tissue beyond that designated "E," with or without associated lymph node involvement
All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant unexplained fever, night sweats or unexplained weight loss exceeding 10% of body weight during the six months before diagnosis.
Bulky disease: A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or ≥ one-third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT.

Table 1. *Lugano classification for staging of lymphomas*[1]

Patients with limited Stage (I to II) disease are further divided into favourable and unfavourable prognosis categories based on specific clinical features such as age; B symptoms; erythrocyte sedimentation rate (ESR); number of involved sites (the definition of the involved site differs in each group classification); sizeable mediastinal mass; bulky disease; and extranodal disease. Various cooperative research groups have employed differing definitions for favourable and unfavourable prognosis disease (**Table 2**).

German Hodgkin Study Group (GHSG)[7,8]
Large mediastinal adenopathy (> one-third maximum transverse thoracic diameter)
More than 2 involved sites
A defined combination of B symptoms and elevated ESR: B symptoms and an ESR over 30 mm/hour; an ESR over 50 mm/hour without B symptoms
Extranodal extension, i.e., any tumor spread involving tissues other than those of the lymph nodes; spleen; thymus; Waldeyer's tonsillar ring appendix; and Peyer's patches
European Organization for the Research and Treatment of Cancer (EORTC)[9]
The mediastinal mass ratio (maximum width of mass/maximum intrathoracic diameter) of >0.35 at T5-T6
Three or more involved sites
Age ≥50 years at diagnosis
A defined combination of B symptoms and elevated ESR: B symptoms and an ESR over 30 mm/hour or an ESR over 50 mm/hour without B symptoms
National Cancer Institute of Canada (NCIC)/Eastern Cooperative Oncology Group (ECOG)[10]
Mediastinal mass ratio >0.33 or a mass >10 cm
More than 3 involved sites
Age ≥40 years at diagnosis
ESR >50 mm/hour
Mixed cellularity histology
National Comprehensive Cancer Network (NCCN)[11]
Bulky disease
Extranodal extension
ESR >50 mm/hour
More than 3 involved sites

Table 2. *Unfavourable risk factors according to GHSG, EORTC and NCIC groups*[7-11]

A retrospective analysis was conducted of 1,173 patients diagnosed with early-stage classical Hodgkin lymphoma, comparing the GHSG, EORTC and NCCN models. The results demonstrated that the three models had similar prognosis classifications for patients with early-stage cHL(Classical HL), with 56%, 55%, and 57% classified as having an unfavourable prognosis, respectively.[12]

Treatment Modalities

Limited stage – Favourable

Radiation therapy (RT) and combined modality therapy (CMT), which includes chemotherapy and RT, result in a cure for most patients with favourable limited-stage HL. However, RT results in high rates of long-term complications, including the risk of secondary cancers and cardiovascular toxicities.[12] To minimize the adverse side effects associated with treatment, recent clinical studies have explored response-based approaches and the use of newer drugs to decrease the strength of conventional chemotherapy and/or RT.[9]

Non-PET adapted approach

The GHSG (German Hodgkin Study Group) HD7 trial reported superior progression-free survival (PFS) with CMT compared to extended field RT alone; however, it did not demonstrate any overall survival (OS) benefit. Treatment-related complications, including secondary solid tumors and pulmonary and cardiovascular diseases, accounted for the majority of deaths.[13] To reduce these complications, subsequent trials explored reducing the dose of RT, as well as the number of cycles of chemotherapy. The GHSG HD10 trial compared 4 groups: 4xABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and 30Gy radiation therapy (RT), 4xABVD and 20 Gy RT, 2xABVD and 30Gy RT and 2xABVD and 20Gy RT. A recent long-term clinical trial follow-up demonstrated that 2xABVD and 20-Gy RT was non-inferior to 4xABVD and the 30-Gy group, reporting a PFS of 87% each and OS of 94% each.[13] The GHSG HD13 trial demonstrated that omission of bleomycin and/or dacarbazine resulted in a significant reduction in tumor control.[14]

PET adapted approach

In the GHSG HD16 clinical trial, patients received 2x ABVD and 20Gy IFRT or PET-guided treatment without IFRT after negative PET-2. The CMT group demonstrated a five-year PFS of 93.4% vs 86.1% in the chemotherapy-only group.[15] Similar results were seen in the United Kingdom RAPID trial[16] and the EORTC H10F trial[9]. In the EORTC H10 trial, Stage I-II HL favourable risk patients were randomized between control arm therapy with ABVD x3 + involved node RT (INRT), with all patients undergoing PET following 2 cycles of ABVD. In the experimental arm (no INRT group), patients received ABVD x2, then a PET scan, followed by ABVD x 2 if it was negative, and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) escalated x 2 plus INRT if positive. In the PET negative group and experimental arm, the difference in PFS was 11.9%, not meeting the non-inferiority endpoint. There was no difference in OS. For patients with PET-positive

disease, the 5-year PFS was 77% vs 91% (P=0.002) and the 5-year OS was 89% vs 96% (P=0.06), favouring escalated BEACOPP compared to ABVD + INRT.[9]

Both the UK RAPID and EORTC H10 trials support the use of radiotherapy despite a negative interim PET. Based on these large international trials, the NCCN and ESMO guidelines recommend CMT with 2 x ABVD with 20-Gy RT in limited stage favourable HL. For PET positive patients after 2 xABVD, the ESMO guidelines recommend 2x escalated BEACOPP plus 30-Gy involved site radiation therapy (ISRT).[4] However, the difference in PFS was small, and there was no OS advantage. Based on these findings, radiotherapy can be omitted in certain patients based on their therapeutic goals and characteristics, thereby avoiding long-term RT sequelae such as secondary malignancies. Case examples include patients with cardiovascular comorbidities receiving a cardiac RT, or avoidance of mediastinal lymph node region RT in young women.[2]

Limited stage – Unfavourable

Non-PET adapted approach

The GHSG HD 11 clinical trial concluded that 4 cycles of ABVD should be followed by 30Gy RT; and that moderate dose escalation using BEACOPP (baseline) did not significantly improve outcomes in limited-stage unfavourable disease.[8] However, the HD14 trial demonstrated intensified therapy with 2 x escalated BEACOPP, and 2 X ABVD (2+2) followed by IFRT significantly improved tumor control. The 2 +2 approach is associated primarily with acute hematologic toxicity; however, no long-term toxicity or effect on OS has been demonstrated to this point.[3]

PET adapted approach

In the H10U trial, 79.9% of patients demonstrated PET 2 negativity. This suggests that PET after 2 cycles of ABVD might help to individualize treatment in a subset of patients with bulky mediastinal disease, or in those who are PET 2 positive in need of an intensified treatment.[9] The H10U study indicates that intensified therapy consisting of 2 cycles of ABVD followed by 2 cycles of escalated BEACOPP, along with 30-Gy INRT, is more effective vs the standard 4 cycles of ABVD and 30-Gy INRT in patients who are PET-2 positive. It is important to note that the majority of patients in the H10 group (77.8% who were PET-2 negative) could still be treated effectively with only 4 cycles of ABVD.[9] A preliminary analysis of the HD 14 trial revealed a decrease in the ovarian reserve; however, no significant differences in female fertility potential after two cycles of escalated BEACOPP and two cycles of ABVD, compared with four cycles of ABVD.[17]

The NCCN and ESMO guidelines recommend 4 cycles of multi-agent chemotherapy followed by 30-Gy IFRT or ISRT for patients with limited stage unfavourable disease. Both 2+2 and 4x ABVD are cited as relevant strategies. A PET-guided strategy similar to that of H10U is recommended by the ESMO guidelines.[11,18] BEACOPP is used only in patients <60 years of age with no comorbidities, and in younger patients following patient counselling regarding the risks of decreased ovarian reserve.

Elderly Hodgkin lymphoma

Prospective trial data are lacking in this population sub group. Intensive regimens such as BEACOPP are not recommended due to increased treatment-related mortality. Two cycles of ABVD combined with 20-Gy IF/ISRT is a viable and successful treatment option for elderly patients with early-stage favourable Hodgkin lymphoma.[19] Four cycles of ABVD have been linked to a significant rate of severe side effects, particularly hematotoxicity and lung toxicity related to bleomycin, leading to an increased risk of treatment-related mortality compared to only 2 cycles of ABVD.[20] In patients with early-stage unfavourable Hodgkin lymphoma, a safer treatment approach is 2 cycles of ABVD followed by 2 cycles of AVD and 30-Gy IF/ISRT. Gunther et al demonstrated that partial omission of bleomycin resulted in a 99% freedom from relapse at 8 years.[21]

Conclusion

The majority of patients with early-stage HL can now be cured with a risk-adapted approach. PET-adapted strategies have been tested to reduce treatment-associated toxicity, which involves reducing RT fields. Long-term survival rates for patients with a favourable risk profile are excellent with ABVD plus 20-Gy ISRT or INRT. Patients in the unfavourable risk group typically receive 4 cycles of multi-agent chemotherapy plus 30-Gy limited-field RT. When optimal tumor control is the primary objective, escalated BEACOPP followed by ABVD (2 +2) is preferred over ABVD. For patients who prioritize the reduction of treatment-associated toxicity, a PET-guided chemotherapy strategy with escalated BEACOPP administered only in PET-positive patients after 2 initial cycles of ABVD is an effective and less toxic alternative to 2+2. Consolidative RT can improve disease control in early-stage HL; however, the omission of RT might be possible in selected patients with PET-negative disease (**Figure 1**). In patients >60 years of age, omission of bleomycin after 2nd ABVD is recommended.

Correspondence:
Dr. Shruthi Kodad
Email: Shruthi.Kodad@saskcancer.ca

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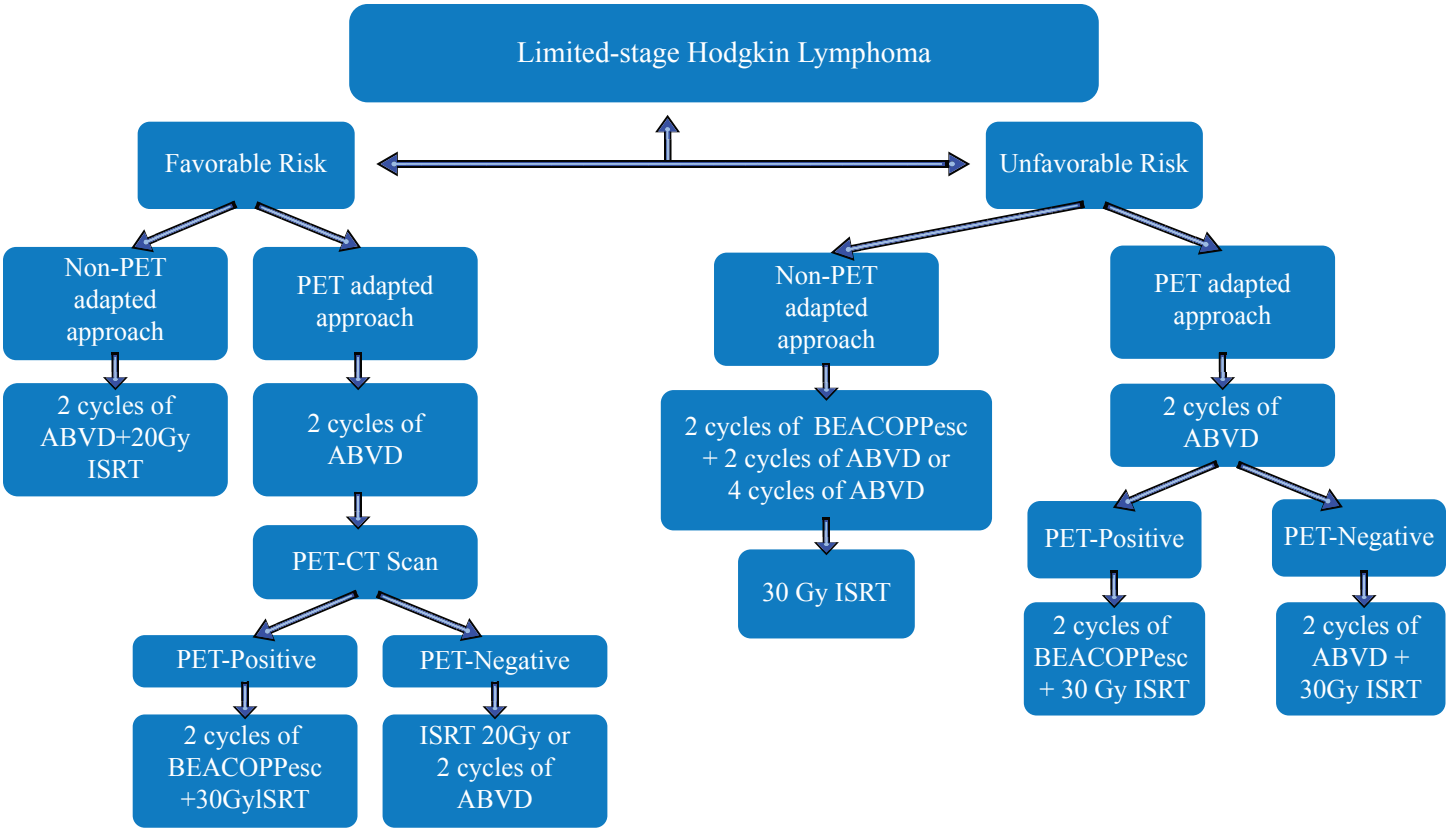

Figure 1. *Non-PET approach based on GHSG HD10[13] and GHSG HD14[3] clinical studies, and PET- guided approach based on EORTC/LYSA/FIL/ H10 studies;[9] Adapted from ESMO guidelines.[4]*

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