



**PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES**

LYMPHOMA

HODGKIN LYMPHOMA

Site Group: Lymphoma – Hodgkin Lymphoma

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1. Introduction

Hodgkin lymphomas are a relatively uncommon subset of malignant lymphomas that affect mainly young adults, although they also arise in children and older populations as well. This guideline relates to the management of these disorders currently at the Princess Margaret Cancer Centre.

2. Prevention

There are no established prevention strategies for Hodgkin lymphoma.

3. Screening and Early Detection

Screening and early detection do not play a role in the management of Hodgkin lymphoma.

4. Diagnosis

The diagnosis of Hodgkin lymphoma (HL) is dependent on histologic assessment of a surgically acquired incisional or excisional biopsy of an involved lymph node or other extra-nodal tissue, to ensure adequate evaluation based on morphology and immunohistochemistry. Unlike other lymphoma subtypes, flow cytometry and cytogenetic assessment do not have an important role in diagnosis of HL. Increasingly, core biopsies obtained under image guidance (CT scan or ultrasound) are used to obtain diagnostic material; such biopsies may be supplemented by fine needle aspiration for immunohistochemical analysis. However, surgical biopsies are preferred when possible in view of the scarcity of neoplastic cells that characterizes HL. The following immunohistochemical panel is advised for HL: CD20, CD3, CD15, CD20, CD30, CD79a, EBER(ISH). The B-cell markers in this panel are important to rule out B cell lymphoma that may look like HL, such as EBV+ large B-cell lymphoma or gray zone lymphoma and to properly diagnose nodular lymphocyte predominant HL. OCT2 immunohistochemistry may be added to the panel in difficult instances of nodular lymphocyte predominant HL. Histological variants of nodular lymphocyte predominant HL should be mentioned in the report, in view of diminished prognosis when compared to the typical disease.

Bone marrow aspiration and biopsy are not required for patients who are staged using (contrast-enhanced) FDG-PET scanning, although may be indicated in patients with uncertain imaging findings or unexplained cytopenias. On rare occasions, bone marrow may represent the primary biopsy site for final diagnosis.

5. Pathology

Patients are treated based on a diagnosis conforming to those described according to World Health Organization criteria, most often after primary evaluation or pathology review by an expert Hematopathologist at the University Health Network.

Histologies:

Nodular lymphocyte predominant HL

Classical HL

- Lymphocyte rich classical HL
- Nodular sclerosis classical HL
- Mixed cellularity classical HL
- Lymphocyte depleted classical HL

6. Management

6.1 Management Algorithms

Staging Investigations:

- Full history and physical examination including performance status
- CBC, ESR, albumin, LDH, LFTs, creatinine,
- CT head and neck, thorax, abdomen, pelvis
- FDG-PET scan (may be combined with contrast-enhanced CT scan)
- MUGA or 2D echocardiogram (in patients at risk for cardiac dysfunction from anthracyclines)
- Additional imaging test(s), e.g. MRI, bone scan, ultrasound, as determined by symptoms or clinical situation
- BM aspirate and biopsy are not routinely required, unless one or more of the following are present: no baseline FDG-PET scan, abnormal CBC (cytopenias), uncertain imaging findings (e.g., to distinguish reactive bone marrow from extensive involvement with HL)
- HBV surface antigen, surface and core antibody, HCV antibody; HIV test if risk factor(s) present
- Review of Pathology by UHN hematopathologist as required

Stage I/II HL

All patients with limited stage cHL should be considered candidates for risk-adapted treatment based on extent of disease and results of interim FDG-PET scanning after 2 cycles of chemotherapy (most often ABVD; for selected unfavourable presentations, escBEACOPP) as defined below:

Two definitions of early favourable HL have been used in recent trials of therapy for patients with stage I and II HL: the presence of any one of the listed risk factors defines the presentation as unfavourable:

GHSB criteria for early favourable HL: absence of:

- Large mediastinal mass ($>1/3^{\text{rd}}$ of maximum intrathoracic diameter)
- ESR ≥ 50 without B symptoms or ESR ≥ 30 with B symptoms
- Extranodal disease
- 3 or more lymph node areas involved (GHSB definition)

EORTC criteria for early favourable HL: absence of:

- age ≥ 50
- 4 or more nodal areas involved (EORTC definition)
- M-T ratio ≥ 0.35
- ESR ≥ 50 (B symptoms: ≥ 30)

Early Stage Favourable presentation

For all presentations, interim response assessment by FDG-PET scan is recommended.

- 1) Involved sites limited to neck, supraclavicular fossa, or other factors associated with low risk of late secondary cancer from radiation (e.g., males, age >40 years):

ABVD x 2 cycles and 20Gy involved site RT in 10-12 fractions

- 2) All other presentations:

ABVD x 2 cycles, assess interim response with FDG-PET scan: (day 11-14 of cycle 2)
Complete metabolic response (Deauville five-point score 1-3): continue with 2 additional cycles of ABVD without radiation (for those with higher risk of late secondary cancer, cardiovascular disease based on lymph node distribution, young age)

Or ABVD x 1 cycle + involved site radiation 30-36 Gy

Partial response (Deauville 4,5): escalate chemotherapy with 2 cycles escBEACOPP + involved field (node) radiation 30-36 Gy

Early Stage Unfavourable presentation:

ABVD x 2 cycles assess interim response with FDG-PET scan: (day 11-14 of cycle 2 of ABVD)

Complete metabolic response (Deauville five-point score 1-3), continue with 4 additional cycles of ABVD or AVD without radiation (for those with higher risk of late secondary cancer, cardiovascular disease based on lymph node distribution, young age)

Or ABVD x 2 cycles + involved site radiation 30-36 Gy

Partial response (Deauville 4,5): escalate chemotherapy with 2 cycles escBEACOPP + involved field (node) radiation 30-36 Gy

For some patients with early unfavourable cHL, initial therapy with two cycles of escBEACOPP followed by 2 ABVD may be appropriate; such patients do not require interim PET imaging and should have response assessed with FDG-PET after completing four cycles of chemotherapy. Omission of radiation has been shown to be non-inferior to CMT for those with a negative end of treatment PET scan, while those with a positive scan should complete IFRT as described in GHSG study HD17.

Nodular Lymphocyte Predominant HL

For patients with stage I, low bulk (< 5 cm) in peripheral nodal area: Involved site RT 30-35 Gy in 20 fractions

All other stage I-II NLPHL: treat with combined modality therapy according to GHSG criteria as favourable or unfavourable, as these patients were excluded from PET-adapted studies:

Favourable presentation: ABVD x 2 cycles + 20 Gy ISRT

Unfavourable presentation: ABVD x 4 cycles + 30 Gy ISRT

Stage IIB with risk factors, III and IV Classical HL

Treatment approach for patients with advanced cHL (GHSG criteria, including stage IIBE) may vary depending on prognostic factors (Hassenclever-Deihl index), age, patient preference, risk of infertility, and comorbidities.

1) ABVD-based approach:

ABVD x 2 cycles, assess interim response with FDG-PET scan (day 11-14 of cycle 2):

Complete metabolic response (Deauville score 1-3): consider omission of bleomycin and treat with AVD x 4 additional cycles

Partial metabolic response (Deauville score 4,5): escalate chemotherapy to escBEACOPP x 4 cycles

2) escBEACOPP-based approach:

escBEACOPP x 2 cycles, assess interim response with FDG-PET scan (day 17-21 of cycle 2):

Complete metabolic response (Deauville score 1-3): continue treatment with 2 additional cycles escBEACOPP *OR* de-escalate treatment and continue with ABVD x 4 cycles

Partial metabolic response (Deauville score 4,5): continue treatment with escBEACOPP x 4 cycles

3) Brentuximab vedotin +AVD for stage IV cHL (for selected patients age <65 with contraindications to therapy escalation)

All patients with advanced cHL should have an end-of-treatment PET scan to determine final response, the need for involved-site radiation for residual FDG-positive sites of disease (as reported in GHSG study HD15) or to direct further investigations and treatment.

Additional considerations:

The ABVD-based approach is based on the UK RATHL trial and SWOG0816, where involved field radiation was not planned as part of protocol therapy for patients with bulky disease or residual FDG-avid masses at the end of therapy. IFRT to areas of FDG uptake at end of treatment was standard in the GHSG HD15 and HD18 studies (regardless of the results of cycle 2 PET in HD18), and is considered appropriate as part of overall management of selected patients with advanced HL regardless of chemotherapy approach.

Stage III and IV nodular lymphocyte predominant HL (NLPHL)

RCHOP X 6

Standard treatment for advanced stage NLPHL has generally been similar to that of cHL, as many previous trials that defined therapy included this histologic subtype (eg HD9, HD15, HD18). However, a number of reports suggest that the outcome of treatment of stage III and IV NLPHL with ABVD appears inferior to that observed in patients with cHL receiving the same therapy. The expression of CD20 on the malignant cells in NLPHL and the activity of rituximab in relapsed and refractory disease suggests that combination chemoimmunotherapy (eg R-CHOP) may be an effective strategy in this uncommon subgroup of patients with HL, although controlled trials of this approach are lacking.

Current evidence suggests that FDG-PET based treatment as described for advanced cHL may also be applied to patients with stage III and IV NLPHL.

6.2 Surgery

Surgery does not play a role in the primary management of most patients with aggressive

lymphoma, outside of the need for an adequate excisional biopsy for accurate diagnosis.

6.3 Chemotherapy

Chemotherapy regimens for Hodgkin lymphoma

	ABVD		BEACOPP		escBEACOPP	
	Dose*	Days	Dose*	Days	Dose*	Days
Bleomycin	10	1, 15	10	8	10	8
Etoposide	-	-	100	1-3	200	1-3
Doxorubicin	25	1,15	25	1	35	1
Cyclophosphamide	-	-	650	1	1200	1
Vincristine	-	-	1.4	8	1.4	8
Procarbazine	-	-	100	1-14	100	1-7
Prednisone	-	-	40	1-14	40	1-14
Vinblastine	6	1,15	-	-	-	-
Dacarbazine	375	1,15	-	-	-	-

* Doses per m²

For patients receiving escBEACOPP, prophylaxis to prevent PJP infection with trimethoprim-sulfamethoxazole (sepra) three times per week and a fluoroquinolone (ciprofloxacin) during the expected neutrophil nadir is recommended. Dose reductions for grade 4 neutropenia (absolute neutrophil count < 0.5 on 2 successive measurements), thrombocytopenia (< 25), infection (febrile neutropenia) are shown below; if episodes of hematologic toxicity recur despite dose reduction, remaining cycles should be given at baseline doses (see table above).

Drug	Application	Day of cycle	Dose level (starting at escalated level)				
			escalated	level 3	level 2	level 1	baseline
Cyclophosphamide	i.v.	1	1,250	1,100	950	800	650
Doxorubicin	i.v.	1	35	35	35	35	25
Etoposide or etoposide phosphate*	i.v.	1-3	200	175	150	125	100
Procarbazine	p.o.	1-7			100		
Prednisone	p.o.	1-14			40		
Vincristine	i.v.	8		1.4 (max. 2 mg total)			
Bleomycin	i.v.	8			10		
G-CSF (daily or pegylated)	s.c.	(from) day 4					

Data are mg/m², unless otherwise indicated. *113 mg etoposide phosphate is equivalent to 100 mg etoposide. This difference is due to different molecular weights.

6.4 Radiation Therapy.

Involved-site RT

The target volume will include the lymph node region or regions initially involved by the disease. Uninvolved nodal regions are not covered intentionally, but partial coverage of these regions may result from the allowance of adequate margins for the involved nodal region(s).

- Uninvolved lung hila need not be covered
- Uninvolved cervical lymph nodes above the level of the larynx need not be routinely covered
- Uninvolved subcarinal and posterior mediastinal lymph nodes need not be covered

6.5 Oncology Nursing

Refer to [general oncology nursing practices](#)

7. Supportive Care

7.1 Patient Education

Young adults

- Fertility preservation should be offered to all patients if age appropriate, in advance of treatment, if it is considered safe to allow a 2-3 week delay in starting chemotherapy.
- Referral to Adolescent & Young Adult (AYA) Program for psychosocial and other supports

Refer to [general patient education practices](#)

7.2 Psychosocial Care

Refer to [general psychosocial oncology care guidelines](#)

7.3 Symptom Management

Venous thromboembolism (VTE) prophylaxis

For patients with new VTE and active lymphoma:

- Treatment with either LMWH or DOACs are acceptable (preferred DOAC edoxaban 60mg PO OD)
- Continue until complete remission and resolution of thrombosis, or indefinitely

Refer to [general symptom management care guidelines](#)

7.4 Clinical Nutrition

Refer to [general clinical nutrition care guidelines](#)

7.5 Palliative Care

Refer to [general oncology palliative care guidelines](#)

8 Follow-up Care

Follow up guidelines: Hodgkin Lymphoma

Response assessment and monitoring for recurrence:

Response assessment at 1 month post treatment:

- Document with P/E, contrast-enhanced CTs of head and neck/chest/abdo/pelvis and FDG-PET/CT scan following completion of chemotherapy or radiation

At each subsequent visit:

- Document history and physical examination, residual toxicity, measure CBC if blood counts have not returned to normal at prior visit, (add TSH every 6 months if radiation to thyroid gland). Consider repeat imaging study only if new symptoms suggesting possible disease recurrence. Patients with previously demonstrated stable post-treatment masses need not be followed with CT scan if asymptomatic.
- Counseling re: physical and psychological health issues, including impact of treatment on quality of life, reproduction, cardiovascular fitness, risk of recurrence, and risk of second malignancy. Smoking cessation for smokers. Attention to screening for breast, colorectal, and lung cancers (patient may be study-eligible).
- Ensure appropriate advice and care from family doctor or cardiologist re: cardiac risk factors and strategies to minimize risk (smoking cessation, BP, cholesterol, lipids, exercise, weight control), particularly for patients who received mediastinal radiation. Consider cardiac stress test for 10-year survivors who received mediastinal RT, particularly if other cardiac risk factors present.
- For women who received involved field radiation therapy which included breast tissue (axilla, infraclavicular, mediastinal): screening mammography and MRI starting 8-10 years post treatment. MRI + mammogram is recommended for women until age 50; subsequent screening of women over age 50 can be screened with mammography alone.

Oncology Clinic Follow-up Frequency:

First year	-	Visits every 3 months
2 - 3 years	-	Visits every 4 months
4 - 5 years	-	Visits every 6 months
> 5 years	-	annual follow up

Patients who have had combined modality therapy will alternate follow up visits between attending medical oncologist/hematologist and radiation oncologist. Family physicians are encouraged to participate in the follow up as outlined, particularly for visits beyond 5 years from treatment. The majority of patients may be discharged to the care of their primary care practitioner by 10 years post-treatment.

Second malignancy screening:

- Breast cancer screening for women age < 40 years at time of completion of combined modality therapy including radiation to the chest (mediastinum, infraclavicular nodes, axillary nodes) should commence breast cancer screening as described above
- Routine primary care follow-up and screening practices are recommended for other potential secondary cancer sites

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