

CHAPTER 11 HODGKIN LYMPHOMA

11.1 Introduction

Hodgkin lymphoma (HL) is one of the best-characterised malignancies of the lymphatic system and one of the forms of malignant disease most readily curable by radiotherapy, chemotherapy or a combination of the two. Modern treatment methods routinely achieve such high cure rates that a very strong emphasis is now placed on achieving cure with the least possible risk of complications from therapy. HL is often portrayed as a model for successful treatment of malignancy. The valuable lessons learned from this disease have been usefully applied to other cancers.

11.2 Incidence of Hodgkin lymphoma in Australia

In 2001, there were 401 new cases of HL in Australia. It was more common in males than females (218 and 183 respectively). The age distribution showed a bi-phasic curve, with an early peak in adolescence to young adulthood, and a later smaller peak at around 50 years of age. During 1992–1997, five-year relative survival was approximately 83%. This was significantly better than the survival recorded during 1982–86. Relative survival from HL in Australia is good compared to many other developed countries.¹

11.3 Pathogenesis and aetiology of Hodgkin lymphoma

Despite its early recognition as a disease entity, the pathogenesis of HL is not fully understood. It is widely considered to originate from cells of the B lymphocyte series, and the neoplastic cell may be a crippled germinal centre cell.² The cause of HL is also unclear, but a strong association with Epstein Barr virus (EBV) has been reported³, and the disease may occur as a complication of HIV infection.⁴ Although most cases are sporadic, clusters of cases from certain geographic regions have been reported⁵, as have familial cases of HL.⁶ No methods for prevention of HL have been shown to be effective, although measures to prevent the spread of HIV infection should prevent some cases at least. It has been suggested that a vaccine against EBV could play a role in prevention of HL, but this has not yet been proven.

11.4 Pathology of Hodgkin lymphoma

The importance of an adequate biopsy cannot be stated too highly. Diagnosis can only be made with confidence when a representative lymph node is sampled and the pathologist has specialist knowledge and experience of lymphomas. Classically, HL is manifest by the presence of typical Hodgkin or Reed-Sternberg cells in a background of a mixed inflammatory cell infiltrate. Often the neoplastic cells are present in relatively small numbers compared to the infiltrating cells. In the WHO classification⁷, the following subtypes of HL are described;

- 1 Lymphocyte predominance Hodgkin lymphoma (LPHL)
- 2 Classical Hodgkin lymphoma
 - nodular sclerosis Hodgkin lymphoma (NSHL)
 - mixed cellularity Hodgkin lymphoma (MCHL)
 - lymphocyte depletion Hodgkin lymphoma (LDHL)
 - lymphocyte-rich classical Hodgkin lymphoma (LRCHL)

11.5 Summary of clinicopathological features

11.5.1 Nodular lymphocyte predominant Hodgkin lymphoma

Clinical	30–50. Male > female. Cervical, axillary or inguinal lymph nodes. Slow onset. Often solitary — stage I or II. Rarely may be disseminated at presentation.
Morphology	Nodular or nodular and diffuse. Purely diffuse subtype questionable. A single typical area is diagnostic. L&H, ‘popcorn’ variant of H-RS cell within large, B-cell rich and FDC +ve nodules, often with a peripheral wreath of histiocytes. May have associated progressive transformation of germinal centres (PTGC).
Immunophenotype	L&H cells: CD20, CD79a, <i>bcl-6</i> , BSAP and CD45+ve Also EMA, CD75, J chain, Oct2 and BOB.1 +ve. CD30 usually –ve. TARC, CD15, Fascin, LMP1, EBER –ve Background cells: CD20 +ve small B-cells. T-cells are present in small numbers and CD57+ve. CD21/23/35+ve FDCs form networks in the nodules. DD: Lack of FDCs or T-cell rich environment suggests T-cell rich B-cell lymphoma.
Genetics	Follicle centre B-cell origin with somatic hypermutation and functional transcripts. Monoclonal but not often detectable, except by single cell PCR. Florid PTGC may be clonal but only within a given follicle.
Behaviour	Stage I or II >80% ten-year survival. Progression to diffuse large B-cell lymphoma in 5%. Progression to diffuse lymphocyte predominant HL. Diffuse lymphocyte predominant HL may be indistinguishable from TCRBCL.

11.5.2 Classical Hodgkin lymphoma

Clinical	<p>Bimodal age: 15–35 years and 50+</p> <p>Typically cervical, mediastinal, axillary or para-aortic lymph nodes. Contiguous involvement. Very rarely extranodal.</p> <p>55% stage I or II. 40% have ‘B symptoms’.</p> <p>Nodular sclerosing: mediastinal involvement.</p>
Morphology	<p><i>Classical Reed Sternberg cell</i>: Large with abundant basophilic cytoplasm, prominent eosinophilic nucleoli. Bi-nucleate or bi-folded nuclei.</p> <p><i>Nodular sclerosing</i></p> <p>Nodular lymphoid aggregates divided by sclerotic bands of collagen with capsular thickening. ‘Lacunar’ variants.</p> <p>BNLI grading: NS Grade 1: >75% lymphocyte-rich</p> <p>NS Grade 2: >25% lymphocyte depleted</p> <p><i>Mixed cellularity</i></p> <p>May be interfollicular. Not nodular or sclerosing.</p> <p>Mixture of eosinophils, neutrophils, histiocytes and plasma cells.</p> <p><i>Lymphocyte rich classical HL</i></p> <p>Nodular or diffuse. Lacks polymorphs. Resembles lymphocyte predominant Hodgkin lymphoma and may have ‘L&H’ variants <i>but</i> defined by immunophenotype, which is that of cHD.</p> <p><i>Lymphocyte depleted</i></p> <p>‘Pleomorphic’ variant of H-RS cell. Rare entity now. Many cases in older series were ALCL or pleomorphic T-cell or B-cell lymphomas.</p>
Immunophenotype	<p><i>H-RS cells</i>: CD15, CD30 +ve and CD45-ve</p> <p>Also BSAP, TARC and Fascin +ve</p> <p>LMP1 often +ve, especially in mixed cellularity HL</p> <p>CD20 –ve or focally/weakly +ve but unreliable</p> <p>J chain, CD43, CD75, Oct2, BOB.1 –ve</p> <p>CD2, CD3 may be very weakly expressed</p> <p><i>Background cells</i>: CD3 +ve small Th2-cells, forming rosettes.</p> <p><i>DD</i>: T-cell rich B-cell lymphoma</p> <p>Anaplastic large-cell lymphoma</p> <p>Lymphocyte predominant Hodgkin lymphoma</p> <p>Diffuse large B-cell lymphoma</p> <p>Some T-cell lymphomas</p>
Genetics	<p>Monoclonal B-cell in >98% of cases. Somatic hypermutated follicle centre cell.</p> <p>Abnormal expression of Oct2 and BOB.1 transcriptional promoters => no J chain or Ig expressed. NF B abnormality prevents apoptosis.</p>

11.6 Prognostic significance of histological subtypes

In patients treated with radiotherapy alone, histological subtype is an important prognostic factor.⁸ Superior progression-free survival occurs in patients with LPHL and NSHL compared to those with MCHL and LDHL. In patients treated with chemotherapy, with or without radiotherapy, the prognostic significance of histological subtype is less important than other prognostic factors such as stage or age. In particular, the difference in prognosis previously reported for NSHL types I and II is no longer apparent in more intensively treated patients.⁹ Nodular LPHL and LRCHL with localised

disease have a tendency to more indolent behaviour and have a relatively good prognosis.¹⁰ Nodular LPHL has features of a low-grade B-cell lymphoma and will be discussed separately later.

11.7 Staging and distribution of disease

The Ann Arbor system¹¹ of staging (see Table 11.1) was developed to characterise the extent of disease in patients with HL, but is also applied to other lymphomas (not used in entities like CNS lymphoma or mycosis fungoides). It is more useful in HL than non-Hodgkin lymphoma (NHL) because of the common tendency of HL to spread in an orderly way to adjacent lymph node groups.¹² Common patterns of spread were recognised early and formed the basis for the initial clinical trials of extended field radiotherapy.¹³ Infradiaphragmatic presentations have been found to have a worse prognosis than supradiaphragmatic¹⁴ presentations; such patients were more likely to be male, elderly and less likely to have nodular sclerosis histology.¹⁵ On the contrary, disease confined to the mediastinum carried a relatively low risk of disease below the diaphragm¹⁶ and was more often seen in females. The nodular lymphocyte predominant subtype was often described with stage I disease confined to the upper neck in younger males.^{10,17} The Ann Arbor system was modified at the Cotswolds meeting to include definitions of bulky disease in the CT era (>10 cm), definition of CT criteria for splenic and liver involvement (focal defects), and definition of a new category of treatment response (CR(u)) with persistent radiological abnormalities of uncertain significance.¹⁸

The staging procedures required in individual cases may be influenced by treatment parameters (e.g. there could be no justification for staging laparotomy if chemotherapy were to be employed in any case), and by the pattern of known disease.

Table 11.1 Ann Arbor Staging System

Stage	Distribution of Disease
I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of diaphragm alone (II) or with involvement of contiguous extralymphatic organ or tissue (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) and/or limited contiguous extralymphatic organ or site (IIIE, IIIES)
IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement

11.8 Initial patient assessment

When a confident diagnosis of HL is made after an adequate biopsy, a comprehensive assessment of the patient is essential, including a detailed history and examination. Careful recording of the size and distribution of all visible and/or palpable lesions is essential. ‘B’ symptoms, namely weight loss greater than 10% in the past six months, fevers over 38 degrees or drenching night-sweats, should be specifically asked about. Other disease-associated symptoms, such as alcohol-induced pain and pruritis, should be recorded. Co-morbid conditions, such as heart disease, which could influence the tolerance of treatment, should also be recorded. Full dental evaluation is recommended if radiotherapy is planned to the oral cavity or salivary glands.

11.9 Blood studies

Routine haematological and biochemical indices should include full blood counts, LDH, liver function tests, ESR, albumin and creatinine, which either document organ function or provide prognostic information. Thyroid function tests should be performed if the thyroid region is to be

irradiated. A test for HIV should be considered, although it is very rare for HIV infection to present as lymphoma.

11.10 Organ function studies

Baseline lung function tests including DLCO (or oxygen saturation) are recommended if Bleomycin¹⁹ or thoracic radiation²⁰ are contemplated. If anthracycline-based chemotherapy is to be given, baseline measurement of left ventricular function is recommended.

11.11 Staging procedures

Guideline — Hodgkin lymphoma — staging procedures	Level of evidence	Refs
All patients should undergo CT scans of at least the neck, chest, abdomen and pelvis.	IV	21, 22
Bone marrow biopsy is recommended in at least those cases with stage >IIA.	IV	23
FDG-PET scanning or, if unavailable, gallium scanning, are recommended for staging in all cases. Positron emission tomography (PET) is superior to gallium.	IV	24-27

11.11.1 CT scanning and chest radiography

Chest radiography alone is inadequate to stage the thorax²¹. All patients should undergo at least CT scanning from neck to pelvis.²² If any site is involved beyond neck to pelvis, it is recommended that baseline CT or MRI studies of the site are performed before commencing therapy, both to facilitate response assessment and to assist in planning radiotherapy if appropriate.

11.11.2 Lymphangiography

This is largely of historical interest, given the disappearance of expertise in this technique with the advent of CT scanning. Unlike CT, it has the capacity to show disease in normal-sized lymph nodes, but positron emission tomography (PET) scanning also has this capability.

11.11.3 Bone marrow examination

Bone marrow aspiration and trephine biopsy have a relatively low yield overall in HL.²⁸ The incidence of bone marrow involvement was 5% in the German HD4–6 study generation, which included 2307 patients in all stages.²³ The marrow positivity rate is particularly low, less than 1%, in patients without B symptoms²⁹ and with otherwise stage I–II disease.³⁰ Nevertheless, despite the extremely low yield in patients with apparently early-stage disease, the procedure is safe and if positive, has a profound impact on the management of the patients with otherwise early-stage disease. Therefore it can be considered even in these cases.

11.11.4 Functional imaging in staging

Cross-sectional structural imaging modalities, such as CT scanning and MRI, are capable of evaluating lymph node size but cannot detect HL in normal-sized lymph nodes or distinguish benign reactive hyperplasia from neoplastic involvement. Additionally, lack of contrast between tumour and normal tissue may make it impossible to visualise disease in sites such as the liver and spleen. Functional imaging can help distinguish benign from malignant nodes and may image disease in the spleen and other organs that is undetected on CT. Scanning with gallium-67^{31,32} and positron emission tomography²⁴⁻²⁶ (PET) using the radiopharmaceutical F-18 fluorodeoxyglucose (FDG) have both been

used in an effort to increase the accuracy of staging in HL. Both gallium and PET scanning may also be useful for response assessment, particularly if a baseline study has been performed before treatment commences. Gallium-67 appears to be less sensitive and accurate than PET²⁷ and also has lower resolution, making interpretation of images more difficult. PET is therefore recommended in preference to gallium scanning for staging in HL. When a functional imaging result is equivocal or may change the treatment strategy, biopsy confirmation may be required.

11.11.5 Staging laparotomy

Staging laparotomy has not been shown to improve survival in randomised trials³³ and is almost never required. It is associated with a small but significant mortality from post-operative complications and a risk of fatal, overwhelming post-splenectomy infection with encapsulated bacteria. There may, however, be rare circumstances, with equivocal imaging results, in which management will be profoundly affected by the results of staging laparotomy. For those centres with the necessary expertise, laparoscopic biopsy of equivocal intraabdominal sites may be a useful alternative to laparotomy. Splenic irradiation is as effective for controlling splenic disease as splenectomy.³⁴ PET scanning may provide clarification of equivocal structural imaging results and obviate the need for laparotomy in some of these rare cases.

11.12 Assessment of 'bulky' sites

The negative prognostic significance of bulky disease sites was first recognised for mediastinal masses before the advent of CT scanning. According to the classical definition, a bulky mediastinal mass has a maximum transverse diameter greater than one third of the maximum internal diameter of the thorax as measured on a PA chest radiograph. In the thorax and at other sites, a mass of 10 cm or more in maximum diameter measured on CT may also be termed 'bulky'.^{18,35} It is important to measure masses in the superior–inferior directions as well as the transverse diameters. In the Stanford V protocol, splenic nodules identified on CT are considered to represent bulky disease.³⁶ The presence of a bulky site should be recorded.

11.13 Clinically useful prognostic indices

Many prognostic factors have been identified for HL and several prognostic indices have been developed as tools to assist in choosing therapy. For patients with limited stage disease, the EORTC index is useful and widely applied. It is described in Section 11.16.1. The Hasenclever index, developed by the German Hodgkin Disease Study Group (HDSG), is widely used to stratify patients with more advanced disease into prognostic groups.³⁷

11.14 Management of Hodgkin lymphoma

11.14.1 General principles

The patient with HL requires expert multidisciplinary supervision at all stages of management. Excellent results are obtained in centres where sufficient numbers of patients are seen to for clinicians to acquire experience of managing this disease.^{38,39}

Fertility

Treatment with chemotherapy or pelvic irradiation may lead to infertility and, given the long life expectancy following successful treatment and young age at which many patients present, it is crucial to address reproductive issues before treatment planning commences, except in cases where emergency treatment is required. Where relevant, that is, when treatment carries a significant risk of affecting reproductive function, referral for harvesting and storage of sperm should be made and appropriate specialist consultations arranged to discuss preservation of fertility in female patients. Ovarian transposition may be considered if pelvic radiotherapy is planned, but results of this procedure are variable.⁴⁰ Function is more likely to be preserved if the ovary is transposed laterally

rather than medially. Hormonal function is more likely to be preserved than reproductive function.⁴¹ Laparoscopic transposition may be effective^{42,43} (see also Chapter 21, including Section 21.2).

Combined-modality therapy

Combined-modality therapy is now used for the majority of patients with early-stage disease and is recommended for all patients with bulky mediastinal masses. The use of combined chemotherapy and radiotherapy offers the potential for both reduced toxicity and superior freedom from progression. Fewer cycles of chemotherapy are generally required and radiotherapy is made less toxic by the use of lower doses combined with smaller radiation fields.⁴⁴

Such treatment protocols require considerable coordination and good working relationships between specialist teams. Early consultations with specialists in both chemotherapy and radiotherapy are recommended to ensure that the proposed combined treatment plan can be safely administered in a timely fashion, and that all relevant investigations, including the imaging studies essential for radiotherapy planning, have been completed.

Surgery

Surgery has no place in the primary treatment of HL but may play a crucial role in obtaining adequate biopsy material for diagnosis, in staging under special circumstances, and in the assessment of residual masses after therapy. PET scanning may reduce the number of cases in which biopsy of a residual mass is required, especially if the scan suggests that residual metabolically-active disease is present. Biopsy may still be required in the presence of a residual mass that is negative on PET.

Radiotherapy

HL is highly radiosensitive. Curative doses of radiation can generally be delivered that are well within normal tissue tolerances. Doses in the range of 35–44 Gy have historically been delivered to wide radiation fields, but it is likely that the dose response curve for radiotherapy alone is flat beyond 40 Gy. In fact, Brinker and Bentzen found no evidence of an increase in efficacy at doses beyond 32.5 Gy.⁴⁵ In the combined modality setting, lower radiotherapy doses are effective and 30 Gy or less may be sufficient after chemotherapy. The German HDSG showed no evidence of a relevant radiotherapy dose effect in the range between 20 Gy and 40 Gy in involved fields and extended fields after four months of modern polychemotherapy in patients with intermediate-stage HL.⁴⁶ Data from a randomised trial by the same group suggest that 30 Gy is as effective as 40 Gy for treating subclinical disease⁴⁷ when radiotherapy alone is given.

Wide-field radiotherapy has a well-established record as a curative therapy in stage I–III Hodgkin disease. When radiotherapy is used as sole therapy, coverage of all tumour sites plus at-risk clinically uninvolved nodal groups is essential because of the high relapse rate with involved-field therapy alone.⁴⁸ With analysis of patterns of failure, the classic extended radiotherapy fields evolved and were modified over the years. The most commonly used treatment fields are as follows:

Mantle field

Treatment in continuity of lymph nodes from the base of the skull, usually to the bottom of the 10th thoracic vertebral body, with customised shielding of the lungs and oral cavity. The following lymph node groups are included: cervical, supra and infraclavicular, axillary mediastinal and hilar nodes. Epirochlear nodes and Waldeyer's ring structures are not included.

Inverted Y field

Treatment in continuity from the bottom of the 10th thoracic vertebral body to the inguinal or femoral nodes, with customised shielding of abdominal viscera and central pelvic structures. The following lymph node groups are included: retroperitoneal nodes of the para-aortic/interaortocaval/paracaval groups, common iliac, internal and external iliac and inguinal nodes with or without femoral nodes.

The spleen is also included in the field, or if the spleen has been removed, the splenic hilar nodes are covered.

Total nodal (TNI) and subtotal nodal irradiation (STNI)

Total nodal irradiation means the sequential administration of mantle and inverted Y fields. Subtotal nodal irradiation is used for stage I–IIA supradiaphragmatic disease and involves the sequential administration of mantle and para-aortic/spleen fields, without irradiation of the pelvis.

Involved-field radiotherapy

Involved-field radiotherapy is the administration of therapeutic radiation to known sites of disease with a margin of normal tissue, without an attempt to give prophylactic treatment to a large volume of clinically uninvolved sites.⁴⁹ Involved fields are commonly used in HL and stage I–II intermediate-grade lymphomas following chemotherapy. In stage III–IV HL, involved-field radiotherapy may be given to bulky or residual sites as consolidation therapy. It may also be used as sole treatment for nodular LPHD and for stage I–II low-grade lymphomas. There is no universally agreed definition for an involved field, but guidelines should be developed to reduce variability between centres. Immediately adjacent uninvolved lymph node sites may be included to facilitate design of an anatomically appropriate radiation field. Typically, an involved field will include a 5 cm margin beyond known disease along the axis of the nodal group (most often in the cranio-caudal dimension), and a 2 cm margin laterally, unless constrained by radiosensitive normal tissues such as lung or kidney.

Quality control

Because of the lifelong potential for toxicity from radiotherapy, every aspect of treatment planning and delivery must be of the highest quality.⁵⁰ The best available imaging should be used to accurately localise all sites of disease. Appropriate knowledge and training is essential for all staff involved in treatment planning. There can be significant variation between radiation oncologists in the design of mantle fields, but the use of consensus guidelines should reduce the risk of errors in shielding design.⁵¹ A CT-based treatment planning system should be used, if available, to ensure adequate coverage of the planning target volume and to reduce radiation dose to normal tissues to a minimum.⁵² Compensators should be used to minimise variations in dose across large treatment volumes.⁵³ The German HDSG found a high rate of errors in radiotherapy treatment planning when mandatory quality assurance was introduced. In a randomised trial of two radiotherapy doses, they found that patients without radiotherapy protocol violations had significantly better freedom from treatment failure than those with violations (82% versus 70%).⁴⁷ They have since instituted a regime of centralised prospective radiation treatment field planning to ensure that radiotherapy quality is maintained.

Chemotherapy

General principles

HL is one of the malignancies most sensitive to chemotherapy. Early studies of single-agent regimens in the 1950s and 1960s showed significant response rates. However, durable responses and apparent cures were rare until the advent of the mechlorethamine, vincristine, procarbazine and prednisolone (MOPP) combination chemotherapy regimen. The enhanced activity against the neoplastic cells exhibited by MOPP was an effect of the different mechanisms of cell killing of the different chemotherapy drugs and their non-overlapping toxicities when given in combination. The concept of ‘cross resistance’ arose. This suggested that resistance could arise to all agents of a particular class of drug, and led to the development of ‘non-cross-resistant’ regimens containing drugs of many different classes. The efficacy of such regimens is consistent with the Coldman-Goldie hypothesis. It soon became clear that dose intensity was important in obtaining the highest cure rates and that treatment should be given as rapidly as recovery from haematological toxicity would permit.

After combination chemotherapy was proven to have high efficacy for advanced disease, subsequent trials showed that it could also reduce the relapse rate and in some circumstances, improve survival

for patients with early-stage disease when combined with extended field radiotherapy. Later trials showed similar efficacy with chemotherapy and involved-field radiotherapy when modern chemotherapy was used (ABVD and similar regimens).

Choice of chemotherapy regimen

Combination chemotherapy is curative in more than 70% of patients with advanced-stage HL and can produce cure rates of more than 90% when combined with radiotherapy in patients with early-stage disease. Numerous combinations of drugs have been shown to be effective, but randomised trials have shown clearly that some regimens are superior to others. Regimens differ in their efficacy and toxicity profiles.

The most commonly used chemotherapy regimens include:

MOPP: mechlorethamine, vincristine, procarbazine and prednisolone. Chlorambucil may be substituted for mechlorethamine to produce the more tolerable ChlVPP or LOPP, which were widely used in the United Kingdom, or by cyclophosphamide to produce COPP.

MOPP was developed at the National Cancer Institute in the mid 1960s.⁵⁴ As a result of the acute (mainly neurologic and gastrointestinal⁵⁵) and late toxicities (sterility⁵⁶ and secondary leukemia⁵⁷), MOPP has been superseded by other regimens as first-line therapy. MOPP variants may still be used as salvage therapy.

ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine

ABVD was originally developed by the Milan group for treatment of MOPP-resistant disease. It was subsequently proved to be superior to MOPP as first-line therapy. Complete response rates were similar in ABVD and MOPP, but ABVD alternating with MOPP produced superior disease-free survival⁵⁸, as did ABVD by itself. ABVD was also less toxic than MOPP, particularly with respect to sterility and secondary leukemia.⁵⁹ This regimen has become a widely used standard for the treatment of advanced HL and as part of combined modality treatment of early-stage disease. The risk of pneumonitis caused by bleomycin⁶⁰, which may rarely be fatal, can be reduced by limiting the total cumulative dose of bleomycin and by careful attention to lung function.

MOPP/ABV hybrid: mechlorethamine, vincristine, procarbazine and prednisolone alternating with doxorubicin, bleomycin, vinblastine.

MOPP alternating with ABVD (non-cross-resistant) was proven superior to MOPP as above. ABVD therapy given for six to eight months was shown to be as effective as twelve months of MOPP alternating with ABVD. Alternating ABVD and MOPP was later shown to be equivalent to a MOPP/ABV hybrid, in which one half cycle of MOPP was alternated with one half cycle of ABVD within a one-month period.⁶¹ A similar study in the United Kingdom, comparing alternating LOPP-EVAP and hybrid LOPP/EVA, also failed to show evidence of superiority for the hybrid regimen.⁶² In a recent randomised trial, MOPP/ABV had similar efficacy to ABVD but was associated with a greater incidence of acute toxicity, myelodysplastic syndrome and leukaemia. ABVD should therefore be considered a standard chemotherapy regimen for treatment of HL.^{63,64}

BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone

BEACOPP (standard or dose-escalated) was developed by the German HDSG in an attempt to further improve treatment results of treatment of advanced Hodgkin disease.⁶⁵ The dose of individual drugs was increased and given every three weeks. The escalated BEACOPP regimen is administered with granulocyte colony stimulating factor (G-CSF) support. Consolidative radiotherapy is given after completing eight cycles of chemotherapy to initial bulky disease or residual disease. The regimen has

significant acute toxicity, especially in its dose-escalated form, and may be unsuitable for older or less fit patients.

Stanford V doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone

Stanford V is an intensive regimen of short duration, given with involved-field radiotherapy to either bulky sites or all sites, depending on the extent of disease. Remarkably good results have been achieved at Stanford University, but these have not been duplicated at other centres. Early results from a European randomised trial showed that patients treated with Stanford V had worse failure-free survival compared with those treated with ABVD or MEC ($P = 0.001$)⁶⁶, but with no difference so far in overall survival.

11.15 Integration of chemotherapy and radiotherapy

When chemotherapy and radiotherapy are given together as components of combined-modality therapy, chemotherapy is generally administered first and to the full intended doses. Radiotherapy is commenced after enough time has elapsed to allow haematological recovery, typically two to four weeks. It is therefore important that radiotherapy is planned in a timely fashion to prevent long delays. Split-course regimens, with radiotherapy sandwiched between cycles of chemotherapy, are not used. Radiotherapy has traditionally been used as emergency therapy for patients presenting with superior vena cava obstruction. However, there is no evidence that this is a superior strategy to commencing urgent treatment with chemotherapy in those for whom chemotherapy will form part of treatment in any case.

ABVD plus mediastinal radiotherapy may result in overlapping cardiac and pulmonary toxicity. These toxicities may be minimised by limiting the volumes of heart and lung exposed to radiation and limiting the radiation dose.

11.16 Treatment recommendations by disease extent

10.16.1 Early-stage disease

Definition of early-stage disease

The definition of early stages of HL has varied between different authors, but in general, they are those with an excellent prognosis. They were originally defined as those suitable for treatment by radiation therapy alone, namely stages IA, IB and IIA without bulky disease. Patients with these stages have an excellent chance of cure, with 84% ten-year relapse-free rates and 80% ten-year overall survival.

Early stage has been divided further into favourable and unfavourable characteristics, according to the widely used EORTC criteria.⁶⁷

Favourable characteristics are

- number of lymph node sites involved by Hodgkin lymphoma ≤ 3
- age ≤ 40 years
- erythrocyte sedimentation rate ≤ 70

Unfavourable characteristics are

- number of lymph node sites involved by Hodgkin lymphoma > 3
- age > 40 years

- erythrocyte sedimentation rate >70
- large mediastinal mass (mediastinal mass ratio >1:3)

Based on subgroup analysis of the results of previous trials, the EORTC attempted to identify a *very* favourable group that could be treated by mantle radiation alone. In two trials, the very favourable group had a relapse rate of 40%, which was greater than that seen in the other groups. The concept of a very favourable group has been abandoned for routine practice. The German HDSG is exploring minimal treatment for stage I lymphocyte predominant histology.

Treatment of early-stage disease

Survival after treatment for early-stage HL is generally excellent and does not depend on whether the initial strategy is extended-field radiotherapy, chemotherapy or combined chemotherapy and radiotherapy. In a meta-analysis, Shore and colleagues reported that overall survival at 12 years was the same for patients with early-stage disease managed by initial extended-field radiotherapy or combined radiotherapy and chemotherapy, but relapse-free survival was better with combined modality.⁶⁸ Survival was, however, inferior for involved-field radiotherapy alone compared to extended field. In the more recent meta-analysis by Specht, there is a suggestion of slightly better long-term survival in patients treated with combined-modality therapy (12% vs 15% dead from HL at ten years; P = .07).⁶⁹

The aim of treatment in early-stage disease is therefore to achieve cure with the least possible toxicity from treatment while preserving an acceptable rate of freedom from progression. Concern about the risk of breast cancer in females under the age of 30 years has limited the use of mantle radiotherapy in this patient group, which can involve extensive exposure of breast tissue. For other adult patient groups treated with extended field radiotherapy, the risk of second malignancy is much lower. The rate of salvage with chemotherapy after primary radiotherapy is very high, but the reverse is not true. Patients with early relapse after primary chemotherapy are often offered high-dose chemotherapy and autologous peripheral blood stem cell transfusion if they are eligible, and are therefore exposed to risks of myelodysplasia and acute leukaemia. A pilot study in early-stage disease of six cycles of ABVD chemotherapy alone has been reported by a Spanish group⁷⁰, although radiotherapy was given to patients with bulky mediastinal disease. This study was too small to draw any reliable conclusions.

Guidelines — Hodgkin lymphoma — approach to treatment	Level of evidence	Refs
Early-stage Hodgkin lymphoma should be subdivided by favourable and unfavourable characteristics and treatment tailored accordingly.	II	66
All subgroups of early Hodgkin lymphoma should be treated with a regimen that covers the spleen, supra-diaphragmatic and para-aortic lymph nodes, such as chemotherapy and involved-field radiotherapy, or subtotal nodal irradiation.	I	34

Target volume for treatment

The lymph node regions that require treatment for early-stage supra-diaphragmatic Hodgkin are the neck, axillae, mediastinum spleen and para-aortic regions. A high incidence of relapse is seen if only the supra-diaphragmatic regions are treated (EORTC H1, and H2 studies).³⁴

The options for treating this volume of lymphoid tissue are:

- radiation treatment alone

- chemotherapy alone
- a combination of radiotherapy and chemotherapy.

More than 40 years of randomised clinical trials have helped better define the concept of early HD and its management. The high cure rate with modern treatment strategies has meant that the emphasis of research has been on reducing the long-term side effects.

The management of patients with early-stage disease and favourable characteristics

Radiation alone involves the use of mantle, splenic and para-aortic fields as described above (subtotal nodal irradiation or STNI). Meta-analysis shows significantly better event-free survival with larger radiation fields.⁶⁹ Overall survival, however, was not improved. For patients with favourable characteristics, this approach has been shown to be superior to mantle radiotherapy alone (H5 trial)⁷¹ and equivalent to or better than chemotherapy alone (NCI trial⁷², Florence–Rome). STNI was accepted as the gold standard for radiotherapy by clinical trials groups (H5, H6, H7, H8, GHSG HD7 trials). The large volume of normal tissues that must be irradiated resulted in unacceptable rates of long-term complications, most notably the development of second cancers.

In an effort to reduce the long-term toxicity, recent trials have tested the use of radiation fields that only cover sites of macroscopic involvement by HL at diagnosis.^{73,74} A limited number of courses of chemotherapy were used to treat those sites of subclinical involvement. EORTC H7 and H8 and GHSG HD7 trials showed that the combination of radiotherapy and chemotherapy gave significantly better event-free survival than STNI. In EORTC H8, event-free survival and overall survival were significantly better than STNI.

While there is broad agreement from the randomised clinical trials for the general approach, there are minor differences in the actual treatments delivered. The EORTC has used six cycles of EBVP (H7)⁷⁵, three cycles of MOPP/ABV (H8), and in its most recent trial (H9), has reverted to six cycles of EVBP. The GHSG has used two cycles of ABVD (HD7), and in HD10 is comparing two versus four cycles of ABVD. The long-term efficacy of only two cycles of ABVD in combination with involved-field radiotherapy has not yet been established. In the meantime, it is considered safer to rely upon four cycles of ABVD and IFRT until new information becomes available from trials in progress.

Similarly, the radiation dose to the involved field has varied from 36 Gy to 40 Gy. GHSG HD10 is testing 20 Gy, and EORTC H9 is comparing 36 Gy with 20 Gy or no IF-RT.

Guidelines — Hodgkin lymphoma (favourable) — chemo and radiation therapy	Level of evidence	Refs
Early-stage Hodgkin lymphoma with favourable characteristics should be treated by a combination of involved-field radiotherapy and systemic chemotherapy.	II	34
Chemotherapy should consist of four cycles of ABVD* .	II	74
Involved-field radiation therapy should be delivered to all the sites that were involved by Hodgkin lymphoma at diagnosis.	II	34

* This recommendation may change following completion of current studies investigating the use of two or three cycles of ABVD plus involved-field radiotherapy.

Management of patients with unfavourable characteristics

Patients with unfavourable characteristics, including more than three sites of involvement, age >40 years, ESR >70 or bulky involvement, have a high risk of relapse with radiation alone. The minimum treatment is a combination of chemotherapy and radiation therapy.⁷⁶

In the EORTC H5 trial, six cycles of MOPP chemotherapy combined with mantle radiotherapy, when compared with STNI, showed an event-free and overall survival advantage (EFS 83% versus 66%, and overall survival 88% versus 75%, respectively). A comparison of MOPP plus IF-RT or ABVD plus IF-RT showed no difference in outcome (H6).

EORTC H7 showed that less intensive chemotherapy with six cycles of EBVP plus IF-RT was inferior to six cycles of MOPP/ABV plus IF-RT. Preliminary results from H8 show no difference between four and six cycles of MOPP/ABV plus IF-RT. The current study H9 compares six cycles of ABVD plus IF-RT with four cycles of BEACOPP plus IF-RT. A randomised trial from India showed that IF-RT improved event-free survival and overall survival in patients with unfavourable stage I–II disease after a complete response to six cycles of ABVD.⁷⁷

Guidelines — Hodgkin lymphoma (unfavourable) — chemo and radiation therapy	Level of evidence	Refs
Early-stage Hodgkin lymphoma with unfavourable characteristics should be treated by a combination of Involved-field radiotherapy and systemic chemotherapy.	II	75, 76
Chemotherapy should consist of six cycles of ABVD.	II	75, 76
Involved-field radiation therapy should be delivered to all the sites that were involved by Hodgkin lymphoma at diagnosis.	II	75, 76

11.16.2 Advanced-stage disease

Definition of advanced-stage Hodgkin lymphoma

The advanced stages of HL are those with a less than excellent prognosis. As with limited disease, there are significant variations between different series in the patients that comprise this group. Stages in the advanced-disease category, for the purposes of these guidelines, are stages I–II with bulky mediastinal mass, IIB, IIIA-B and IV-B. At all stages of disease, cure is possible with chemotherapy or combined-modality therapy, and long-term survival exceeds 50% for all groups.

Management of advanced-stage disease

Chemotherapy is the mainstay of therapy for patients with advanced HL. Apart from a favourable group of patients with stage IIIA disease who could be cured with total nodal irradiation, the outlook for patients with advanced disease was uniformly dismal until MOPP combination chemotherapy was developed at the National Cancer Institute in the mid 1960s.⁵⁴ This produced cure rates of over 50% of patients with stage III–IV disease⁷⁸ and revolutionised the management of HL.

Patients with advanced HL require more cycles of chemotherapy to obtain optimum freedom from progression and survival compared to early-stage patients treated with combined-modality therapy. Recent evidence suggests that patients with advanced disease and multiple adverse prognostic factors may benefit from the use of chemotherapy that is more intensive than ABVD.

Guideline — Hodgkin lymphoma — advanced disease	Level of evidence	Refs
Chemotherapy should be used for all patients with advanced Hodgkin lymphoma.	III	78, 79

In the pre-chemotherapy era, it was recognised that patients with limited stage IIIA disease, with infradiaphragmatic involvement confined to the upper abdomen (stage III1A), had a better prognosis,

when managed with extended-field radiotherapy than other stage IIIA patients (stage III2A). MOPP chemotherapy improved freedom from progression and survival for these patients when added to radiotherapy in non-randomised studies. Patients with stage III1A and stage III2A treated by radiotherapy alone had DFS survivals of 64% and 32% respectively. Survival was better when radiotherapy was combined with chemotherapy.⁷⁹ With the advent of more effective chemotherapy regimens such as ABVD, this distinction is no longer clinically relevant. Wide-field radiotherapy no longer forms part of first-line therapy for these patients.

Hasenclever prognostic index for patients with advanced Hodgkin lymphoma

Hasenclever and Diehl studied analysed data on more than 5000 Hodgkin's disease patients for prognostic features. Multivariate analysis identified seven prognostic factors. Each factor contributed about a 7% decrement in freedom-from-progression (FFP) at five years, according to an analysis in 1618 patients. The international prognostic score may permit comparisons of populations across studies and can be used in the evaluations of outcome. In a randomised trial, BEACOPP was superior to COPP/ABVD in each of three prognostic groups (international prognostic score 0–1, 2–3, 4+), but the most striking difference was among patients in the highest risk group.⁸⁰

The Hasenclever index is as follows:

1. a serum albumin level of less than 4 g per decilitre
2. a haemoglobin level of less than 10.5 g per decilitre
3. male sex
4. an age of 45 years or older
5. stage IV disease (according to the Ann Arbor classification)
6. leukocytosis (a white-cell count of at least 15,000 per cubic millimetre)
7. lymphocytopenia (a lymphocyte count of less than 600 per cubic millimetre, a count that was less than 8% of the white-cell count, or both)

The score predicted the rate of freedom from progression of disease as follows:

0 factors (7% of patients), 84%

1 factor (22% of patients), 77%

2 factors (29% of patients), 67%

3 factors (23% of patients), 60%

4 factors (12% of patients), 51%

5 factors or higher (7% of patients), 42%

Treatment recommendations in advanced Hodgkin lymphoma

Choice of chemotherapy regimen

Over the years, sequential randomised trials in North America and Europe have gradually selected a small group of chemotherapy regimens with high efficacy and low levels of late toxicity. ABVD is the most widely used of these regimens. It exhibits low toxicity mainly because of the avoidance of an alkylating agent. As discussed above, ABVD produces disease control comparable to or superior to

alternating MOPP and ABVD or MOPP/ABV hybrid regimens, with frequent preservation of fertility and a low leukaemia rate.

The efficacy and safety of alternating MOPP and ABVD or hybrid regimens was studied in two comparative phase III trials. In the Milan study, stage IB, IIA bulky, IIB, III A and B, and IV patients received MOPP/ABVD or hybrid MOPP and ABVD, each for a minimum of six cycles followed by 30 Gy to initial sites of bulky disease.⁸¹ At ten years, the FFP rate was 67% versus 69% (p = NS) and the overall survival rate was 74% versus 72% for the alternating and hybrid regimens, respectively (p = NS). A total of 23 second malignancies were documented among 427 patients, including 11 secondary leukaemias.

Guideline — Hodgkin lymphoma (advanced) — chemotherapy regimen	Level of evidence	Refs
ABVD chemotherapy is recommended as a standard chemotherapy regimen for advanced Hodgkin lymphoma patients with an international prognostic score <4.	II-IV	64, 65
ABVD is superior to alternating MOPP/ABVD or MOPP/ABV hybrid because of lower toxicity.	II	64, 65

Optimum number of cycles of chemotherapy in advanced disease

Guideline — Hodgkin lymphoma (advanced) — chemotherapy regimen	Level of evidence	Refs
Chemotherapy should be given for a minimum of six cycles.	IV	64, 65
A minimum of two further cycles of chemotherapy should be given after a complete response as been attained.	IV	64, 65

Management of the patient with multiple adverse risk factors

The German HDSSG randomised 1201 patients with advanced-stage disease to COPP/ABVD, BEACOPP, or to increased-dose BEACOPP, with most patients receiving consolidative radiation therapy to sites of initial bulky disease (≥ 5 cm). Patients included those with stages IIB and IIIA, patients with risk factors, and stage IIIB and IV patients. After eight chemotherapy cycles, initial bulky sites received 30 Gy and residual disease sites received 40 Gy. On this basis, the majority of patients received consolidative radiotherapy. At five-year overall survival was 83% for COPP/ABVD, 88% for BEACOPP, and 91% for increased-dose BEACOPP. The actuarial rate of secondary acute leukaemias five years after diagnosis of HL was 0.4% for COPP/ABVD, 0.6% for BEACOPP, and 2.5% for increased-dose BEACOPP.⁸⁰

Stanford V chemotherapy involves a similar aggressive approach with multiple chemotherapeutic agents. After twelve weeks of chemotherapy, patients receive 36 Gy consolidative radiotherapy to initial disease sites > 5 cm or macroscopic splenic disease.^{36, 40} A group of 142 patients with bulky stage II, III or IV HL were treated with Stanford V and followed a median of six years.¹⁰ Six-year FFS was 89% and OS was 96%. No secondary leukaemia or myelodysplasia occurred. Fertility was preserved in a significant proportion of both men and women as evidenced by a total of 43 conceptions post-treatment.

No group of patients with advanced HL has been identified with a prognosis so poor that high-dose therapy and autologous stem cell transplantation is recommended as part of initial therapy.⁸² Due to its efficacy and acceptable toxicity, the standard-dose BEACOPP regimen is recommended as a suitable treatment for younger fit patients with multiple adverse factors.

Guideline — Hodgkin lymphoma — prognostic score — stem cell use	Level of evidence	Refs
BEACOPP (standard dose) should be considered in patients younger than 65 with advanced Hodgkin lymphoma and a prognostic score ≥ 4 .	II	80
There is no group of patients that can be prospectively identified with a prognosis so poor that high-dose chemotherapy and haematopoietic stem cell transplantation can only be recommended for relapsed patients as primary treatment.	IV	82

Use of radiotherapy in patients with advanced disease but without bulky mediastinal mass

The use of combined-modality therapy for advanced disease remains controversial. It has not been adequately investigated in prospective randomised trials. The Southwest Oncology Group (SWOG) study of MOPP/BAP⁸³ with or without RT and the EORTC–GPMC trial of MOPP/ABV with or without RT routinely irradiated patients who achieved less than complete remissions.⁸⁴ The subsequent outcomes for these patients were excellent and suggested a benefit from radiotherapy. The SWOG trial showed no improvement in overall survival, but showed prolonged disease-free survival in radiotherapy-treated patients, especially those with bulky disease. A recently published analysis of the EORTC–GPMC trial reported the results for 421 patients who obtained a complete remission after 6–8 cycles of MOPP/ABV and were randomised to 16–24 Gy involved-field radiotherapy to all initially involved sites, or no further treatment. There was no benefit from radiotherapy⁸⁵ in patients who had achieved complete remission.

Guideline — Hodgkin lymphoma — optimal radiotherapy	Level of evidence	Refs
Radiotherapy is not recommended after modern chemotherapy as routine treatment to non-bulky sites in advanced Hodgkin lymphoma that have attained complete response.	II	85
In bulky sites and in sites that fail to achieve complete remission after chemotherapy, radiotherapy can improve freedom from progression in advanced Hodgkin lymphoma.	II	83, 84

Management of the patient with a bulky mediastinal mass

Guideline — Hodgkin lymphoma — bulky mediastinal mass	Level of evidence	Refs
Consolidative involved-field radiotherapy is recommended after chemotherapy for patients with bulky mediastinal masses.	IV	83
Chemotherapy should be given for a minimum of six cycles.	II	83, 84

11.17 Management of Hodgkin lymphoma with special features

11.17.1 Management of nodular lymphocyte predominant Hodgkin lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) has a more indolent behaviour than any of the other histological types and has immunophenotypic characteristics of a low-grade B-cell lymphoma of follicle centre cell origin (see Section 11.5.1). In randomised trials, NLPHL has been grouped with other HL variants, despite its different behaviour. The great majority of patients have

stage I–II disease at presentation and there is a male predominance. Diehl and colleagues reviewed the outcome for patients from 17 centres in Europe and the United States and confirmed that, with adequate treatment, survival is superior for patients with NLPHL compared to the classical or lymphocyte-rich variants, at least partly due to their younger age and other favourable prognostic factors at presentation.¹⁰ Relapses are common with advanced NLPHL and occur later than those of other HL variants, but do not have the same grave prognostic significance. However, there is no continuing pattern of late relapses, as seen in follicle-centre lymphoma. Most patients with early-stage disease are cured by their primary treatment.^{86–88}

Excellent long-term survival and freedom from treatment failure (>80%) has been attained in stage I–IIA disease with extended field radiotherapy. Salvage therapy is usually effective. Mantle radiotherapy alone can produce excellent results in supradiaphragmatic disease.⁸⁹ Relapses within radiation fields treated to 36–40 Gy are rare. Patients with non-bulky stage IA disease have been treated with involved-field radiotherapy with excellent results.⁸⁶ No randomised trials have addressed the question of whether chemotherapy leads to improved survival when combined with radiotherapy specifically in NLPHL. There are no reliable data on the long-term outcome of stage I–II disease treated with chemotherapy alone, although relapses at sites of previous involvement are common with this modality. Response rates for patients with advanced disease treated with chemotherapy are high but relapse is common, although survival, even with multiple relapses, is usually long. The optimum chemotherapy regimen for NLPHL has not yet been established, but standard HL regimens are effective. There is currently insufficient evidence to support ‘watchful waiting’ as an appropriate initial management strategy, but in children with indolent NLPHL, some authors have reported that no further treatment may be necessary in selected cases after complete surgical excision.^{90,91} Patients with advanced disease resistant to chemotherapy may respond to Anti CD-20 antibody therapy with rituximab.⁹²

Guideline — Nodular lymphocyte predominant Hodgkin lymphoma	Level of evidence	Refs
Stage I–IIA nodular lymphocyte predominant Hodgkin lymphoma should be treated with radiotherapy	IV	86, 89
Involved-field radiotherapy should be used for non-bulky stage IA nodular lymphocyte predominant Hodgkin lymphoma.	IV	86, 89

11.17.2 Management of Hodgkin lymphoma in pregnancy

The prevalence of HL in women of childbearing age inevitably leads to diagnosis of some cases of this disease during pregnancy. The conflicting requirements to (a) institute optimum treatment of the malignancy as soon as possible, and (b) avoid harm to the foetus, can lead to difficult management dilemmas. Nevertheless, good treatment outcomes are usually achieved. Lishner et al. reported that a cohort of 40 pregnant patients with HL fared just as well as a set of matched controls.⁹³ There are no randomised clinical trials in pregnant patients with HL. Management is influenced by the extent and anatomic location of the disease and by the age and viability of the foetus, and therefore must be individualised in each case. Patients with a viable foetus should have an early delivery when this is safe. In other cases, treatment may be delayed for weeks or even months until the foetus can be delivered safely, if there is no critical need for immediate therapy and the disease status is closely monitored.⁹⁴ In many cases, however, therapy must be commenced during pregnancy and treatment may differ from the usual recommendations for treatment in non-pregnant patients because of the need to protect the foetus. A decision may be taken to terminate the pregnancy to facilitate timely treatment. Some authorities have recommended the termination of pregnancy when HL is diagnosed in the first trimester or if chemotherapy has been delivered inadvertently during this period⁹⁵, with its associated risks of teratogenesis and foetal growth retardation. Ultimately, the choice of treatment strategy must be decided by the patient with as much support and information from the multidisciplinary team as possible.

Staging in pregnancy

Staging workup in pregnancy is limited by the risks of radiation exposure to the foetus, especially in the first trimester. CT scanning is therefore avoided but plain radiographs of the chest cause insignificant foetal radiation exposure and are safe. MRI scanning involves no ionising radiation exposure and is the cross-sectional imaging technique of choice in pregnancy.⁹⁶ Abdominal and pelvic ultrasound may also be useful. The Society of Nuclear Medicine recommends against any radionuclide scanning during pregnancy, but recognises that this advice needs to be balanced by the maternal risks of inadequate diagnosis and the potential of inappropriate treatments being more injurious to the developing fetus.⁹⁷ If functional imaging is essential for adequate treatment planning, the short physical half-life and fairly rapid urinary excretion of FDG, allowing minimisation of foetal exposure by catheterisation or frequent voiding, combined with good hydration/diuresis, make FDG-PET scanning a better choice than Ga-67.

Treatment of pregnant patients with non-bulky stage I–II supradiaphragmatic disease with radiotherapy

Supradiaphragmatic radiotherapy has been used successfully during pregnancy⁹⁸ and avoids exposure of the foetus to chemotherapy, which can be administered after the pregnancy is completed. The foetal radiation exposure is related to the size and position of the uterus, the extent and location of the radiation field, and the use of shielding of the uterus. Radiotherapy should be avoided completely in the first eight weeks of gestation. In phantom studies simulating a patient with a first trimester pregnancy treated to 40 Gy, treatment of the neck and axilla, but not the mediastinum, led to radiation doses to the foetus of less than 0.1 Gy without shielding of the fetus.⁹⁹ For local field irradiation in the region of neck-mediastinum, and for mantle treatment, the radiation dose to a shielded embryo was 0.028–0.186 Gy and 0.042–0.245 Gy depending upon the distance from the field isocenter and the field size used, respectively. The corresponding dose for an unshielded foetus always exceeded 0.1 Gy. Therefore it is recommended that the radiation field should be as distant from the uterus as is consistent with providing adequate tumour coverage, and that shielding should be used to minimise foetal exposure. Upon delivery of the child, combined-modality therapy can be safely completed. An alternative strategy is to use initial chemotherapy as discussed below.

Treatment of pregnant patients with bulky mediastinal mass, stage III or IV disease, or infradiaphragmatic disease, using chemotherapy

Patients with disease in these categories generally require chemotherapy as first-line therapy because they have advanced disease or because they cannot receive radiotherapy during pregnancy due to the risks of radiation exposure to the foetus. Chemotherapy options in pregnancy include the use of a single agent, such as vinblastine¹⁰⁰, to buy time until definitive therapy can be given, or immediate treatment with multi-agent chemotherapy at full doses.^{101,102} Successful deliveries of healthy babies have occurred with a range of chemotherapy regimens. No data exist to support any particular regimen as the treatment of choice in pregnancy, although it is reasonable to avoid or minimise exposure to alkylating agents.

11.17.3 Management of Hodgkin lymphoma in the elderly

Elderly patients have inferior progression-free survival and higher mortality from HL. They are also more likely to die with intercurrent illness or suffer a fatal toxicity from treatment. Disease in elderly patients appears on average to be more biologically aggressive¹⁰³, with a higher percentage of patients with B symptoms, advanced disease and unfavourable histology.¹⁰⁴ More aggressive disease, combined with a reduced capacity to undergo aggressive treatment, can make management of older patients technically challenging. Studies with MOPP/ABV hybrid and BEACOPP show that these regimens are much more toxic in elderly patients, and suggest that they should be given with caution, if at all, to persons over the age of 60 years. Forsyth and colleagues concluded that ‘the main reason for the poorer prognosis of patients aged 70 years and over was the increasing difficulty of

chemotherapy delivery associated with advancing age'.¹⁰⁵ The cumulative doses of doxorubicin and bleomycin in ABVD can pose particular problems for senior patients.

Nevertheless, it is important not to be nihilistic. HL is potentially curable in the elderly. Where possible, older patients should be treated with curative intent, particularly if they are found to have good organ function, including pulmonary and cardiac, and have disease with otherwise favourable characteristics. Similar principles apply to their management as to the management of younger persons with HL. Better results are likely to be achieved in elderly patients with early-stage disease with combined-modality therapy.¹⁰⁶

11.17.4 Standard response categories for Hodgkin lymphoma

As discussed in Section 11.7, treatment response criteria for HL were revised at the Cotswolds meeting. The criteria, which are given below, are also widely used in response assessment for patients with NHL and other types of lymphoma.

Complete remission (CR) — The patient has no clinical, radiological or other evidence of HL, although changes due to treatment (e.g. radiation fibrosis) may be noted.

Complete remission unconfirmed/uncertain (CR[u]) — The patient has residual stable abnormalities of uncertain significance on structural imaging (e.g. CT) at sites of known involvement by HL after attaining an excellent partial remission. Clinically, and on ESR criteria, the patient should have no other evidence of disease, with functional imaging (PET or gallium) being negative. Criteria for assigning CR[u] to various sizes of lymph nodes have been determined by some groups.¹⁰⁷

Partial remission (PR) — This is defined as a decrease by at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions. There should be resolution of B symptoms and no new lesions.

Progression of disease (PD) — This is defined as 25% or greater increase in the size of at least one measurable lesion, or the appearance of new lesions, or recurrence of these symptoms.

11.17.5 Response assessment during therapy course

No level II evidence is available to define the optimal timing of response assessment during treatment. The rate of response of lesions as assessed by structural imaging modalities such as CT is variable. Residual masses are common after treatment. Functional imaging with PET or gallium scanning may facilitate earlier response assessment than CT scans.

The recommendations for response assessment depend on the treatment modality.

- Assessment of response after definitive radiation therapy alone

Clinical, radiological, functional imaging and biochemical, full blood count (FBC), erythrocyte sedimentation rate (ESR) assessment should be performed 4–6 weeks after completion of treatment. There is no role for response assessment during therapy.

- Assessment of response after chemotherapy alone or after chemotherapy followed by radiotherapy

Physical assessment is recommended before each planned cycle. The timing of radiological response assessment may vary with the planned number of cycles and depend on whether radiotherapy is to be given to all involved sites after chemotherapy. As a minimum, at least one interim assessment should be made before the planned chemotherapy is completed, and a further assessment should be made upon completion of therapy if the first assessment did not show a complete response. Upon completion of all therapy, clinical, radiological, functional imaging and

biochemical, FBC and ESR assessment should be performed. Functional imaging reassessment is unnecessary after treatment if an interim response assessment showed complete response.

11.17.6 Functional imaging

The predictive value of intercycle review in determining outcome remains unclear. Response assessment using gallium in 37 patients after the fourth cycle of chemotherapy showed gallium negativity to be associated with very low risk of relapse.¹⁰⁸ Assessment following one cycle of chemotherapy is also reported to have prognostic influence with a negative predictive value of 92% but a positive predictive value of only 57%.¹⁰⁹ The prognostic influence of gallium and PET intercycle and following treatment may be stage-dependent. The negative predictive value for gallium post-treatment in patients with stage I–II disease was 94% as compared with 64% for patients with stage III and IV disease.³² The positive predictive value for PET performed post-treatment ranges from 60% to 100%. The negative predictive value has ranged from 74% to 96%.^{25,110,111} Response assessment during therapy remains a clinical research question. Current studies of functional imaging do not permit recommendations on changes to treatment policies.

11.17.7 Response assessment at completion of treatment

This has been arbitrarily set at four to six weeks for clinical, radiological, biochemistry, FBC and ESR. Functional imaging can be performed two to three weeks following chemotherapy and radiotherapy, allowing for physiologic uptake due to thymic hyperplasia, bilateral hilar and diffuse lung uptake. Response assessment criteria have changed to be consistent with the Cotswolds revision of the staging system for Hodgkin disease in 1989¹⁸ as discussed in Section 11.7. A new category of response was added, CR[u] (unconfirmed/uncertain complete remission), acknowledging that patients with HL can have a residual structural abnormality following treatment, which does not indicate persistent lymphoma.

Guideline — Hodgkin lymphoma — CT and PET scanning	Level of evidence	Refs
Functional imaging is recommended in addition to CT scanning to assess definitive response to treatment.	IV	25, 32, 108, 110
PET scanning rather than gallium scanning is recommended for response assessment after treatment for Hodgkin lymphoma.	IV	25, 110, 111

Other predictors of relapse

A change in ESR following treatment was found to be a strong predictor of relapse and survival for patients with early-stage HL treated in the H2 and H5 trials by the EORTC.¹¹² Relapse predictors included patients with a persistently elevated ESR (defined as >30 mls/hr), patients with a normal ESR before therapy but oscillating between normal and elevated following therapy, and those patients with an elevated ESR before therapy, but oscillating between normal and elevated after therapy.

Role of biopsy in the assessment of residual mass

When the only evidence of persistent disease is that on functional imaging and CT, and this significantly alters treatment policy (e.g. proceeding to high-dose therapy and autograft), a biopsy should be performed.

Follow-up recommendations to detect relapse

These recommendations are largely arbitrary. The small number of studies in this area would question the value of repeating multiple biochemical analyses, FBCs and ESR.^{107,113} In one study of 709

patients with stage I and II disease, 69% of relapses were suspected primarily by history and physical examination.

Recommendations

Clinical review is recommended three-monthly during the first and second year, four-monthly during the third year, six-monthly in the fourth and fifth years, and annually thereafter.

The type of imaging investigations and frequency may depend on the sites of original disease. Note that these recommendations do not take into account second malignancies, which are addressed under long-term follow up.

Long-term follow up to detect complications of therapy

For early and advanced-stage patients, the risks of death due to causes other than HL exceed those due to HL at 13–15 years. The relative risk of mortality for these patients remains significantly elevated more than 20 years following treatment.^{114,115}

Recommendation

Follow up of patients treated for HL should be indefinite. The optimal frequency of follow up is uncertain, but should be at least annually after five years. Patients should be informed of the increased risk of second malignancies and encouraged to seek early medical attention. Similarly, the general practitioners of patients should be aware of the increased risk of second malignancies in patients undergoing long-term follow up.

Specific investigations and clinical assessments

Thyroid function tests

For patients having radiotherapy to the neck, thyroid function tests (TSH, T4) should be performed yearly for an indefinite period following treatment.¹¹⁶ Hypothyroidism can occur from the first year following treatment up to and beyond twenty years.

Clinical examination of the thyroid

There is an excess risk of thyroid cancer. An annual examination of the thyroid gland is advised. Any thyroid abnormality, in particular any nodule, should be fully investigated.

Full blood count

The risk of leukaemia and myelodysplastic syndrome (MDS) is maximal between three and 12 years following treatment.¹¹⁷ Accordingly, a yearly FBC should be performed.

Chest x-ray

There is an increased risk of lung cancer following chemotherapy and radiotherapy for HL.^{118,119} Smoking in this population significantly increases the risk of lung cancer. Therefore all patients should be encouraged to stop smoking.¹²⁰ The role of routine chest radiography is unclear and no specific recommendation is possible.

Mammography

There is an increased risk of breast cancer in women previously treated with mantle irradiation alone or in combination with chemotherapy. The majority of studies indicate this increased risk is restricted to women undergoing radiotherapy at the age of thirty or younger, although excess absolute risk has been seen in older patients.^{121,122} The increased risk of breast cancer is apparent ten years after treatment and this risk persists more than 25 years after diagnosis of HL.

Women should receive information about the potential increased risk of breast cancer. Mammographic screening should begin ten years following treatment and to be performed yearly and

in conjunction with breast self examination.¹²³ The use of mammography in women younger than thirty years remains controversial. Any breast mass developing in women previously irradiated for HL should be investigated. This may include ultrasound and biopsy.

Chemoprevention

There is no established role for chemoprevention in relation to breast cancer in this patient group.¹²⁴

11.17.8 Management of primary refractory Hodgkin lymphoma

Patients who experience progressive disease during chemotherapy-based induction therapy or who have disease progression within 60 days of completing induction therapy have ‘primary refractory’ HL.¹²⁵ Their prognosis is poor and survival with conventional-dose salvage chemotherapy is less than 10% at ten years. The best chance for long-term survival in primary refractory disease is with high-dose chemotherapy and autologous stem cell transplantation (ASCT)¹²⁶ although primary refractory patients have inferior survival compared to patients treated with ASCT who relapsed after attaining a complete remission. In highly selected cases, radiotherapy may achieve long-term survival, but this may best be delivered in conjunction with high-dose therapy and ASCT.

Guideline — Primary refractory Hodgkin lymphoma	Level of evidence	Refs
Patients with primary refractory Hodgkin lymphoma should be treated with high-dose chemotherapy and autologous stem cell transplantation.	IV	126

11.17.9 Management of relapsed Hodgkin lymphoma

The rate of relapse after primary treatment for HL is related to the initial management strategy, the original extent of disease, and the influence of other prognostic factors. The relapse rate for early-stage patients is lowest in those treated with combined-modality therapy, and is higher in patients treated with radiotherapy or chemotherapy as single modalities. The relapse rate in advanced-stage disease is most accurately predicted by the international prognostic index. Due to the difficulty of assessment of residual masses and the possibility of change in histology or development of a NHL, it is recommended that recurrence is confirmed by biopsy before embarking on salvage therapy. The choice of salvage therapy is dependent upon the initial treatment strategy, the extent of relapsed disease, and the time that has elapsed from completion of primary treatment.

Key point

Biopsy is recommended to confirm first recurrence in all cases.

Relapse after initial radiation therapy

Combination chemotherapy without high-dose therapy results in durable ten-year disease-free and overall survival^{127,128}. It is the treatment of choice for relapse after radiotherapy. ABVD chemotherapy is recommended if there are no contraindications to its use. If there is a localised relapse outside the original radiation field, consolidation involved-field radiotherapy to the relapsed disease may improve progression-free survival.

Relapse after initial combination chemotherapy treated with conventional chemotherapy only at relapse

The prognosis for patients who relapse after initial combination chemotherapy is determined mainly by the duration of the first remission. Patients whose initial remission after chemotherapy was shorter

than one year (early relapse) do much worse than those with late relapses (relapses after more than one year)^{129,130} and have the most to gain from aggressive treatment strategies.

11.17.10 Relapse within one year

Relapse after initial combination chemotherapy—role of high-dose chemotherapy and haematopoietic stem cell transplantation.

Relapse after initial combination chemotherapy should be treated with re-induction with a chemotherapy regimen, followed by high-dose chemotherapy and ASCT¹³¹⁻¹³³. Patients who are responsive to re-induction with second-line chemotherapy have a better prognosis. Complete remission rates with ASCT are higher if only one previous chemotherapy regimen has failed, compared to two or more treatment failures. ASCT has been associated with higher rates of freedom from treatment failure than conventional-dose salvage chemotherapy in randomised studies.^{134,135}

Myeloablative allogeneic transplantation is inferior to ASCT because of the high mortality associated with the procedure and subsequent complications associated with graft versus host disease.¹³⁶

Relapse after initial combination chemotherapy—role of involved-field radiation post ASCT

Involved-field radiation therapy for residual masses after high-dose therapy results in improved progression-free survival.^{137,138} It is uncertain whether there is a significant effect on overall survival.

If high-dose therapy is contraindicated

Salvage chemotherapy with or without consolidation radiotherapy is recommended in patients who are fit enough for a curative approach.¹³⁹

11.17.11 Relapse after one year

Relapse after initial radiation therapy

Salvage conventional chemotherapy is recommended, as above, if primary treatment was radiotherapy.^{127,128}

Relapse after initial combination chemotherapy

Salvage chemotherapy with or without radiotherapy should be used if high-dose therapy is relatively or absolutely contraindicated.¹³⁵ High-dose therapy incorporating ASCT also improves freedom from treatment failure in this subgroup¹³⁵ and in particular, may be considered in high-risk subgroups. The ideal choice of salvage chemotherapy for patients who are not treated with high-dose therapy and stem cell transplantation is not known. The original regimen or a non cross-resistant one may be used.

Radiotherapy for localised relapse

In highly selected patients with only limited nodal recurrence following initial chemotherapy, radiation therapy (with or without additional chemotherapy) may provide long-term survival of up to 50%.^{140,141}

Palliation of patients who have had multiple relapses

Once curative options are exhausted, symptoms may respond to single-agent palliative chemotherapy¹⁴² or to localised radiotherapy (level III). Recruitment into clinical trials is recommended.

11.18 References

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