INTERNAL MEDICINE JOURNAL

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doi:10.1111/imj.15503

POSITION PAPER

Assessment and management of newly diagnosed classical Hodgkin lymphoma: a consensus practice statement from the Australasian Lymphoma Alliance

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Key words
Hodgkin lymphoma, PET adapted, chemotherapy, HL, radiotherapy.

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Received 7 May 2021; accepted 26 August 2021.

Abstract

The management of Hodgkin lymphoma (HL) has undergone significant changes in recent years. Due to the predilection of HL to affect younger patients, balancing cure and treatment-related morbidity is a constant source of concern for physicians and patients alike. Positron emission tomography adapted therapy has been developed for both early and advanced stage HL to try and improve the outcome of treatment, while minimising toxicities. The aim of this review is to digest the plethora of studies recently conducted and provide some clear, evidence-based practice statements to simplify the management of HL.

Introduction

Hodgkin lymphoma (HL) is a lymphoid malignancy of B-cell origin. Classical HL (CHL), accounting for 90–95% of cases, is the focus of this paper.[1] Nodular lymphocyte predominant HL (NLPHL) comprises the remaining 5–10%. In Australia, the annual incidence of HL is approximately 2.4–2.9/100 000 (500–600 cases/year).[2] CHL incidence has a bimodal age distribution, with a peak in patients aged 15–30 years and a second peak in patients aged >50 years. With an imperative to maximise cure while minimising long-term toxicity, a HL diagnosis in young adulthood brings additional implications for fertility, and patient engagement in therapeutic decision-making is required.

Methodology

This consensus practice statement was undertaken by a panel of lymphoma experts with particular interest in HL under the auspices of the Australasian Lymphoma Alliance (ALA) in accordance with the ALA policy for consensus practice statement development (Supporting Information Methodology S1).

Funding: None.
Conflict of interest: T. Cochrane: Honoraria – Celgene. S. A. Gangatharan: received conference registration funding from AstraZeneca and Roche. Advisory board for AstraZeneca. MJD: advisory boards for MSD and Takeda, Research funding from MSD.

Diagnosis

The diagnostic, malignant Hodgkin Reed–Sternberg (HRS) cells comprise only a minority of cells in the tumour, with the bulk of the cellular infiltrate being a rich milieu of inflammatory cells and sometimes regions of fibrous sclerosis. Excisional biopsy is preferred; however, a good quality core biopsy may suffice. Classic HRS are derived from germinal centre B-lymphocytes crippled during maturation. Typical immunohistochemistry for HRS cells are CD30+/CD15+/CD45−; the B-cell antigens CD20/C79a are frequently negative; however, PAX5 is demonstrable in most cases.[1] The histological pattern of the surrounding inflammatory infiltrate further subtypes CHL into four histological variants: (i) nodular sclerosis; (ii) mixed cellularity; (iii) lymphocyte rich; and (iv) lymphocyte deplete.[1] These subtypes do not impact on treatment selection.

Clinical features

Contiguous nodal spread is typical. Most patients present with cervical and mediastinal lymphadenopathy. Isolated infradiaphragmatic disease, seen in 10% of patients, is more common in older individuals. Constitutional ('B') symptoms defined as unexplained pyrexia (>38°C), drenching night sweats in the previous month, or significant (>10% in 6 months) weight loss, occur in 40% of patients. Pruritis and chest pain following alcohol consumption are described. Bone marrow involvement occurs in the minority (<10%) of cases.[3]

Recommendation

- Diagnostic workup as per Table 1. (I,A)

Staging and risk stratification

Staging is according to the modified Ann Arbor classification (Table 2).[3] Early stage HL (ESHL) is risk stratified into favourable (ESHL-F) and unfavourable (ESHL-U) risk groups, with notable differences between the German Hodgkin Study Group (GHSG) and the European Organisation for Research and Treatment of Cancer (EORTC) (Table 3).[4] Lymph node areas used in these

Table 1 Diagnostic workup

	Diagnostic investigation	Rationale for test	Comment
Histopathology	Core or excision biopsy of a PET avid lesion	For diagnosis	
Bloods			
	FBE	Pre-treatment assessment	
	Full biochemistry†	Pre-treatment assessment	
	ESR	Risk stratification	
	Hepatitis B/C/HIV serology	Pre-treatment assessment	
	Beta HCG	Pre-treatment assessment	For females of reproductive age
Imaging	PET-CT with full contrast-enhanced CT‡	Staging, risk stratification and for subsequent response assessment	A separate contrast-enhanced CT is not required provided the initial PET scan included a contrast-enhanced CT
	CXR	Staging and risk stratification	
Bone marrow	Bone marrow aspirate and trephine	Not recommended if PET-CT done. Consider performing if there are unexplained cytopenias	Homogenous uptake is likely reactive, consider bone marrow involvement if there is focal or multifocal avidity on PET scan
Functional organ assessment	Cardiac assessment (MUGA or echo)	Pre-Rx assessment	
	Pulmonary function	Pre-Rx assessment and for subsequent comparisons	Ensure DLCO is examined
Other	Reproductive counselling and fertility preservation	To consider sperm/oocyte/embryo/ovarian tissue preservation pre-treatment where feasible	Referral to a reproductive specialist particularly for female patients who want to preserve their fertility must be done expediently

†Full biochemistry includes electrolytes, urea, creatinine, liver function test and lactate dehydrogenase.
‡As per Cheson *et al.*,[3] staging should involve a PET-CT, where the CT component is low dose. A contrast-enhanced CT (either done at the same time as the PET-CT or at another time) is favoured as it provides superior characterisation of disease extent, if radiotherapy is planned.
CT, computed tomography; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; FBE, full blood examination; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; MUGA, multigated acquisition; PET, positron emission tomography.

Internal Medicine Journal **51** (2021) 2119–2128

Table 2 Ann Arbor staging with Cotswold's modification

Stage	Disease extent
I	One node or a group of adjacent nodes
II	Two or more nodal groups on the same side of the diaphragm
II-bulky	II as above with bulky† disease
III	Nodes on both sides of the diaphragm
IV	Additional non-contiguous extra lymphatic involvement
A	Add to stage if there are no B-type symptoms
B	Add to stage if there are B symptoms (10% weight loss over 6 months, fevers >38°, recurrent drenching night sweats
E	This is added to stage I or II disease only when there is direct extension into an extranodal site‡

†Bulk is defined as a single nodal mass of at least 10 cm, or greater than a third of the transthoracic diameter.
‡Lymph nodes, spleen, Waldeyer's ring and thymus are considered nodal sites, with others defined as extranodal.[3]

Table 3 Staging and risk factors

	GHSG	EORTC
Early stage favourable	Stage I or II and no risk factors present	Stage I or II (supradiaphragmatic disease only) and no risk factors present
Early stage unfavourable	Stage I, IIA with any risk factor listed below. Stage IIB with risk factor C or D	Stage I or II with at least one risk factor
Advanced stage	Stage IIB with risk factor A or B or stage III or IV	Stage III or IV
Risk factors	A. Bulky mediastinal mass B. Extranodal involvement C. Raised ESR (≥50 or ≥30 with B symptoms) D. Three or more nodal sites	Bulky mediastinal mass Age ≥50 years Raised ESR (≥50 or ≥30 with B symptoms) Four or more nodal sites

EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group.

definitions differ from lymph node regions in the Ann Arbor classification (Table S1). Advanced stage HL (ASHL) includes stage III/IV disease and in the GHSG classification, stage IIB disease with bulk or extranodal disease. The International Prognostic Score (IPS)[5] is a tool to further risk-stratify ASHL (Table 4); however, there are no published trials that determine management by IPS score.

FDG-PET in staging and response assessments

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan is the modality of choice for initial staging and response assessments in HL. FDG-PET scans are visually scored using a 5-point scale relating FDG-PET avidity to mediastinal and liver blood pool (Deauville Score (DS); Table S2). FDG-PET is an integral component of response adapted therapy. Interim FDG-PET scans (iPET) are generally conducted after 2 cycles of therapy (iPET2). Trial definitions may differ when defining the cut-off for negative iPET; some use ≤DS2,[6–8] others use ≤DS3.[9] A negative end of chemotherapy (EOCT) FDG-PET scan, consistently defined as ≤DS3, is considered a complete remission. A positive EOCT-PET scan requires further investigation as differentiating residual HL from benign causes of FDG avidity can be difficult; when biopsy is not practical, serial FDG-PET may be considered.

Table 4 International prognostic score: adverse risk factors

Serum albumin, <40 g/L
Haemoglobin, <105 g/L
Male sex
Stage IV disease
Age, ≥45 years
White cell count, ≥15 × 10^9/L
Lymphocyte count, <0.6 × 10^9/L or <8% of white cell count

Each factor present is given 1 point. Score is out of 7.

Recommendations

- Accurate staging and risk stratification must be documented in all patients with HL. (I,A)
- PET is the preferred modality for staging and response assessment. (I,A)

Management

Principles of radiation therapy

The goal of radiation therapy (RT) within a multimodality approach is to optimise local control. Over time, RT doses and volumes have dramatically reduced as the understanding of radiation-induced carcinogenesis and late effects has evolved. Improvements in systemic therapy efficacy and RT technologies have allowed target volumes to reduce from historical total nodal irradiation,[10] to modern involved node (INRT) or involved site (ISRT) radiotherapy,[11] with excellent cure rates maintained. Of note, INRT and ISRT are critically dependent on the adequacy of pre-chemotherapy imaging. The smaller INRT volume may be considered a 'special case of ISRT' when there is optimal pre-chemotherapy imaging: localising initial disease sites on pre-chemotherapy PET/CT acquired with the patient in the RT treatment position. Technical RT guidelines are

Table 5 Chemotherapy regimens

ABVD regimen (1 cycle is given every 28 days)			
Drug	Dose	Route	Day
Doxorubicin	25 mg/m^2	IV	1 and 15
Vinblastine	6 mg/m^2	IV	1 and 15
Dacarbazine	375 mg/m^2	IV	1 and 15
Bleomycin	10 000 IU/m^2	IV	1 and 15
eBEACOPP regimen (1 cycle is given every 21 days			
Drug†	Dose	Route	Day
Bleomycin	10 000 IU/m^2	IV	8
Etoposide	200 mg/m^2	IV	1 to 3
Doxorubicin	35 mg/m^2	IV	1
Cyclophosphamide	1250 mg/m^2	IV	1
Vincristine	1.4 mg/m^2 (max 2 mg)	IV	8
Prednisolone	40 mg/m^2	PO	1 to 14
Procarbazine	100 mg/m^2	PO	1 to 7

†A corticosteroid pre-phase should be considered prior to commencing eBEACOPP in patients >40 years.

published by the International Lymphoma Radiation Oncology Group (ILROG).[12]

Principles of chemotherapy

Doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) is commonly used (Table 5). Maintaining dose intensity is important, and ABVD does not require G-CSF as primary prophylaxis, even with grade 4 neutropenia.[13] Monitoring of respiratory symptoms is required with bleomycin, with omission of bleomycin advisable if new respiratory symptoms develop. Bleomycin must be used with caution in patients >60 years.

Escalated BEACOPP (Table 5) is an intensive regimen, reserved for patients aged <60 years. For patients aged 40–59 years, caution is advised due to the increase in treatment-related mortality (TRM); the GHSG recommends hospital admission in cycle 1 for the neutropenic phase.[14] Dose reductions may be required according to toxicities[15] and prophylactic medications (filgrastim, pneumocystis jirovecii and antiviral prophylaxis are recommended).

Early stage favourable HL

ESHL-F accounts for approximately 45% of ESHL.[16] Following first-line therapy, 5-year OS is >90%.[17] Chemotherapy plus consolidation RT (combined modality therapy, CMT) is the current standard of care.[18] For patients with ESHL-F according to GHSG criteria, 2 cycles of ABVD (ABVD×2) followed by 20 Gy RT, is acceptable. The GHSG HD10 randomised trial[19] of 1190 patients confirmed that treatment intensity could be safely reduced from 4 cycles of ABVD to 2, and 30 Gy of RT to 20 Gy.

Three PET-adapted trials in ESHL-F have confirmed the benefit of CMT. RAPID[8] and EORTC H10[7] used 3 cycles of ABVD plus RT as the standard arm and randomised patients with negative iPET (≤DS2) to CMT versus ABVD alone (3 or 4 cycles). GHSG HD16[6] attempted to omit RT in patients with a negative PET after ABVD×2. All three trials revealed increased rates of progression (by 7–12%) with chemotherapy alone.

iPET has utility for PET-adjusted intensification of therapy. EORTC H10[7] demonstrated superior outcomes in a combined analysis with ESHL-U when therapy was changed to eBEACOPP for 2 cycles (eBEACOPPX2) plus RT in patients with positive iPET2 (≥DS3). If escalation to eBEACOPP is not possible, good outcomes are still achievable,[8] with 87% PFS for patients with positive iPET3 receiving total ABVD×4 plus 30 Gy RT, at median 62 months follow up.

Recommendations

- CMT consisting of abbreviated ABVD plus RT is the standard of care. (I,A)
  - Two cycles ABVD and 20 Gy RT for patients who fit GHSG favourable criteria. (II,A)
    OR
  - Three cycles of ABVD and 30 Gy RT. (II,A)
- Positive iPET post 2 cycles of ABVD identifies patients at higher risk of treatment failure:
  - Treatment escalation with 2 cycles eBEACOPP followed by 30 Gy RT is preferred. (II,A)
    OR
  - Four total cycles of ABVD plus RT may be used if escalation to BEACOPP is inappropriate. (II,A)
- No clear risk group has been identified in whom RT might be omitted without potential detriment in PFS (I,A). RT omission may be considered if the radiotherapy field exposes the patient to unacceptably high risk of long-term toxicity (as determined by a radiation oncologist). In this context, no fewer than 3 cycles of ABVD should be delivered.

Early stage unfavourable HL

ESHL-U accounts for approximately 55% of ESHL. Five-year patient outcomes on contemporaneous protocols are 90–95% PFS and 95% OS.[7,20] The standard CMT used to benchmark other therapeutic strategies is 4 cycles of ABVD plus 30 Gy RT.[18]

GHSG HD14[20] randomised patients with ESHL-U to ABVD×4 plus 30 Gy RT, or eBEACOPP×2 then ABVD×2 (so-called '2 + 2') plus 30 Gy RT. Patients who received '2 + 2' plus RT had improved 5-year PFS:

95.4% versus 89.1%, ($P < 0.001$). The improved 10-year PFS of '2 + 2' regimen (91.2% vs 85.6%; $P < 0.0001$) was confirmed, without differences in OS or secondary malignancies.[21]

In the ESHL-U cohort of EORTC-H10,[7] a PET-adapted approach was compared to ABVD×4 plus 30 Gy RT. In the PET-adapted arm, patients with negative iPET2 (≤DS2) received additional ABVD×4 alone (total, 6 cycles ABVD). Of the 594 patients who were iPET2 negative, those who received CMT had a 92.1% 5-year PFS, versus 89.6% in the ABVD-alone arm. The criteria for non-inferiority were not met, and CMT remains the standard of care for patients with negative iPET2 after ABVD×2. Patients with positive iPET2 (≥DS3) after ABVD×2 in EORTC-H10 either received 2 further cycles of ABVD plus 30 Gy RT (standard arm) or received eBEACOPP×2 plus 30 Gy RT (experimental arm). The intensification to eBEACOPP was associated with improved 5-year PFS: 90.6% versus 77.4% ($P = 0.02$).[7]

GHSG HD17[22] has demonstrated that FDG-PET may identify patients in whom RT may be omitted following intensified initial chemotherapy using the '2 + 2' regimen. In the PET-adapted arm, patients with negative EOCT-PET (≤DS2) did not receive RT; this PET-guided approach was non-inferior to CMT (5-year PFS of 95.9% for no RT vs 97.7% for CMT). A greater risk for treatment failure (5-year PFS 81.6%) is evident if EOCT-PET is DS ≥4.

A chemotherapy-only approach may be considered for patients in whom CMT is not appropriate due to the high risk of radiation-induced toxicity, as determined by a radiation oncologist.

Recommendations

- CMT using 4 cycles of ABVD followed by 30 Gy RT is an accepted standard. (I,A)
- The 2 + 2 regimen (eBEACOPP ×2 + ABVD ×2) is another accepted standard chemotherapy regimen and PET directed omission of RT may be considered in patients treated with the 2 + 2 regimen if the EOCT PET is negative. (II,A)
- A positive iPET after 2 cycles of ABVD identifies patients at higher risk of treatment failure. Treatment escalation with eBEACOPP ×2 followed by 30 Gy RT is preferred. (II,A)Completing 4 total cycles of ABVD and RT[18] should be considered where escalation to eBEACOPP is not appropriate.
- A chemotherapy-alone strategy may be considered for patients at high risk of RT-induced complications. Options include:
    - '2 + 2' regimen, if EOCT-PET is negative. (II,A)
    - ABVD ×2 then iPET directed
        - If iPET2 is negative, complete an additional ABVD ×4 or AVD ×4. (II,A)
        - If iPET2 is positive consider changing to eBEACOPP ×4 (in young, fit patients). (III-3,B)

Advanced stage HL

ASHL is typically managed with chemotherapy alone. Six cycles of ABVD (ABVD×6) achieve 5-year FFS of 61–85% and OS of 73–87%[23] and remains a standard against which new therapies are compared. Escalated BEACOPP for 6 cycles yields improved PFS and OS relative to ABVD in patients aged <60 years,[24] but comes with increased short and long-term toxicities. Interim PET-stratified approaches have been evaluated in an attempt to select the patients most likely to benefit from an intensified approach.

Patients with negative iPET2 after ABVD×2 may have bleomycin safely omitted for subsequent cycles. In the RATHL study[9] of 1200 patients with stage IIA-IVB HL (58% had stage III/IV), the omission of bleomycin did not adversely impact survival: patients with negative iPET2 scans (≤DS3) were randomised to 4 further cycles of ABVD versus AVD: 3-year PFS was 85.4% and 84.0%, respectively, with non-inferiority demonstrated.[25] Treatment escalation to eBEACOPP for those with positive iPET2 scans resulted in 3-year PFS of 68%.[9] Compared with historical controls of ABVD alone,[26,27] this approach may have a PFS benefit, but head-to-head studies are lacking.

In patients with negative iPET2 following 2 cycles eBEACOPP, treatment may be de-escalated from 6 cycles of eBEACOPP to 4 cycles, with improved safety profile. In GHSG HD18,[28] patients with ASHL (stage IIB-IVB) were commenced on eBEACOPP, and those who were iPET2 negative (≤DS2) were randomised to 2 versus 4 additional cycles of eBEACOPP. In the recent 5-year update[29] among iPET-negative patients, a total of 4 cycles of eBEACOPP was found to be non-inferior to 6 cycles of eBEACOPP (5-year PFS, 91.0% vs 90.9%, respectively).[29] A post hoc analysis found equivalent 3-year PFS rates for patients with DS3 and DS1-2 on iPET2; hence, GSHG HD21 uses DS ≤3 to define a negative iPET2.[30]

In patients with negative iPET2 following 2 cycles of eBEACOPP, de-escalation to ABVD to complete a total of 6 cycles of treatment, delivers comparable survival outcomes to 6 cycles of eBEACOPP. In the AHL2011 study,[31] 800 patients with stage IIB-IVB HL commenced eBEACOPP, with iPET2 performed after cycle 2. Patients assigned the standard arm received a further 4 cycles of eBEACOPP, those in the experimental arm were de-escalated to 4 cycles of ABVD if iPET2 was negative (≤DS3). AHL2011 demonstrated that de-escalating to

ABVD did not compromise outcome (5-year PFS 86.2% vs 85.7% respectively).

Brentuximab vedotin (BV) combined with AVD (A-AVD) has been compared to ABVD chemotherapy in untreated ASHL[32] and resulted in a 7% improvement in 3-year PFS (83% vs 76%)[33]; patients with higher risk disease (stage IV, IPS score 4–7 and extranodal disease) appeared to have greater benefit from A-AVD. Notably, there were greater incidences of peripheral neuropathy and neutropenia with A-AVD. Currently, BV is not TGA approved for the treatment of untreated ASHL.

Conventionally, consolidation RT has been considered for patients with ASHL with bulky disease or incomplete response. The role of PET-directed consolidative RT at the EOCT has been difficult to evaluate in randomised studies due to issues of power and feasibility. Data support the omission of RT after eBEACOPP if the EOCT-PET scan is negative.[34] HD607[35] randomised 296 patients treated with ABVD with negative iPET *and* EOCT-PET to consolidation RT versus observation. There was no difference in 6-year PFS, and pre-subgroup analyses did not detect differences in outcomes based on baseline bulk.

Recommendations

- PET-adapted treatment is preferred for fit patients aged <60 years. (I,A)
- PET-adapted strategies include:
  - ABVD×2, escalating to eBEACOPP if iPET2 is positive (III-3,B), or continuing with AVD if iPET2 is negative. (II,A)
  - eBEACOPP×2, continuing to 4 instead of 6 cycles of eBEACOPP if iPET2 is negative. (II,A)
  - eBEACOPP×2, de-escalating to additional ABVD×4 if iPET2 is negative. (II,A)
- If a PET-adapted approach is not possible, acceptable alternatives are ABVD×6 or 6 cycles of eBEACOPP. (I,A)
- RT may be omitted if EOCT-PET is negative after eBEACOPP and if iPET *and* EOCT-PET are negative when ABVD is used. (II–III,A)
- If EOCT-PET is positive at sites of the original HL, RT should be considered if FDG-avid residual disease is ≥2.5 cm and is safely encompassable within the RT field. (Note: If there is a concern of disease progression on the EOCT-PET, consider a repeat biopsy and manage as refractory HL.) (III-2,B)

Elderly HL patients

In the context of HL, elderly is defined as >60 years. Older patients are more likely to have mixed cellularity histology, stage III/IV disease, infradiaphragmatic presentation, less bulk and higher incidence of B-symptoms.[36]

Tolerance to ABVD is compromised in older patients. Increased incidence of bleomycin toxicity during ABVD is reported (5–36%), with TRM approaching 25%.[37] Bleomycin lung toxicity rates increase when patients receive >2 cycles of ABVD.[38,39] Even with bleomycin omitted, grade 3–4 adverse events were 40% in the AVD arm of GHSG HD13 trial.[39] There is no role for treatment escalation (e.g. eBEACOPP) due to unacceptably high TRM.[36]

Many studies in ESHL included patients up to 70–75 years.[6–8,19,40] Thus, in fit patients aged ≤75 with ESHL a reasonable option would be 2–4 cycles of A(B)VD (depending on risk factors) plus RT.

The management of ASHL in older patients is challenging, with notable under-representation in clinical trials.[9,23] Attempts to use a tolerable, yet effective, chemotherapy regimen for older patients have not demonstrated a clear advantage of one regimen over the other.[41,42] If co-morbidities allow, an anthracycline-based regimen is preferred.[36]

For very frail patients, better-tolerated regimens such as ChlVPP[15] are available, but have inferior outcomes. Careful assessment of frailty and discussion around treatment goals are necessary prior to starting therapy.

Recommendations

- Treatment strategies for ESHL in the fit elderly group (61–75 years) are in line with prior sections for younger patients; 2–4 cycles of A(B)VD, followed by RT. (I,A)
- The treatment strategy for ASHL is 6 cycles of chemotherapy. (I,A)
- Anthracycline-based chemotherapy should be used where possible in older patients with HL. Consider A(B)VD or CHOP(42)or PVAG(41). (III-3,B-C)
- Bleomycin must be used with caution in patients >60 years, and if used, should be limited to 2 cycles. (III-2,B-C)
- eBEACOPP should not be used in patients >60 years. (II,A)

Surveillance of late effects

Long-term survivors of HL are at risk of late treatment-induced toxicities (Table S3). These include second malignant neoplasms (SMN), cardiovascular and pulmonary toxicity, endocrinopathies and infertility. Secondary malignancy, cardiovascular and pulmonary deaths constitute the leading causes of non-HL mortality.[43–46] Long-term surveillance is recommended and should commence 5 years after completion of treatment.[47] Primary prevention and risk minimisation strategies are strongly encouraged.

Second malignant neoplasms

Although solid cancers account for most SMN in HL survivors, the standardised incidence ratio for haematological malignancies is greater: 4.2 for solid cancer versus 10.4 for haematological malignancy.[48] An increased risk of solid tumours begins approximately 5 years after therapy and continues to rise for >30 years,[49] whereas the risk for secondary haematological malignancies is greatest in the first 10 years.[50] Incidence and relative risk of death from SMN are associated with younger age at treatment.[43,48] Of note, reported incidences of morbidity and mortality of SMN are largely derived from historical regimens and may not reflect contemporary protocols or techniques.

The risk of secondary breast cancer is greatest in female patients receiving supradiaphragmatic, 'mantle' extended-field RT and aged <30 years at the time of RT. Alkylator exposure and/or pelvic RT are protective, putatively through ablative effects on ovarian function.[48,51–54] Higher RT doses[52] and large volumes[55] increase the risk, which may be up to 32-fold using historical doses and fields.[56] With contemporary RT techniques, secondary breast cancer rates have substantially reduced,[57] with one report suggesting CMT may not confer any greater risk of breast cancer relative to chemotherapy alone.[58]

Therapy-related myeloid neoplasms are well-recognised risks in long-term survivors of HL, and typically have a poor prognosis.[59,60] Alkylating agents and topoisomerase II inhibitors are leukemogenic; regimens using these agents may result in a greater risk relative to ABVD.[24,59] There is also thought to be an effect from combined exposure to both alkylators and RT.

Patients receiving neck RT are at risk of thyroid neoplasms[61] RT-induced thyroid cancer risk is dose-dependent: reportedly up to 14.6-fold greater after <20 Gy,[46,54] whereas doses >20 Gy may produce lower risk due to the cytocidal effect of RT on radio-sensitive thyroid tissue.[46,54] Other risk factors include female sex, age <10 years at the time of RT and longer time since treatment.[46]

Smokers with exposure to thoracic RT are at the greatest risk of lung cancer,[62] with a multiplicative effect observed.[56] The risk of secondary lung cancer is also increased in patients with exposure to alkylating agents (particularly procarbazine), even in the absence of thoracic RT.[48]

Late organ toxicities

Patients with prior exposure to anthracyclines and/or mediastinal RT have lifelong risks of cardiac sequelae. Treatment-induced cardiotoxicities are dose-related and include cardiomyopathies, coronary artery disease, arrhythmias, valvular and pericardial disease.[63,64]

Bleomycin exposure[65] and thoracic RT are known causes of pulmonary toxicity. Risks for late lung fibrosis are dose-related and greater in patients with acute treatment-induced pneumonitis or pre-existing interstitial lung disease.

Endocrinopathies are common late toxicities. Hypothyroidism-risk following neck RT is dose-dependent, and those at a younger age at the time of RT.[66] Rates of hypothyroidism are inversely proportional to time since treatment, but remain elevated for >25 years.[66] Risks of RT-induced hyperthyroidism are dose-dependent, with the radiation-related excess risk also persisting for >25 years.[67] Chemotherapy-induced hypothyroidism can be seen following bleomycin and cyclophosphamide.[66] Premature gonadal insufficiency and infertility are associated with alkylating chemotherapy agents and/or pelvic RT. These risks are age-related in both sexes, with higher rates of toxicity observed in patients aged >30 years at the time of therapy.[68] Although ABVD is considered to be lower risk, transient azoospermia can occur, but usually recovers by 2 years. Bone density loss can ensue following premature gonadal insufficiency, steroid or alkylating agent use.

Recommendations

- Screening and surveillance of late effects are outlined in Table S3.[69-72] (IV,A)

Conclusion

The diagnosis, workup and management of HL present unique challenges. Evidence-based options are now available for all stages of HL, accommodating patients' values and priorities. The informed consent process for therapy, particularly in young patients, requires detailed discussion of the pros and cons of each approach. Ideally, all patients with newly diagnosed HL should be discussed at a multi-disciplinary team meeting including specialists in pathology, radiology, nuclear medicine, haematology and radiation oncology. Physicians' concerns about the increased risks of intensive therapies may be partially addressed through recent data on iPET driven approaches. Although Programmed-Death-1 inhibitors and BV have a clear role in relapsed/refractory HL, there are presently no convincing data to justify routine use in the front-line setting. An important goal of newer regimens is to improve upon outcomes achieved by ABVD and eBEACOPP in higher risk HL, including reduction in both short and long-term toxicities.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Methodology S1. Consensus practice statement.
Table S1. Lymph node site categorisation by study group.
Table S2. Deauville score.
Table S3. Recommended surveillance for late effects of oncological treatments for HL.
Table S4. Levels of evidence.
Table S5. Grades of recommendations.