PANEL DISCUSSION: MYELOMA & LYMPHOMA

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Multiple myeloma

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Introduction

Multiple myeloma is the third most common form of haematological malignancy after non-Hodgkin’s lymphoma and leukaemia and is characterised by uncontrolled proliferation of a clone of plasma cells within the bone marrow.

Diagnosis is based on laboratory and radiographic findings and depends on three abnormal results:

- Bone marrow containing more than 15% plasma cells (normally no more than 4% of the cells in the bone marrow are plasma cells)
- Generalised osteopaenia and/or lytic bone deposits on plain film radiography
- Blood serum and/or urine containing an abnormal protein.

Median survival with conventional therapy is about 3 years, whilst stem-cell transplant can achieve a median survival of more than 5 years[1]. Overall, the prognosis is poor with the most recent statistics from the USA showing a relative 5-year survival of 29%[2]. Death results from bacterial infection, renal insufficiency and thromboembolism.

Staging

The staging system devised by Durie and Salmon is the most widely used (Table 1)[3]. Other groups have proposed new systems to more accurately and simply stage and/or classify myeloma patients into prognostic categories. Whilst none have gained universal acceptance two are under active consideration, both of which recognise the serum β2 microglobulin level as the core measurement[4,5].

Radiology

Almost 80% of patients with multiple myeloma will have radiological evidence of skeletal involvement and the skeletal survey remains the best method of identifying lytic deposits within bone. Myeloma lesions are sharply defined, small lytic areas (average size 20 mm) of bone destruction with no reactive bone formation. The pattern of destruction may be geographic, moth-eaten or permeated. Pathological fractures are common. Generalised osteopaenia may be the only bone manifestation of myeloma in up to 15% of patients. Normal bone surveys are noted in 10% of myeloma patients.

The bone scan is often normal or may show areas of decreased uptake (photopaenia). Skeletal scintigraphy may be helpful in evaluating areas not well visualised on plain film radiographs such as the ribs and the sternum. ⁹⁹ᵐ⁹¹⁷⁹⁹⁹⁹mTechnetium methoxyisobutylisonitrile (⁹⁹ᵐ⁹⁹⁹⁹mTc-MIBI) has been shown to be superior to plain film radiography and skeletal scintigraphy in detecting bone and bone marrow involvement[6]. Positron emission tomography (PET) using the glucose analogue fluorine-18 fluorodeoxyglucose is reliable in detecting active myeloma both within bone and at extramedullary sites[7].

A recent study using multidetector computed tomography (MDCT) in patients with stage III myeloma provided more detailed information on the risk of vertebral fractures compared with plain film radiography and magnetic resonance imaging (MRI)[8]. It is likely there will be an increasing role for this technique in patients who are severely disabled or who are unable to undergo MRI examination.

Different imaging patterns can be identified on MRI though lack of specificity should be noted[9,10]. Normal marrow is present on MRI at diagnosis in 50–75% of patients with early untreated (stage I) myeloma and in about 20% of patients with advanced and treated (stage III) disease.
Table 1  Staging system

| Stage | Criteria | Cell mass |
|-------|----------|-----------|
| I     | All of the following: Haemoglobin > 10 g/100 ml Normal serum calcium < 12 mg/100 ml Normal bone structure or solitary bone lesion only on radiography Low M component production rates IgG < 5 g/100 ml IgA < 3 g/100 ml Urine light chain M component on electrophoresis < 4 g/24 h | Low <0.6 × 10^{12} cells/mm^{2} |
| II    | Fitting neither stage I nor stage III | Intermediate |
| III   | One or more of the following: Haemoglobin < 8.5 g/100 ml Serum calcium > 12 mg/100 ml Advanced lytic bone lesion High M component production rates IgG > 7 g/100 ml IgA > 5 g/100 ml Urine light chain M component on electrophoresis > 12 g/24 h | High >1.2 × 10^{12} cells/mm^{2} |

Subclassifications: A, relatively normal renal function (serum creatinine value < 20 mg/100 ml [175 mmol/l]); B, abnormal renal function (serum creatinine value > 20 mg/100 ml [175 mmol/l]).

Compression fractures in multiple myeloma

Several criteria exist for differentiating benign from malignant vertebral body compression fractures[111]. However, these should be applied with caution to patients with multiple myeloma as normal signal intensity within a compressed vertebral body on spinal magnetic resonance images does not preclude the diagnosis of multiple myeloma. Patients being treated for multiple myeloma may suffer acute back pain secondary to vertebral body collapse even after effective chemotherapy due to resolution of the tumour mass that was supporting the bony cortex.

Assessment of response to treatment

The role of radiology in the assessment of treatment response is limited and sequential quantification of biological markers of disease (monoclonal protein levels and bone marrow plasmacytosis) is sufficient to assess response to chemotherapy.

Relationship of radiology to laboratory values and prognosis

Patients with at least two lytic foci are classified in advanced disease subgroups and aggressive systemic treatment is usually indicated. Patients with the normal and variegated patterns tend to have a lower tumour burden than those with the focal and diffuse marrow involvement patterns on MRI. High levels of serum β2 microglobulin correlate with a poor prognosis and remain the single most powerful determinant of outcome[12]. No correlation between this finding and appearances on MRI has yet been demonstrated.

Complications

The complications of multiple myeloma can be summarised as

- Spinal cord compression
- Pathological fractures
- Secondary amyloidosis
- Renal impairment
- Predilection for recurrent pneumonia due to leuco-paenia
- Thromboembolism.

A pathological fracture affects about 50% of patients at some time with many of the fractures affecting the vertebral bodies. Spinal cord compression resulting from vertebral body fracture may occur in up to 25% of patients and has been described as the presenting feature in 12% of patients[13]. Magnetic resonance is the imaging investigation of choice.

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Extranodal lymphoma—neck

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Abstract

Non-Hodgkin’s lymphoma (NHL) is the third most frequent malignant tumour in the head and neck, basocellular carcinoma of the skin and mucosal squamous cell carcinoma being the most frequent. Although nodal enlargement is the most common presentation in the head and neck, NHL may occur in extranodal locations. Two distinct extranodal sites are recognised: extranodal lymphatic locations or involvement of the ring of Waldeyer, and extranodal extralymphatic locations. Neck extranodal NHL does not show pathognomonic imaging signs. However, if more than one extranodal mass is detected, if the mass appears huge without necrosis or ulceration, or when associated with large, non-necrotic adenopathies, the diagnosis of NHL can be suggested. The possibility of NHL should be kept open in any infiltrating soft tissue mass in the head and neck region. While fine needle aspiration is often helpful to reach a diagnosis of squamous cell carcinoma, formal biopsy is usually required to diagnose lymphoma. Head and neck Hodgkin’s lymphoma is less common than NHL. Furthermore, extranodal involvement only rarely occurs in Hodgkin’s lymphoma.

Keywords: Head and neck neoplasms; lymphoma.

Introduction

Non-Hodgkin’s lymphoma (NHL) is a heterogeneous group of neoplasms originating from lymphocytes or their derivatives. NHL has varying clinical presentations and different courses and prognoses. Various classifications have tried to predict the outcome of these tumours. The current WHO classification divides lymphoid malignancies largely into T-cell and B-cell neoplasms (both constituting NHL), and Hodgkin’s disease. The T-cell phenotype is a poor prognostic factor[1].

NHL is a disease of the middle-aged and elderly, with only few cases occurring before the age of 40. It represents about 5% of head and neck malignancies.
About 11% of NHLs present with lesions in this region, and about 50% of patients with head and neck disease have systemic disease.

NHL can involve virtually any site in the extracranial head and neck. Nodal involvement is common. Extracranial involvement occurs in about one-quarter of patients with head and neck NHL [2]. Two distinct extracranial sites are recognised: extranodal lymphatic spread or involvement of Waldeyer’s ring, and extranodal extralymphatic spread [3]. Extranodal lymphatic and extralymphatic locations occur with more or less similar frequency.

**Involvement of Waldeyer’s ring (extranodal lymphatic spread)**

In this group, the disease may be limited to the tonsils in Waldeyer’s ring; multiple locations in different tonsils may be present. The disease may also extend beyond the borders of Waldeyer’s ring, showing an infiltrative pattern of growth. Differentiation between squamous cell carcinoma and NHL in Waldeyer’s ring is frequently difficult and sometimes impossible based on radiological findings, especially when there is extension outside the tonsils. Findings suggesting the diagnosis of NHL are multiple non-contiguous sites of disease (rarely seen in squamous cell carcinoma) and the association with large, non-necrotic lymph nodes, especially when they are bilateral, non-contiguous and in unusual draining routes for squamous cell carcinoma (Fig. 1). However, non-necrotic nodes are not specific for lymphoma; the nodes associated with keratinising squamous cell carcinoma show a tendency for central necrosis, and those with the non-keratinising form may become quite large without the occurrence of necrosis. Furthermore, nodal hypodensities are sometimes observed in patients with NHL, also when untreated (Fig. 2) [3,4].

The diagnosis of NHL can be strongly suggested if there is an association between a location in the ring of Waldeyer and an extralymphatic location, as synchronous sites of non-mucosal squamous cell carcinoma are exceedingly rare [5].

There is a known association between NHL of the ring of Waldeyer and involvement of the gastrointestinal tract with the same disease; the stomach is most frequently involved. Lymphatic extranodal head and neck NHL occurring simultaneously with gastrointestinal involvement or recurring in the gastrointestinal tract can be explained by the existence of mucosa-associated lymphoid tissue (MALT), distinct from the somatic lymphoid tissue in lymph nodes [6]. Lymphocytes derived from MALT show the capacity of ‘homing’ back to their mucosa of origin or to other MALT sites (gut, Waldeyer’s ring, bronchus and lung, salivary tissue).

**Extranodal extralymphatic spread**

The sinonasal cavity and palatum are most frequently involved. In this location, bone alterations are often present. Lymphoma has been reported to be associated with bone remodelling, aggressive bone destruction [7], or with permeation through bone with no or only slight bone destruction. Based on the imaging findings, in most cases differentiation with a sinonasal carcinoma is not possible (Fig. 3).
Contrast-enhanced CT-images. (a) Axial image at the level of the oropharynx showing a large soft tissue mass (arrows) in the right palatine tonsil, extending into the glossotonsillar sulcus, slightly displacing the tongue base, and into the inferior part of the masticator space (reaching the mandible). Large adenopathy (arrowhead). (b) Coronal reformatting shows a large oropharyngeal mass (arrows), also extending into the soft palate. A large area of liquefaction is present within the parajugular adenopathy (arrowhead). Biopsy of the tonsillar mass revealed NHL.

Lethal midline granuloma\(^1\). It is a progressively destructive condition, involving the nose and paranasal sinuses.

Figure 3 Coronal gadolinium-enhanced T1-weighted spin echo image. Moderately enhancing, naso-ethmoidal soft tissue mass on the left side involving the left orbit. Retro-obstructive inflammatory changes in the left maxillary sinus. The findings are compatible with a malignant neoplasm but based on the imaging characteristics further differentiation is not possible. Biopsy showed NHL.

Figure 4 Coronal gadolinium-enhanced T1-weighted spin echo image of the sinonasal region obtained after unsuccessful treatment by antibiotics and steroids of a vesicle-like lesion on the hard palate, rapidly progressing to palatal destruction. A large defect is seen in the hard palate (arrows). Biopsy revealed T-cell NHL (courtesy of Davide Farina, MD, University Hospital of Brescia, Italy).
Primary involvement of the orbital structures and soft tissues of the cheek is nearly as common as the sinonasal/palate locations. Orbital NHL is reported to be bilateral in 40% of cases (Fig. 5)[5]. In cases of conjunctival involvement, differentiation has to be made from preseptal cellulitis, which is usually unilateral and of sinus origin; preseptal pseudotumour is rare. Intraorbital NHL can resemble pseudotumour or other tumours; differentiation is often difficult on radiological criteria.

Involvement of the subcutaneous tissues of the face produces a rather characteristic appearance. Lesions near the mucosa or submucosa can not be differentiated from minor salivary gland tumours. Leading to erosion of the sinonasal and adjacent structures. When left untreated, NK/T-cell lymphoma of the nasal type will eventually cause death by extension to the central nervous system, infection or haemorrhage. Radiologically, midfacial bone destruction with relatively little associated soft tissue thickening is seen (Fig. 4). This condition resembles the findings in other diseases, including Wegener’s granulomatosis, although in the latter the sinonasal changes are less extensive.

Masses in the canine fossa, associated with bone remodelling or destruction, can represent many possible etiologies (ranging from fungus sinusitis to different...
kinds of benign and malignant tumours); differentiation from carcinoma is not possible in cases of bone destruction[7]. An isolated nodular soft tissue mass in the canine fossa is likely to be lymphoma arising in the infraorbital lymph node, representing nodal disease[8]. Apart from the infraorbital lymph node, the ill-known facial lymph node group includes the zygomatic node, buccal nodes and peri-mandibular node; all these nodes may be the site of origin of lymphoma[9].

Skeletal, deep facial spaces, laryngeal and thyroid gland locations of NHL may occur, proving that this disease may infiltrate virtually any tissue of the head and neck (Figs 6–8)[3].

When lymphoma is in the differential diagnosis, other diseases should also be considered, including inflammatory pseudotumour, Wegener’s granulomatosis, sarcoidosis, and sometimes eosinophilic granuloma[9]. In the head and neck region, inflammatory pseudotumour most commonly occurs in the orbit, but it has been reported in other head and neck locations such as the nasal cavity, maxillary sinuses, larynx and trachea, nasopharynx and parapharyngeal space, and skull base[10]. Wegener’s granulomatosis primarily affects the upper respiratory tract, lungs and kidneys. In 18–22% of the cases, it also involves the orbit. Wegener’s granulomatosis limited to the orbits is very rare. As in Waldeyer’s ring lymphoma, the association of an extralymphatic soft tissue mass with neck adenopathies showing unusual appearances for squamous cell carcinoma suggests the diagnosis of lymphoma.

Conclusion

The possibility of an extranodal lymphoma location should be kept open in any infiltrative soft tissue mass in the head and neck. Although there are no specific imaging characteristics, sometimes the correct diagnosis can be suggested. Apart from correctly defining the extent of the lesion, the radiologist has an important role in avoiding diagnostic delays and misdiagnosis.

Key points

- Single or multiple extranodal locations occur frequently in head and neck NHL, also in the absence of regional adenopathies or other disease sites.
- Extranodal NHL may occur in lymphatic tissue (i.e. Waldeyer’s ring) and/or extralymphatic locations.
- NHL is a possible cause in any infiltrative soft tissue mass in the head and neck.
- The imaging features do not allow a reliable differentiation from other malignancies or other disease processes, which may show a similar anatomic distribution. Tissue sampling, while anticipating the possibility of lymphoma, is the most efficient way to establish the diagnosis.

References

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Extranodal manifestations of lymphoma in the abdomen

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Introduction

Lymphoma accounts for 5–6% of malignancy in adults in the UK and about 10% of all childhood cancers. In the USA in 2003 it is estimated that 53 400 new cases of non-Hodgkin’s lymphoma (NHL) were diagnosed and that the total number of deaths was 23 400. NHL accounts for 5% of new cancers in men and 4% of new cancers in women each year in the USA. According to the National Cancer Institute, the USA age-adjusted incidence rate for NHL was 15.5 per 100 000 in 1996. Hodgkin’s disease (HD) is less common than NHL and it is estimated that in the USA there were 7600 new cases of HD in 2003 and 1300 deaths. In the UK there were 10 100 new cases of NHL in 1999 and 2215 new cases of HD; there were 4630 deaths from NHL and 264 deaths from HD in 2001. The lifetime risk of developing NHL is approximately 1 in 83, and males are affected slightly more often than females in both types of lymphoma:

- HD, M 1.4:F 1
- NHL, M 1.1:F 1.

While the incidence of HD remains approximately stable, that of NHL has risen by approximately 60% in the USA since 1960. The increased incidence is evident for all age groups, but is much more marked with increasing age. This marked increase has been noted in international cancer registries of seven European countries and also in all geographical areas of the USA. The mortality for NHL has also increased steadily over the last few decades. Several hypotheses have been used to explain the striking increase. Some may be artefactual, where new NHL classification techniques and systems have led to a diagnosis of NHL in some patients who would previously have had other diagnoses; improved imaging techniques have undoubtedly led to more NHL diagnoses, particularly central nervous system (CNS) lymphoma; it has also been estimated that in 10–15% of cases a reclassification of cases previously called HD contributes to the apparent increase in NHL incidence. Part of the increase is a consequence of the increased incidence of lymphomas associated with immune deficiency, particularly secondary to human immunodeficiency virus (HIV) infection. Nevertheless, even when factors such as accuracy and completeness of diagnosis, the effect of HIV and occupational exposures are considered, the reason for most of the increase in NHL remains unexplained.

HD shows a bimodal peak distribution, the first in the third decade of life, and the second between 65 and 75 years of age; but, in recent years, this has become less obvious, with a decrease in the incidence in patients over...
55 years. However, NHL is a disease mainly of the elderly with an increasing incidence over the age of 50 years and a median age at diagnosis of 65 years.

**Pathology**

**Classification**

**NHL**

The importance of any classification is first its clinical relevance and second its translatability to allow communication of new knowledge and comparison of clinical results. In this context, the reproducibility and widespread use of the Rye modification of the Luke–Butler classification introduced in 1966 has proved to be reliable for HD (Table 1). This contrasts greatly with the profusion of classifications for NHL, although since its introduction in 1982 the Working Formulation has resulted in some degree of consensus. The recognition that most NHLs arise from the cells of the germinal follicle of the lymph node led to the development of a Working Formulation of NHL for clinical usage (Table 2). This classification was widely employed until the introduction of the REAL (Revised European American Classification of Lymphoid Neoplasms) classification, and completely superseded the plethora of previous classifications, which were largely unsatisfactory. The Working Formulation was based upon the idea that lymphoma is a result of clonal expansion of T or B lymphocytes at a particular point in their normal maturation. B lymphocytes (bone marrow-derived) are concerned with antibody production and develop into plasma cells that produce immunoglobulin. If normal maturation is prevented the arrested cell multiplies, resulting in lymphoma; the type and grade of lymphoma which results depends on the stage of maturation at the time of insult. T lymphocytes (thymic-derived) do not contain immunoglobulin but are also concerned with immune response. T-Cell lymphomas are either central T-cell lymphomas which are immature (e.g. diffuse lymphoblastic lymphoma), or those derived from more mature T lymphocytes, which are termed peripheral T-cell lymphomas. Histiocytic lymphomas do not fall into either of these categories.

The majority of NHLs (over 90%) are B-cell lymphomas. NHLs, which arise at stages of development occurring within the germinal centre of the node, have a follicular pattern, whereas lymphomas which arise outside the germinal centre have a diffuse architectural pattern. The Working Formulation designated each lymphoma according to characteristics of the cell type at the time of arrested maturation and overall divided NHL into low-grade, intermediate and high-grade tumours. The ‘miscellaneous’ group did not fulfil all the requirements of the main three categories.

The Working Formulation had important practical implications:

- Therapy was based on the grade of lymphoma
- The grade of lymphoma carried important prognostic significance
- The classification of lymphoma predicted possible transformation into a higher grade
- The detailed subclassification of lymphomas allowed standardisation of therapies and comparison of results from different centres.

**Table 2 A working formulation of NHL for clinical usage**

| Grade          | Classifications                                      |
|----------------|------------------------------------------------------|
| Low-grade      | A: Small lymphocytic: consistent with chronic lymphocytic leukaemia or with plasmacytoid features |
|                | B: Follicular, small cleaved cell                     |
|                | C: Follicular, mixed small cleaved and large cell     |
| Intermediate   | D: Follicular, large cell                            |
|                | E: Diffuse, small cleaved cell                       |
|                | F: Diffuse, mixed small and large cell               |
|                | G: Diffuse, large cell                               |
| High-grade     | H: Large cell immunoblastic                          |
|                | I: Lymphoblastic (convoluted or non-convoluted)      |
|                | J: Small non-cleaved cell (Burkitt or non-Burkitt type) |
| Miscellaneous  | Composite                                             |
|                | Histiocytic                                           |
|                | Mycosis fungoides                                    |
|                | Extramedullary plasmacytoma                          |
|                | Hairy cell                                            |
|                | Unclassifiable                                       |

More recently, in 1994, improvement in the understanding of NHL and the recognition of new clinicopathological entities resulted in the introduction of the REAL classification by the International Lymphoma Study Group, which is now being adopted internationally (Table 3).

The REAL classification is a consensus list of all lymphoid neoplasms that appear to be distinct clinical entities. Unlike the Working Formulation it utilises all available features (morphology, immunophenotype, genetics and clinical features) to define each entity.
This practical consensus approach differentiates it from previous morphological classifications and should enable widespread usage by pathologists and clinicians.

In 1995, under the auspices of the World Health Organization (WHO), the European Association for Haematopathology and the Society for Haematopathology collaborated on a project to classify all tumours of haematopoietic and lymphoid lineages. The proposals were reviewed by a Clinical Advisory Committee (CAC) and the result is the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, which is an updated version of the REAL classification.

The WHO classification stratifies neoplasms by lineage: myeloid, lymphoid, histiocytic/dendritic and mast cell. The classification is a list of distinct disease entities which are defined by a combination of morphology, immunophenotype, and genetic features, and which have distinct clinical features. It recognises three major groups of lymphoid neoplasms: B cell; T cell and NK cell; and Hodgkin lymphoma (HL). It includes the leukaemias, as they represent circulating phases of particular neoplasms. Thus B-cell chronic lymphocytic leukaemia and B-cell small lymphocytic lymphoma are the same entity, as are lymphoblastic lymphoma and lymphoblastic leukaemia. The definition of distinct clinical diseases means that classification by histological grade of aggressiveness is neither helpful nor possible. However, within the B and T/NK categories two major groups are recognised—precursor neoplasms, corresponding to the early stages of differentiation, and mature or peripheral neoplasms, corresponding to more differentiated stages. The main lymphoid groups are shown in the Table 3.

The approach is thought to represent a significant advance in the ability to identify and treat disease entities with international consistency. A study to address this issue of consistency showed that expert haematopathologists, given adequate material, could correctly classify the entity in over 95% of cases.

### Staging classifications

The Ann Arbor staging system was introduced for HD in 1970 and takes into account the extent of nodal disease and the presence of extranodal extension. However, an increasing recognition of the influence of tumour bulk as an independent prognostic indicator within each stage, and the routine application of new diagnostic techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), led to a modification of the Ann Arbor classification in 1989, known as the Cotswolds classification (Table 4). This system is
similar to the Ann Arbor classification, but Stage III is subdivided and an additional qualifier ‘X’ denotes bulky disease. Both the Ann Arbor and Cotswold systems are applied to NHL, but are of less value, as the prognosis in NHL is more dependent on histological grade and other parameters, such as tumour bulk and specific organ involvement, than on stage. In NHL, the critical question is whether or not disease is limited and, therefore, potentially treatable with radiotherapy, or whether it is disseminated.

Childhood NHL exhibits a clinical spectrum somewhat different to adult lymphoma with more frequent extranodal involvement, there being a very high incidence of lymphoma in the gastrointestinal tract (GIT), solid abdominal viscera including the kidneys and pancreas, and extranodal sites in the head and neck. The staging system of Murphy is most widely used (Table 5).

**Table 4** Staging of lymphoma (Cotswolds classification)

| Stage | Area of involvement |
|-------|---------------------|
| I     | One lymph node region or extralymphatic site |
| II    | Two or more lymph node regions on the same side of the diaphragm |
| III   | Involvement of lymph node region or structures on both sides of diaphragm, subdivided thus: |
| III(1*) | with involvement of spleen and/or splenic hilar, coeliac and portal nodes |
| III(2*) | with para-aortic, iliac or mesenteric nodes |
| IV    | Extranodal sites beyond those designated E |

Additional qualifiers

| A | No symptoms |
| B | Fever, sweats, weight loss (to 10% of body weight) |
| E | Involvement of single extranodal site, contiguous in proximity to a known nodal site |
| X* | Bulky disease |
|   | Mass >1/3 thoracic diameter at T5 |
|   | Mass >10 cm maximum dimension |

**Table 5** Murphy’s staging system for childhood NHL

| Stage | Criteria for extent of disease |
|-------|--------------------------------|
| I     | A single tumour (extranodal) or single anatomical area (nodal) with the exclusion of the mediastinum or abdomen |
| II    | A single tumour (extranodal) with regional nodal involvement |
| III   | Two or more nodal areas on the same side of the diaphragm |
|     | Two single (extranodal) tumours with or without regional node involvement of the same side of the diaphragm |
|     | A primary gastrointestinal tract tumour, usually in the ileocaecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected |
|     | Any of the above with initial CNS and/or bone marrow involvement |

Prognostic stratification enables the choice of more aggressive therapies for those at higher risk. However, the applicability of the IPI to other more rare forms of NHL and to follicular NHL is uncertain.
Although the REAL classification has changed our understanding of the clinical pattern and prognosis of the disease, the treatment in the individual NHL subtypes is still largely dictated by the previous broad categorisation into low- and high-grade lymphomas, as well as the sites of involvement. At one end of the scale, patients presenting with low-grade lymphomas who are asymptomatic may simply be followed without treatment until symptoms develop or transformation occurs. At the other end of the scale, patients presenting with high-grade disease may be successfully treated with multi-agent chemotherapy with most attaining a remission and up to 50% of patients achieving long-term disease-free survival. The development of antibody therapies has added a new dimension to NHL and the immunological subtype is now an additional important consideration in defining treatment, particularly for B-cell lymphomas. However, once relapse occurs, particularly if remission is short, further response to salvage chemotherapy is difficult to sustain. Current investigation is directed towards high-dose therapy with autologous bone marrow transplant.

Radiotherapy has a role in low- and intermediate-grade NHL but is usually inappropriate for treatment of high-grade lymphomas which are frequently widely disseminated tumours.

Overall, 10-year survival rates in patients treated with radiotherapy for low-grade Stage I and II disease are in the order of 90%. The major differences between the clinical features of HD and NHL are shown in Table 6.

Broadly, NHL is disseminated at presentation more frequently than HD and, although the majority of adult patients with NHL present with superficial lymphadenopathy, involvement of the viscera is more common in all types of NHL than it is in HD.

**Extranodal disease**

In about 40% of cases, the vast majority of which are NHL, lymphoma arises in extranodal sites. There is a propensity for lymphomas associated with immuno-deficiency and also those which develop in childhood to arise extranodally. Secondary extranodal lymphoma occurs due to spread of lymph node disease into adjacent structures and organs, and may be seen in both HD and NHL. The presence of extranodal disease is an adverse prognostic factor as recognised in the IPI. The increase in the incidence of NHL has been much more marked for extranodal sites, especially in the GIT, CNS and eye. Furthermore, visceral lymphoma can mimic many other disease entities, making recognition of the radiological appearances of extranodal lymphoma increasingly important. As with nodal disease, CT is generally excellent in the depiction of extranodal lymphoma. There are specific areas where MRI and ultrasound perform better, as indicated in the relevant sections. In addition, fluorine-18-labelled fluorodeoxyglucose positron emission tomography (18F-FDG-PET) is generally more sensitive and accurate in the staging of extranodal disease and splenic infiltration, largely because of its ability to demonstrate bone marrow involvement. However, it has yet to replace CT as a primary staging modality.

**Abdomen**

**Spleen**

The spleen is involved in 30–40% of patients with HD. In the majority of cases this occurs in the presence of nodal disease above and below the diaphragm, but it is the sole abdominal focus of disease in 10% of adults presenting with HD clinically confined to sites above the diaphragm. To date, all imaging techniques have been unreliable in the detection of splenic involvement, partly because in the vast majority of cases of splenic HD, nodules are less than 1 cm in size. An enlarged spleen is not a reliable indicator of disease; one-third of patients with HD and splenomegaly do not have enlargement of the spleen; however, one-third of normal-sized spleens in patients with either HD or NHL are found to contain tumour at laparotomy.

Occasionally, focal splenic nodules exceeding 1 cm are seen on cross-sectional imaging. These lesions have a non-specific appearance, are usually hypoechoic on ultrasound, isodense on unenhanced CT, and enhance to a lesser extent than normal parenchyma following intravenous injection of contrast medium. Splenic lymphoma can take the form of a solitary lesion, miliary nodules or multiple low attenuation masses. Detection of such lesions has improved with the advent of multislice CT, since the entire spleen can be imaged in the portal venous phase of enhancement, and lesions of a few millimetres in size can be identified. The differential diagnosis of focal lesions includes opportunistic infection, and occasionally sarcoid or metastases, which can appear identical. Infectious nodules tend to be smaller and more uniform in size.

In early studies, the sensitivity of ultrasound in demonstrating splenic involvement was extremely low (not exceeding 35%), although in a more recent study ultrasound was more sensitive than CT (63 vs. 37%), detecting nodules down to 3 mm in size and identifying diffuse infiltration more often than CT. Although this low accuracy for the detection of splenic involvement on imaging is disappointing, failure to detect splenic infiltration in HD is now of less clinical disadvantage than before. This is because patients with early-stage disease who relapse due to untreated splenic infiltration can be salvaged by multi-agent chemotherapy, following primary treatment with radiotherapy. This has also resulted in the cessation of staging laparotomy for Stages I and II HD in most European centres.
Table 6  Key differences between the clinical features of HD and NHL

| Clinical features | HD          | NHL          |
|-------------------|-------------|--------------|
| Fever, night sweats, loss of weight | 40%         | 20%          |
| Spread            | Tends to be by contiguous spread | Multiple remote nodal groups are often involved |
| Age               | Uncommon in childhood | More frequent 40–70 years |
| Nodal groups      |             |              |
| Thoracic          | 65–85%      | 25–40%       |
| Para-aortic       | 25–35%      | 45–55%       |
| Mesenteric        | 5%          | 50–60%       |
| Extranodal disease|             |              |
| Central nervous system | <1%    | 2%           |
| Gastrointestinal tract | <1%    | 5–15%        |
| Genitourinary tract | <1%    | 1–5%         |
| Bone marrow       | 3%          | 20–40%       |
| Lung parenchyma   | 8–12%       | 3–6%         |
| Bone              | <1%         | 1–2%         |
| Stage at diagnosis | >80% Stage I–II | >85% Stage III–IV |

Up to 40% of patients with NHL have splenic involvement at some stage. Primary splenic NHL is rare, accounting for 1–2% of all NHL. It is a particular feature of mantle cell and splenic marginal zone lymphomas where massive splenomegaly can occur. In contradistinction to HD, the presence of splenomegaly generally indicates involvement, and infarction is a frequent complication. Primary disease usually presents as a mass or masses rather than splenomegaly alone. Where there is diffuse infiltration, serial measurements of splenic volume during treatment may be helpful in the assessment of response to treatment. However, despite excellent results in some series, splenic volumes and indices have not gained widespread acceptance, being somewhat cumbersome. Unfortunately, the intrinsic tissue contrast of MRI is insufficient for consistent recognition of diffuse infiltration, though intravenous superparamagnetic iron oxide (SPIO) may improve detection of diffuse and focal infiltration, as may ultrasmall SPIO. Finally, \(^{18}\)F-FDG-PET may detect splenic infiltration more accurately than CT or Gallium-67 scintigraphy.

Liver

In HD, nearly 5% of patients have liver involvement, nearly always associated with splenic involvement. In NHL, at presentation, about 15% of patients have hepatic infiltration though the incidence is higher in the paediatric population and in recurrent disease. True primary lymphoma of the liver is extremely rare, though the incidence is increasing especially in immunocompromised patients. It is indistinguishable radiologically from other forms of hepatic malignancy such as hepatocellular carcinoma or metastatic disease. Up to 25% of patients are hepatitis B- or C-positive.

As with splenic disease, in untreated patients, liver lymphoma usually occurs as microscopic or small macroscopic foci of tumour confined to the portal triad.

Detection of liver involvement by cross-sectional imaging is usually difficult. Large focal areas of involvement, detectable on ultrasound, CT or MRI, are seen in only 5–10% of patients with liver disease and resemble metastatic disease from other sources. In both HD and NHL the lesions are well-defined, frequently large, hypoechoic on ultrasound and hypodense relative to the normal parenchyma on both enhanced and unenhanced CT scans. As in metastatic disease, on T1-weighted MR images, the lesions are hypointense and on T2-weighted images they are hyperintense relative to the liver. It has been suggested that MRI may be more sensitive than CT in the detection of focal hepatic pathology. Occasionally, especially in children, a form of liver infiltration is demonstrated as low-density soft tissue infiltrating the porta hepatitis and the margins of the portal veins.

Cross-sectional imaging is relatively insensitive to the detection of the more common diffuse microscopic liver infiltration. However, in contradistinction to the unreliability of splenomegaly, liver enlargement is strongly suggestive of infiltration in NHL particularly. To date, despite initial enthusiasm, attempts to detect the diffuse form on MRI have not been successful, though some work suggests that SPIO may increase the sensitivity of MRI for focal lesions.

Involvement of the bile ducts and gall bladder is rare, but has been described in AIDS-related lymphoma (see section on AIDS).

GIT

The GIT is the most common site of primary extranodal lymphoma, being the initial site of involvement in 5–10% of adult patients. HD of the GIT is extremely rare.
Primary gastrointestinal lymphomas develop from the lymphoid elements in the lamina propria and constitute about 1% of gastrointestinal tumours, occurring most frequently in two age-related peaks, the first below the age of 10 years (Burkitt’s lymphoma) and a second between 50 and 60 years of age (most GALT-type and also high-grade intestinal T cell associated with enteropathy). Primary lymphomas of the GIT usually involve only one site. The criteria for the diagnosis of primary gastrointestinal lymphoma include:

- Absence of superficial or intrathoracic lymph nodes
- Normal white cell count
- No involvement of liver or spleen
- Lymph node involvement if present must be confined to the drainage area of the involved segment of gut.

A modified Ann Arbor staging system takes account of these criteria. Stage I is where disease is confined to the visceral wall, and Stage II is where there is local extension to adjacent organs (IEI) or draining lymph nodes.

Secondary gastrointestinal involvement is common because of the frequent origin of lymphoma in the mesenteric or retroperitoneal nodes. Typically, multiple sites are involved.

In both the primary and secondary forms, the stomach is the most commonly involved organ (51%), followed by the small bowel (33%), the large bowel (16%), and the oesophagus (<1%). In 10–50% of cases the involvement is multicentric. In children, the disease appears almost exclusively in the ileum and ileocaecal region.

**Stomach**

Primary lymphoma of the stomach accounts for about 2–5% of gastric tumours. Radiologically, the appearances reflect the gross pathological findings: common appearances are multiple nodules, some with central ulceration, seen readily at endoscopy or barium meal, or a large fungating lesion with or without ulceration. About one-third of cases present with diffuse infiltration with marked thickening of the wall and narrowing of the lumen, sometimes with extension into the duodenum, indistinguishable from scirrhous carcinoma. Localised polypoid forms have also been described. Only about one-tenth are characterised by diffuse enlargement of the gastric folds, similar to the pattern seen in hypertrophic gastritis and Menetrier’s disease.

Because the disease originates in the submucosa, these signs are best demonstrated endoscopically or on barium studies, but do not reflect the extent of the disease. CT has proved particularly valuable, often showing extensive gastric wall thickening with a smoothly lobulated border. Unlike gastric carcinoma, the walls of the stomach are usually clearly separable from the surrounding organs. The presence of associated bulky retroperitoneal adenopathy extending below the renal hilum should suggest the correct diagnosis.

Gastric mucosa-associated lymphoma tissue (MALT) lymphomas, especially low-grade ones, usually result in minimal gastric mural thickening, which may not be recognisable even with dedicated CT studies utilising an oral water load and intravenous smooth muscle relaxants. Endoscopic ultrasound (EUS) is of more value in local staging and assessment of response to treatment, but multi-organ involvement occurs in up to 25% of patients, so extensive staging may be necessary.

**Small bowel**

Lymphoma accounts for up to 50% of all primary tumours of the small bowel, occurring most frequently in the terminal ileum and becoming less frequent proximally. Sixty percent are of B-cell lineage. Patients with AIDS are prone to lymphoma and the pattern resembles that found in immunocompromised patients. Multifocal disease is present in up to 50% of cases. As it usually originates in the lymphoid follicles, mural thickening is typical and results in constriction of segments of bowel with obstructive symptoms which are common at presentation. Thickening of the bowel is well demonstrated on CT with displacement of adjacent loops. As the tumour spreads through the submucosa and muscularis propria, it creates a tube-like segment, which ultimately becomes aneurysmal, presumably because of destruction of the muscularis and autonomic plexus in the affected segment. Alternating areas of dilatation and constriction are the most common manifestation. Occasionally, the lymphomatous infiltration is predominantly submucosal, resulting in multiple nodules or polyps of varying size, scattered throughout the small bowel but predominantly in the terminal ileum. This form is particularly prone to intussusception which is a classical mode of presentation, usually ileocaecal or ileoileal. This is the commonest cause of intussusception in children over 6 years. Barium studies may show multiple polypoid filling defects, with or without irregular thickening and ulceration of the valvulae.

Enteropathy-associated T-cell lymphoma (associated with gluten-sensitive enteropathy) and immunoproliferative small intestinal disease (IPSID) (alpha-chain disease) affect the jejunum and ileum; malabsorption and acute abdominal presentations secondary to perforation are common.

Secondary invasion of the small bowel by large mesenteric lymph node masses causing displacement, encasement or compression may also be seen. Omental thickening, peritoneal enhancement and ascites cannot be differentiated from peritoneal carcinomatosis and usually occurs in advanced abdominal disease, though it may be seen at presentation in Burkitt’s lymphoma.
Colonic and rectal involvement

Primary lymphoma accounts for only 0.05% of all colonic neoplasms and usually involves the caecum and rectum rather than other parts of the colon. Conversely, secondary involvement is usually widely distributed and multicentric. The most common form of the disease is a diffuse or segmental distribution of nodules 0.2–2 cm in diameter, typically with the mucosa intact. A focal form appears as a large polyoid mass, often in the caecum, and is indistinguishable from colonic cancer, unless there is concomitant involvement of the terminal ileum which is more suggestive of lymphoma. The mass may have a large intraluminal component. In very advanced disease, there may be marked thickening of the colonic or rectal folds resulting in focal strictures or ulcerative masses with fistula formation. Colonic involvement is a particular feature of ARL and Burkitt’s lymphoma, but MALT-types also occur, usually causing nodularity.

Oesophagus

Intrinsic oesophageal involvement is extremely uncommon, usually involves the distal third of the oesophagus and can result in a smooth tapered narrowing. Occasionally, both the fundus and distal oesophagus are involved by a bulky fungating tumour.

Pancreas

Primary pancreatic lymphoma is extremely rare and accounts for only 1.3% of all cases of pancreatic malignancy and 2% of patients with NHL. Secondary pancreatic involvement usually occurs in association with disease elsewhere, most commonly due to direct infiltration from adjacent nodal masses, which may be focal or massive. Intrinsic involvement of the pancreas most commonly results in a solitary mass lesion, indistinguishable from a primary adenocarcinoma on ultrasound, CT or MRI. Biliary and pancreatic ductal obstruction as well as invasion or narrowing of the portal vein are commonly seen at CT. Calcification and necrosis are rare. The presence of a large mass in the head of the pancreas, with only mild biliary or pancreatic ductal dilatation, should raise the possibility of lymphoma, especially if there is retroperitoneal nodal enlargement below the level of the renal veins. Less commonly, diffuse palpable masses or diffuse uniform enlargement of the pancreas is seen. Involvement is far more common in NHL than HD, particularly in ARL.

Genitourinary tract

The genitourinary tract is very rarely involved at the time of presentation, although in end-stage disease more than 50% of cases will have involvement of some part of the genitourinary tract. The testicle is the most commonly involved organ, followed by the kidney and perirenal space. Involvement of the bladder, prostate, uterus, vagina and ovaries is extremely rare.

Kidney

Renal involvement is detected in about 3% of all patients undergoing abdominal scans for the staging of lymphoma. Primary or isolated renal lymphoma is extremely rare. Although CT is more sensitive in identifying lymphomatous renal masses than ultrasound or urography, a large discrepancy exists between the radiological detection and incidence at autopsy (up to 50% having involvement in autopsy series), presumably because renal involvement is a late phenomenon. It is extremely unusual for the detection of renal involvement to alter the disease stage, close to 90% of cases are due to high-grade NHL, renal function is usually normal and in more than 40% of patients the disease occurs at the time of recurrence only. Diffuse large B-cell lymphoma and Burkitt’s lymphoma are the histological subtypes that most commonly involve the kidneys.

Multiple masses is the most frequent pattern of disease seen in up to 60% of cases, which on CT may show a typical ‘density reversal pattern’ before and after contrast administration, with the lesions being more dense than the surrounding parenchyma before contrast medium administration and less dense after.

Solitary masses occur less frequently (10–20%) and may be indistinguishable from renal cell carcinoma. An important feature of renal masses occurring in NHL is that in over 50% of cases there is no evidence of retroperitoneal lymph node enlargement on CT, suggesting that the kidneys are involved by haematogenous spread.

Direct infiltration of the kidney is the second most common type of renal involvement, occurring in 25% of cases. Invasion occurs from the retroperitoneum into the renal hilum and sinus, encasing the renal vessels and simulating a transitional cell carcinoma, an important differential diagnosis. Not infrequently, a soft tissue mass is seen in the perirenal space, occasionally encausing the kidney without evidence on CT of invasion of the parenchyma.

Diffuse infiltration of the kidneys with global renal enlargement without focal nodules is a less common manifestation, usually without lymph node enlargement. The appearance after intravenous contrast medium injection is variable, but usually the normal parenchymal enhancement is replaced by homogeneous non-enhancing tissue. This pattern can be seen with Burkitt’s lymphoma. After successful treatment, the appearance can revert entirely to normal. A particularly rare form of disease is isolated periureteric lymphoma, which has been described in NHL and HD.
**Bladder and prostate**

Although primary lymphoma of the bladder is extremely rare, secondary lymphoma of the bladder is more common and is found in 10–15% of patients with lymphoma at autopsy. Such secondary involvement can affect the wall of the bladder intrinsically or in contiguity from the adjacent involved nodes. Microscopic involvement is far more common than gross involvement, but this too can be associated with haematuria. The appearances on CT and MRI are non-specific with either diffuse widespread thickening of the bladder wall or a large nodular mass—both patterns indistinguishable from transitional cell carcinoma.

Primary bladder lymphoma accounts for less than 1% of all bladder tumours. There is a female preponderance in the 6th and 7th decades, and a history of cystitis is common, explaining the high incidence of MALT-type lymphomas. Solitary or occasionally multiple sessile masses are most often seen.

Unlike primary lymphoma of the bladder, where the response to chemotherapy/radiotherapy is good, lymphomatous involvement of the prostate carries a poor prognosis. It is usually intermediate or high-grade and produces irritative obstructive symptoms. Solitary nodules are uncommon and in the majority of cases involvement is diffuse, with infiltration throughout the prostate and periprostatic tissue. Secondary involvement of the prostate is far more common than primary prostatic involvement and direct extension into the prostate from pelvic lymph nodes is often seen in very advanced disease.

**Testis**

Testicular lymphoma is the most common testicular tumour in men over the age of 60, but accounts for only 5% of all testicular neoplasms. At presentation it is seen in about 1% of men with NHL (more commonly in Burkitt’s lymphoma) but is practically non-existent in HD. As in other sites of lymphomatous involvement of the genitourinary tract, the frequency of involvement discovered at autopsy is much higher: 18% of men with NHL. There is an association with lymphoma of Waldeyer’s ring, the CNS, and skin.

On ultrasound, the lesions usually have a non-specific appearance, with focal areas of decreased echogenicity. However, a well-recognised pattern is a diffuse decrease in reflectivity of the testicle without any focal abnormality. As involvement is bilateral in 10–25% of cases, it is extremely important to examine the contralateral side. MRI offers little advantage over ultrasound in evaluation of the testis.

**Female genitalia**

In advanced, widespread lymphomatous disease, the female genital organs are frequently secondarily involved. However, isolated lymphomatous involvement is rare, accounting for approximately 1% of extranodal NHL. Most are diffuse large B cell in type. Around 70% of women affected are postmenopausal and present with vaginal bleeding. The tumours originate predominantly in the uterine cervix where on CT and MRI a large mass can be seen. Involvement of the uterine body usually produces diffuse enlargement, often with a lobular contour similar to a fibroid, with a relatively homogeneous signal intensity in spite of large tumour size. Similarly, primary lymphoma of the cervix and/or vagina is characterised by a large, exophytic, soft tissue mass. Involvement of these gynaecological organs is best demonstrated by MRI, since masses are seen as high signal intensity lesions on T2 weighting and are therefore clearly distinguished from the surrounding normal tissues, including the uterus, cervix, and vaginal wall. Characteristically, the mucosa is spared and the low signal intensity junctional zone is intact. MRI is excellent in follow-up and assessment of response to treatment. Ovarian lymphoma is less common and carries a worse prognosis than uterine lymphoma because the tumours are more advanced at the time of discovery. The appearance on cross-sectional imaging is indistinguishable from primary ovarian carcinoma. Disease is often bilateral, and DLBCL or Burkitt’s lymphoma is the usual subtype. The presence of large bilateral homogeneous masses with moderate enhancement on MRI, without haemorrhage, necrosis or calcification, may suggest this diagnosis.

**Adrenal glands**

Primary adrenal lymphoma is rare, occurring in men over 60 years of age. Secondary involvement of the adrenal glands in lymphoma is usually demonstrated on routine abdominal CT for staging (where it is seen in up to 6% of cases of NHL) as presentation with adrenal insufficiency is extremely rare. Involvement is usually bilateral and the appearances are indistinguishable from bilateral metastases, but readily distinguishable from adenomas. Non-lymphomatous bilateral hyperplasia of the adrenal glands has been described. The reason for this is unclear.

**MALT lymphoma**

Whilst extranodal involvement can be seen in any subtype of NHL, some forms of B-cell NHL occur exclusively in extranodal locations, i.e. the extranodal marginal zone lymphomas. They represent around 8% of all types of lymphoma and, for convenience, are divided into MALT types and generic types.
Pathology and clinical features

The MALT lymphomas arise from mucosal sites that normally have no organised lymphoid tissue, but within which acquired lymphoid tissue has arisen as a result of chronic inflammation or autoimmunity. Examples include Hashimoto’s thyroiditis, Sjögren’s syndrome and Helicobacter-induced chronic follicular gastritis. The association between gastric MALT lymphoma and Helicobacter pylori infection was established in 1991 by Wotherspoon et al who found the organism in over 90% of cases. The detectability of H. pylori has been shown to diminish as lymphoma evolves from chronic gastritis.

Patients with Sjögren’s syndrome or lymphoepithelial sialoadenitis are at 44 times the risk of developing lymphomas, of which over 80% are MALT type. Patients with Hashimoto’s thyroiditis have a 70 fold increased risk of thyroid lymphoma.

The histological hallmark of MALT lymphoma is the presence of lymphomatous cells in a marginal zone around reactive follicles, which can spread into the epithelium of glandular tissues to produce the characteristic lymphoepithelial lesion. In up to 30% of cases, transformation to large cell lymphoma occurs.

The commonest site of involvement is the GIT (50% of cases) and within the GIT, the stomach is most often affected (around 85% of cases). The small bowel and colon are involved in IPSID, previously known as alpha-chain disease. Other sites commonly affected include the lung, head, neck, ocular adnexae, skin, thyroid, and breast.

Most cases occur in adults with a median age of 60 and with a slight female preponderance. Most patients present with Stage IE or IIE disease, which tends to be indolent. Bone marrow involvement is seen in 20% of cases, but the frequency varies depending on the primary site, being higher with MALT lymphoma of the lung and ocular adnexae. Multiple extranodal sites are involved in up to 10% of cases, but this does not appear to have the same poor prognostic import as in other forms of NHL, as it may not reflect truly disseminated disease. Nonetheless, extensive staging investigations may be necessary.

Imaging features

GIT

Often gastric MALT lymphoma, especially low-grade, causes minimal mucosal thickening, and CT may be normal, even if dedicated gastric CT is carried out with an oral water load and intravenous smooth muscle relaxants. A recent study suggested that low-grade MALT lymphoma was more likely to cause shallow ulceration and nodulation, whereas higher grade ones were more likely to produce more massive gastric infiltration and polypoid masses. EUS is more accurate than CT pre- and post-treatment, defining wall depth and lymph node involvement. In addition, staging with EUS can help predict response to treatment of H. pylori.

In the colon and small bowel, MALT lymphoma is manifest as mucosal nodularity, which can be appreciated in barium studies.

Lymphoma in the immunocompromised

The WHO classification recognises four broad groupings associated with an increased incidence of lymphoma and lymphoproliferative disorders:

- Primary immunodeficiency syndromes
- Infection with HIV
- Iatrogenic immunosuppression after solid organ or bone marrow allografts
- Iatrogenic immunosuppression from methotrexate (usually for autoimmune disorders).

The development of lymphoma in these settings is multifactorial, but mostly related to defective immune surveillance, with or without chronic antigenic stimulation.

Lymphomas associated with HIV

Lymphoma is the first AIDS-defining illness in up to 5% of HIV patients. The incidence of all subtypes of NHL is increased 60–200 fold. Various types are seen, including those seen in immunocompetent patients, such as BL and DLBCL (especially in the CNS), but some occur much more frequently in the HIV population (e.g. primary effusion lymphoma and plasmablastic lymphoma of the oral cavity). The incidence of HD is also increased up to eight fold.

Most have a marked propensity to involve extranodal sites, especially the GIT, CNS (less frequent with the advent of highly active antiretroviral therapy), liver, and bone marrow. Multiple sites of extranodal involvement are seen in over 75% of cases. Peripheral lymph node enlargement is seen in only 30% of cases at presentation.

Most tumours are aggressive, with advanced stage, bulky disease and a high serum LDH at presentation. DLBCL tends to occur later on when CD4 counts are under 100 × 10^6/l, whereas BL occurs in less immunodeficient patients. EBV positivity occurs in up to 70% of cases depending on the precise morphological variant, whereas primary CNS DLBCL is associated with EBV in over 90% of cases; interestingly, EBV positivity is seen in nearly all cases of HD associated with HIV.

In the chest, NHL is usually extranodal; pleural effusion and lung disease are common, with nodules, acinar and interstitial opacity being described. Hilar and
mediastinal nodal enlargement is generally mild. There is a wide differential diagnosis and in one study the presence of cavitation and nodal necrosis predicted for mycobacterial infection rather than lymphoma.

Within the abdomen, the GIT, liver, kidneys, adrenal glands and lower genitourinary tract are commonly involved. Mesenteric and retroperitoneal nodal enlargement is less common than in immunocompetent patients, but there are no apparent differences in the CT features of patients with or without AIDS, at least in relation to the small bowel.

Regarding primary CNS lymphoma (PCNSL), certain features such as rim enhancement and multifocality are seen more often than in the immunocompetent population. This can cause confusion with cerebral toxoplasmosis, though the location of PCNSL in the deep white matter is suggestive. Quantitative 18F-FDG-PET uptake can help in the differentiation of PCNSL, toxoplasmosis and progressive multifocal leukoencephalopathy (PML).

**Post-transplant lymphoproliferative disorders (PTLD)**

These occur in 2–4% of solid organ transplant recipients, depending on the type of transplant, the lowest frequency being seen in renal transplant recipients (1%) and the highest in heart–lung or liver–bowel allografts (5%). Marrow allograft recipients in general have a low risk (1%). Most are associated with EBV infection and appear to represent EBV-induced monoclonal or, more rarely, polyclonal B-cell or T-cell proliferation in a setting of reduced immune surveillance as a consequence of immunesuppression. The clinical features are variable, correlating with the type of allograft and type of immunosuppression. PTLD develops earlier in patients receiving cyclosporin A (mean 15 months) rather than azathioprine (mean interval 48 months). EBV-positive cases occur earlier than EBV-negative cases, the latter occurring 4–5 years after transplantation. In all cases, extranodal disease is disproportionately more common. In patients receiving azathioprine, the allograft itself and the CNS are often involved, whereas in patients who have received cyclosporin A, the GIT is affected more than the CNS. The bone marrow, liver and lung are often affected, as are the tonsils.

In the lung, multiple or solitary pulmonary nodules occur, with or without mediastinal adenopathy. Reticulonodular opacity is rare, whereas pleural effusions are common and a confluent, patchy airspace opacity is another pattern.

Abdominal PTLD is characterised by a relatively high frequency of extranodal disease, especially of the GIT and liver. Multiple segments of bowel may be affected and there is a propensity for PTLD to develop in the allograft.

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Lymphoma and myeloma: monitoring treatment response with $[^{18}\text{F}]$FDG-PET and other functional imaging techniques

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Abstract

Structural imaging approaches, such as assessing tumour size with computed tomography (CT) or other cross-sectional imaging techniques, are commonly used to demonstrate tumour response but are constrained by poor reproducibility, a relatively slow response and residual non-malignant masses. Cancer therapy also produces alterations in tumour glucose metabolism, angiogenesis and apoptosis that not only occur earlier than changes in tumour size but also are detectable using a range of functional imaging techniques. The reproducibility of many of these techniques at least equals that of measurements of tumour size. In lymphoma, assessing the glucose metabolic response to therapy with fluorine-18-labelled fluorodeoxyglucose positron emission tomography ($[^{18}\text{F}]$FDG-PET) has greater accuracy than CT, is potentially more cost-effective and may identify non-responders earlier in the course of treatment. Angiogenesis imaging in lymphoma with contrast-enhanced CT or magnetic resonance imaging or conventional scintigraphy may emerge as less expensive and more widely available alternatives to $[^{18}\text{F}]$FDG-PET that may be particularly appropriate in assessing response to anti-angiogenesis therapy. In multiple myeloma, functional imaging techniques for assessment of treatment response are emerging but require further validation.

Keywords: Therapeutic monitoring; glucose metabolism; angiogenesis; lymphoma; multiple myeloma.

Introduction

The ideal marker of tumour response to therapy would (a) accurately and reproducibly distinguish responding patients from those demonstrating no response or progressive disease, (b) identify non-responders early in their course of treatment so that the morbidity of ineffective therapy can be avoided, and (c) produce sufficient benefit at low cost. Structural imaging approaches, such as assessing tumour size with computed tomography (CT) or other cross-sectional imaging techniques, are commonly used to demonstrate tumour response to therapy but fall well short of these ideals. Cancer therapy also produces alterations in tumour physiology that not only occur earlier than changes in tumour size but also are detectable using a range of functional imaging techniques. This paper discusses the principals of using functional imaging to monitor treatment response and summarises the results of their application in lymphoma and myeloma.

Limitations of structural imaging

Tumour masses may shrink only slowly during treatment such that structurally-based follow-up imaging is often reserved until completion of therapy. Even then, a residual mass may remain although no active disease is present (Fig. 1). For lymphoma, a recent health technology assessment in the UK included a meta-analysis of the performance of CT in detecting active residual disease at completion of chemotherapy and found low diagnostic specificity of only 45% (95% confidence limits 27–64%)\(^{[1]}\). Decision modelling indicated that this low specificity would result in a CT-based strategy for management of patients with lymphoma on completion of therapy leading to 36% of patients receiving unnecessary radiotherapy. Furthermore, the average survival benefit and cost per patient for the CT-based strategy were only marginally better than for a hypothetical management strategy in which all patients received consolidation therapy without imaging\(^{[1]}\).

These diagnostic difficulties are compounded by the errors involved in measuring tumour size on CT. Threshold values for the change in relative size of a tumour mass are used as criteria for partial response and tumour progression. However, the reproducibility of such measurements has proved poor. A recent study reported that uni-dimensional measurements of tumour size performed by different observers using the same
CT image differed to such a degree that nearly 30% of tumours would have been misclassified as progressive disease using response evaluation criteria in solid tumours (RECIST)\[^2\]. Even with a single observer, this figure was close to 10% whilst the intra-observer error proved even worse for bi-dimensional measurements\[^2\]. Studies of in vivo reproducibility in which the same subject undergoes CT twice (test–retest protocol) are scarce but have been performed for automated volumetric measurement of lung nodules for which more than 95% of repeated measurements fell within standard criteria for tumour progression and response\[^3\]. However, the in vivo reproducibility of the manual measurements used in clinical practice has not been reported.

![Figure 1 Imaging of lymphoma at completion of therapy. Top row: residual disease. Bottom row: inactive. Both cases demonstrate residual masses on conventional CT (A,D). Residual disease demonstrates increased values on perfusion CT (B) and increased \(^{18}\text{F}\)FDG uptake on PET (C). Inactive disease demonstrates low perfusion (E) and low \(^{18}\text{F}\)FDG uptake (F).](image)

**Potential functional imaging markers of response**

Various aspects of tumour biology can be utilised as functional markers of tumour response. Gallium scintigraphy, which assesses both tumour vascular permeability and transferrin receptor expression, has been used as a response marker for lymphoma for many years but is becoming superseded by assessment of tumour glucose metabolism with fluorine-18-labelled fluorodeoxyglucose positron emission tomography (\(^{18}\text{F}\)FDG-PET). Tumour perfusion, reflecting angiogenesis, is also emerging as a functional response marker. Tumour perfusion can be assessed in vivo using PET with \(^{15}\text{O}\)-labelled water but such studies require an on-site cyclotron. Perfusion imaging using scintigraphy with technetium-99m-sestamibi (\(^{99}\text{Tc}\)-m-MIBI) or \(^{201}\text{Tl}\)-thallous chloride, or dynamic contrast-enhanced (DCE) CT or magnetic resonance imaging (MRI), offer cheaper and more widely available alternatives. The in vivo (test–retest) reproducibility of these functional imaging techniques is favourable when compared to anatomical measurements (Table 1)\[^3\–8\].

When using functional markers of tumour response, it is important to be aware that certain treatments can induce direct physiological effects upon the tumour or adjacent tissues and so mask the therapeutic response. For example, it is well recognised that radiotherapy often results in locally increased \(^{18}\text{F}\)FDG uptake lasting 3–6 months. Similarly, radiotherapy can cause a temporary increase in tumour perfusion and vascular permeability\[^9\]. Therefore, the timing of functional imaging for therapeutic monitoring must take these factors into account.

Although perfusion and glucose metabolism are sometimes coupled in untreated tumours, studies in which both parameters have been measured before and after treatment show that perfusion and glucose metabolism may not change in parallel in response to therapy (Table 2)\[^10\–13\]. In three of these four studies, the changes in perfusion were of greater magnitude. Anti-angiogenesis agents appear particularly associated with uncoupling of flow and metabolism following therapy, probably reflecting drug-induced hypoxic stimulation of glucose metabolism. In one study, perfusion increased in breast cancers failing to respond to treatment but decreased in tumours that subsequently proceeded to partial or complete response\[^13\]. However, a study of androgen-independent prostate cancer treatment demonstrated a negative correlation between prostate specific antigen (PSA) response and change in perfusion\[^12\]. Thus, the choice between glucose metabolism or angiogenesis-based functional response markers may depend upon both tumour type and treatment regime. However, by implementing perfusion CT on integrated PET/CT systems, it will be possible to monitor changes in both functional parameters, as well as any morphological change, in a single examination, remote from the on-site cyclotron needed for \(^{15}\text{O}\)-water PET.

A novel functional marker of response that can be imaged in vivo in humans is the process of apoptosis, or programmed cell death, which is an important feature of tumour response to radiotherapy or chemotherapy. Apoptosis can be imaged using \(^{99}\text{Tc}\)-Annexin-V which binds to phosphatidylserine, a component of the outer leaflet of the membrane lipid bilayer that becomes exposed early in the apoptotic process.

**Lymphoma**

For lymphoma imaging, \(^{67}\text{Ga}\)-gallium citrate has incremental value over CT, especially in evaluation of a residual mass post-therapy. Nonetheless, interpretation of gallium images in the abdomen is complicated by physiological bowel uptake and the diagnostic performance of \(^{67}\text{Ga}\)-gallium citrate is exceeded by that of \(^{18}\text{F}\)FDG-PET\[^14\].
Table 1 Comparison of test–retest repeatability of imaging response markers [references in square brackets]

|                  | CT: automated volume measurement | $[^{18}F]$FDG-PET: SUV | CT perfusion (ml/min/ml) | DCE-MRI (ml/min/ml) |
|------------------|---------------------------------|------------------------|--------------------------|---------------------|
| Coefficient of  | –                               | 13.7–17.5% [4,5]       | 28.4% [6]                | 30% [7]             |
| repeatability    |                                 |                        |                          |                     |
| Inter-test       | 9.6% [3]                        | 10.0% [4,5]            | 13.3% [6]                | 7.7% [8]            |
| variability      |                                 |                        |                          |                     |

Table 2 Changes in perfusion and glucose metabolism following cancer treatment

| Study            | Perfusion technique | Tumour       | Drug                      | Findings                                                                 |
|------------------|---------------------|--------------|---------------------------|--------------------------------------------------------------------------|
| Mullani et al[10] | $^{15}$O-water PET  | Various      | Endostatin                | At high doses, perfusion falls but metabolism increases                  |
| Mankoff et al[11] | $^{15}$O-water PET  | Breast       | Doxorubicin ± other agents| Perfusion increases in NR, but falls in PR and CR; NS difference in metabolism between groups |
| Kurdziel et al[12]| $^{15}$O-water PET  | Prostate     | Thalidomide               | Perfusion change inversely correlated with metabolic change              |
| Willett et al[13] | Perfusion CT        | Rectal Ca    | Bevacizumab               | Significant fall in perfusion; NS change in metabolism                  |

NR, no response; PR, partial response; CR, complete response; NS, not statistically significant.

Table 3 summarises the results of a meta-analysis considering the diagnostic performance of CT and $[^{18}F]$FDG-PET in determining treatment response at completion of therapy[11]. $[^{18}F]$FDG-PET has high accuracy in all patients and in patients with a residual mass on CT (Fig. 1). This meta-analysis was performed as part of a UK Health Technology assessment of PET which modelled the impact on cost and health outcomes associated with five possible strategies for management of various categories of patient with Hodgkin’s disease at completion of therapy. Table 4 summarises the results for a 40-year-old male which are broadly representative of the findings for all patient types. Directing patients to surveillance or consolidation treatment on the basis of $[^{18}F]$FDG-PET alone produced the greatest life expectancy at lowest cost.

An interim $[^{18}F]$FDG-PET examination performed during the treatment protocol can also identify non-responders at an early stage with the potential to reduce morbidity and the cost of continuing with treatment to which the patient is unlikely to respond. Persistent $[^{18}F]$FDG uptake after two to four cycles of chemotherapy indicates a high likelihood of relapse[15] (Table 5). $[^{18}F]$FDG-PET may also have a role in radiotherapy planning, especially if acquired using an integrated PET/CT system. However, further validation of this approach is required.

Angiogenesis is a recognised feature of lymphoma, with high microvessel density being found particularly in high-grade disease. Anti-angiogenesis agents are also being tested in this disease. Thus, there is potential for perfusion imaging to be used as a marker for residual lymphoma activity following treatment. Indeed, a correlation between perfusion and glucose metabolism within

Table 3 Meta-analysis of the diagnostic performance of CT and $[^{18}F]$FDG-PET in diagnosing residual disease on completion of lymphoma therapy (from Bradbury et al[11])

|                      | Sensitivity (95% CI) | Specificity (95% CI) |
|----------------------|----------------------|----------------------|
| CT                   | 0.75 (0.58–0.88)     | 0.45 (0.27–0.64)     |
| $[^{18}F]$FDG-PET in CT+ residual masses | 0.80 (0.59–0.94) | 0.89 (0.74–0.97)     |
| $[^{18}F]$FDG-PET (CT+ or CT−) | 0.81 (0.63–0.92) | 0.95 (0.90–0.99)     |

Table 4 Modelled costs and life expectancy gains for different strategies for management of a 40-year-old male patient with Hodgkin’s disease (from Bradbury et al[11])

| Strategy               | Cost (£) | Life-years | Cost/life-year (£) |
|------------------------|----------|------------|--------------------|
| All surveillance       | 5042     | 11.5       | 438                |
| All consolidation      | 3963     | 11.9       | 333                |
| CT only                | 4030     | 11.9       | 339                |
| $[^{18}F]$FDG-PET if CT+ | 4049     | 12.1       | 335                |
| $[^{18}F]$FDG-PET only | 3792     | 12.2       | 311                |
residual lymphoma masses following therapy has been demonstrated using $^{15}$O-water and $[^{18}$F]FDG-PET$^[16]$. Some of these patients underwent additional $^{99}$Tc$^{m}$-MIBI scintigraphy with MIBI uptake detected only in masses demonstrating specific uptake values (SUV) for $[^{18}$F]FDG above 6.0. Only one case with high $[^{18}$F]FDG uptake demonstrated no MIBI uptake. This patient’s disease progressed despite salvage therapy probably reflecting multi-drug resistance, a recognised cause for low MIBI uptake. A study of $^{201}$TI-thallous chloride scintigraphy in patients with follicular lymphoma demonstrated 100% sensitivity and 87% specificity for detection of residual disease following radiotherapy amongst the 35 of 41 (85%) in whom the baseline $^{201}$TI images were positive$^[17]$. Similarly, a perfusion CT study suggested that perfusion values below 20 ml/min/100 ml implied inactive lymphoma whilst high values were only found in active high-grade lymphoma (Fig. 1)$^[18]$. A preliminary dynamic contrast-enhanced MRI study has documented normalisation of peak enhancement values following therapy$^[19]$. However, further research is required to confirm the clinical utility of angiogenesis imaging in this context.

Preliminary work suggests that a $^{99}$Tc$^{m}$ Annexin-V uptake in follicular lymphoma 24 h after the last fraction of radiotherapy correlates with cytological evidence of apoptosis and predicts the type and onset of clinical response$^[20]$.  

| Author            | Type of lymphoma | Number of patients | Relapse rate: PET $^+$ve | Relapse rate: PET $^-$ve |
|-------------------|------------------|--------------------|--------------------------|--------------------------|
| Jerusalem et al   | NHL              | 28                 | 100%                     | 62%                      |
| Spaepen et al     | NHL              | 70                 | 96%                      | 15%                      |
| Mikhael et al     | NHL              | 23                 | 88%                      | 0%                       |
| Mikhael et al     | HD               | 32                 | 100%                     | 8%                       |
| Kostakoglu et al  | HD/NHL           | 23                 | 87%                      | 13%                      |

NHL, non-Hodgkin’s lymphoma; HD, Hodgkin’s disease.

### Myeloma

$[^{18}$F]FDG-PET and $^{99}$Tc$^{m}$-MIBI imaging are emerging techniques that can overcome the limitations of bone scintigraphy and skeletal surveys in diagnosis and staging of multiple myeloma. However, their use in therapy monitoring has been limited to date. A small series showed that changes in $[^{18}$F]FDG uptake following therapy were concordant with clinical outcome$^[21]$. A larger series studying $^{99}$Tc$^{m}$-MIBI imaging in multiple myeloma included 14 patients who were imaged during conventional chemotherapy and 29 patients following high-dose sequential therapy with autologous peripheral blood progenitor support$^[22]$. $^{99}$Tc$^{m}$-MIBI uptake remained unchanged during conventional chemotherapy but following high-dose chemotherapy, nine of ten patients in complete remission had negative MIBI images whilst five of six with progressive disease demonstrated persistent uptake. Results were variable amongst patients in partial remission.

A preliminary dynamic contrast-enhanced MRI study that included post-therapy imaging of the bone marrow in nine patients with multiple myeloma found peak enhancement values to normalise in three patients comprising two good responders and one with partial response$^[19]$. Peak enhancement values did not normalise but decreased following therapy in three partial responders and one non-responder whilst values increased in two further non-responders.

### Summary

The use of conventional structural criteria for monitoring tumour response presents significant difficulties, particularly in the assessment of patients with lymphoma and multiple myeloma. In lymphoma, the use of functional imaging response markers has greater accuracy, is potentially more cost-effective and may identify non-responders earlier in the course of treatment. Similar techniques are emerging for assessment of treatment response in multiple myeloma.

### Key points

- Assessment of tumour response using structural imaging criteria such as tumour size is constrained by poor reproducibility, a relatively slow response and residual non-malignant masses.
- Tumour glucose metabolism, angiogenesis and apoptosis are functional response markers that can be readily imaged with good reproducibility in patients with cancer.
- In lymphoma, assessing therapeutic response with $[^{18}$F]FDG-PET is more accurate and potentially more cost-effective than structural imaging.
- In lymphoma, $[^{18}$F]FDG-PET can identify non-responders early in the course of therapy, allowing further ineffective treatment to be withheld.
- In multiple myeloma, functional imaging techniques for assessment of treatment response are emerging but require further validation.

| Author            | Type of lymphoma | Number of patients | Relapse rate: PET $^+$ve | Relapse rate: PET $^-$ve |
|-------------------|------------------|--------------------|--------------------------|--------------------------|
| Jerusalem et al   | NHL              | 28                 | 100%                     | 62%                      |
| Spaepen et al     | NHL              | 70                 | 96%                      | 15%                      |
| Mikhael et al     | NHL              | 23                 | 88%                      | 0%                       |
| Mikhael et al     | HD               | 32                 | 100%                     | 8%                       |
| Kostakoglu et al  | HD/NHL           | 23                 | 87%                      | 13%                      |
Angiogenesis imaging with contrast-enhanced CT or MRI or conventional scintigraphy may emerge as less expensive and more widely available alternatives to [18F]FDG-PET that may be particularly appropriate in assessing response to anti-angiogenesis therapy.

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