Clinical Update on Non-Hodgkin Lymphoma

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The term non-Hodgkin lymphoma (NHL) covers a spectrum of malignant disorders arising from cells of the immune system and manifesting predominantly as lymphadenopathy or solid tumour. The classification of NHL is complex and ever-evolving, with more than 50 different subtypes listed in the latest WHO classification of lymphoma (1). In this clinical update, we address the distinction between low-grade (indolent) and high-grade lymphoma, and discuss the principles of diagnosis and management that are of particular relevance to the non-specialist physician who may encounter patients with NHL during their initial presentation, during therapy and during periods of follow-up.

How common is NHL?

NHL is the 6th commonest malignancy with 13,000 new cases of NHL diagnosed annually in the UK (2, 3). The commonest indolent lymphoma is Follicular Lymphoma. The commonest aggressive lymphoma is Diffuse Large B Cell Lymphoma (DLBCL) (**Figures 1 & 2**).

What causes NHL?

Most NHLs arise from mature B lymphocytes with a smaller proportion derived from T lymphocytes. Lymphoma results from the progressive accumulation of DNA alterations that lead to loss of the normal regulatory processes that control cell growth, proliferation and survival. Particular subtypes of lymphoma associate with specific, acquired genetic abnormalities; for example the translocation of the *BCL2* oncogene in Follicular Lymphoma or translocation of the *MYC* oncogene in Burkitt Lymphoma (4).

Certain subtypes of NHL are associated with infections including Epstein Barr Virus, Helicobacter pylori or Hepatitis C(5). NHL is more common in patients who are immunosuppressed, such as patients with HIV or recipients of organ transplantation. There is a slightly elevated risk in family members but NHL is not generally considered hereditary. For the majority of patients presenting with NHL there is no clear aetiological factor.

How do patients with non-Hodgkin lymphoma present?

NHL commonly presents with lymphadenopathy or splenomegaly. This may develop over months or years in low-grade lymphoma but may progress much faster in high-grade lymphoma. Lymphoma may also present as a solid, extranodal tumour that may mimic

other forms of cancer. Lymphoma may be suspected early if lymphadenopathy is clinically detectable. However, in many patients lymphoma is not considered until radiological detection of intra-abdominal or thoracic lymphadenopathy. Lymphadenopathy is often detected as an incidental finding during investigation of an unrelated condition. Symptoms, when present, may result from local compression by the enlarging lymph node or tumour mass. Lymphoma may also cause systemic symptoms including fever, sweats and weight loss. These are termed "B symptoms". They are described in about half of high-grade lymphomas but are not specific to the diagnosis. Sweats as an isolated symptom are almost never the presenting symptom of lymphoma. Some patients experience pruritus.

Routine blood tests such as renal or liver function may be abnormal if the respective organs are involved by lymphoma. Bone marrow involvement may cause anaemia, thrombocytopenia and neutropenia. Lactate dehydrogenase (LDH) is often elevated in high-grade lymphomas but the test is not specific. There is currently no blood test specific for a diagnosis of NHL. In many patients presenting with lymphoma all routine blood tests will be normal.

Although the presenting features of NHL are diverse the crucial feature prompting suspicion of lymphoma is almost always the finding of persistent lymphadenopathy, splenomegaly or an extranodal mass.

Criteria for and urgency of referral

In many patients the diagnosis of lymphoma is not initially suspected and referral is made to the service most appropriate to investigate their symptoms. However, unexplained lymph node enlargement that is persistent, bulky or rapidly enlarging is an indication for referral on a suspected cancer pathway. Local referral pathways vary from region to region but patients should be referred to whichever team is most appropriate to arrange biopsy of the anatomical location of the lymphadenopathy. BOX1.

How is the diagnosis of non-Hodgkin lymphoma made?

Radiology or clinical features may be suggestive of lymphoma, however, a diagnosis of lymphoma cannot be made without a biopsy. All patients with lymphadenopathy should have a full blood count performed before biopsy to exclude Chronic Lymphocytic Leukaemia, as this diagnosis can be made from analysis of the peripheral blood alone. An excision lymph node biopsy is preferable (6). Where this is technically challenging a radiologically guided core biopsy frequently yields sufficient material for diagnosis. Fine needle aspiration (FNA) is not usually sufficient to allow a diagnosis of lymphoma. The administration of corticosteroids prior to biopsy can make interpretation of lymphoma histology extremely difficult and delay diagnosis; corticosteroids should not be given to patients with suspected lymphoma without specialist advice. Bone marrow biopsy is sometimes performed for staging but is rarely the diagnostic investigation. A normal bone marrow biopsy does not exclude a diagnosis of lymphoma

Lymphoma pathology is complex and should be overseen by a specialist lymphoreticular histopathologist in a lymphoma referral centre. All new diagnoses should be discussed at a lymphoma multidisciplinary meeting (MDT). Diagnosis may require iterations of

immunohistochemical staining and molecular analysis of chromosomal aberrations by fluorescent in situ hybridization. It is recommended that all new cases are discussed at a specialist lymphoma multidisciplinary meeting.

Staging refers to the extent of involvement of the tumour according to the Ann Arbor classification [table 1]. Staging is performed by contrast enhanced CT scan of neck to pelvis and/or PET-CT scan (**Figure 3**). For most lymphoma subtypes a pre-treatment prognostic score can be assigned. In DLBCL, the International Prognostic Index (IPI) is calculated based upon age, stage, LDH, extranodal disease and performance status(7).
BOX2

How is non-Hodgkin lymphoma treated?

Management varies from the requirement for no treatment at all through to urgent admission for intensive, inpatient chemotherapy. The principles of treatment differ for high-grade and low-grade lymphoma. NHL should be managed by a specialist physician who forms part of a lymphoma multidisciplinary team in a secondary care setting.

Treatment of high-grade lymphoma

High-grade NHL may progress rapidly and requires urgent treatment. It is usually treated with curative intent using combination chemotherapy, combined, in B-cell tumours, with Rituximab, a monoclonal antibody against the B cell-specific surface antigen CD20. The immunochemotherapy regimen most commonly used for DLBCL is R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone). This is given as an outpatient, once every three weeks for a total of 6 cycles. It is generally well tolerated in younger (<75years) patients who are otherwise fit. Several large, randomised studies confirmed a survival benefit when Rituximab was added to CHOP (8, 9). Several large, randomised international trials have examined more intensive regimens and the use of bone marrow or stem cell transplantation in the first-line treatment of DLBCL(10, 11). However, none of these has yet shown a survival improvement over RCHOP. More intensive regimens, given as inpatient treatment, are required to treat Burkitt lymphoma. More intensive regimens are also used to treat high-risk forms of DLBCL, including the so-called "double hit" lymphomas (with translocation of both *MYC* and *BCL2* oncogenes). However, evidence to support this approach is limited to non-randomised retrospective studies. After completion of immunochemotherapy, patients may be offered localised radiotherapy.

In general patients with high-grade lymphoma respond very well to treatment and high cure rates (60-70%) are now achieved(10). During the follow-up period, routine surveillance scanning is not warranted and is better targeted at those patients who develop features suggestive of relapse. In the absence of relapse, patients are usually discharged from follow-up after 2-5 years. Patients with DLBCL who reach 2 years from treatment without relapse have a life expectancy equal to that of the age-matched population(12).

Patients who fail first-line chemotherapy are harder to treat. Those responding to second-line therapy are consolidated with autologous stem cell transplantation.

Treatment of low-grade lymphomas

In contrast to high-grade lymphoma, indolent lymphomas are not considered curable with conventional therapy. An exception is the small number of indolent lymphoma patients who present with localised lymphadenopathy. These patients may be cured by surgical excision or by radiotherapy. However, most indolent lymphoma patients present with advanced stage and their lymphoma is best managed as a lifelong, chronic disease. Indolent lymphomas tend to progress slowly and, in many patients, present few if any symptoms at diagnosis. Randomised trial evidence confirms that early treatment of asymptomatic patients with chemotherapy does not prolong their life expectancy(13-15). Treatment of asymptomatic patients with follicular lymphoma with Rituximab may delay the time until formal chemotherapy is required but there is no evidence it alters the long-term progression of the disease (16). Therefore, patients diagnosed with indolent lymphoma are usually placed on a "watch and wait" policy. Most patients with small volume, asymptomatic indolent lymphoma may be safely watched for many years and many will never require treatment(15).

Indications to start treatment include: systemic symptoms, bulky lymphadenopathy, progressive nodal enlargement, threatened compromise of vital organ function(17). Treatment involves immunochemotherapy. In several randomised trials Rituximab improved the survival of patients with follicular lymphoma when combined with chemotherapy (18-20). Typical first-line regimens include R-CHOP or R-Bendamustine(21). Treatment is given as an outpatient for 4-6 months. After chemotherapy is completed, patients typically follow a relapsing remitting course with remissions lasting several years. Patients may require multiple lines of therapy during their lifetime. Maintenance Rituximab given every two months for two years after initial immunochemotherapy increases the length of remission but there is currently no evidence of prolonged survival(22). In follicular lymphoma the length of first remission is a major determinant of outcome and those patients whose first remission is more than two years have excellent outcomes(23). A proportion of patients with low-grade lymphomas will transform to high-grade disease (24).

What are the complications of chemotherapy?

Chemotherapy is associated with early and late toxicity, the nature of which depends upon the exact treatment used. Patients should expect to receive detailed written information about the risks and benefits of their proposed chemotherapy.

Common short-term side effects include temporary hair loss. Nausea is generally well controlled with antiemetic drugs. Changes in taste and loss of appetite are common. Many patients undergoing chemotherapy experience fatigue that can sometimes take many months to recover. Most chemotherapy regimens are myelosuppressive, with potential for anaemia, thrombocytopenia and neutropenia. R-CHOP is considered moderately myelosuppressive and typically renders patients neutropenic (neutrophil count <1.0) for one or two days, usually beginning 7-10 days after each treatment. Neutropenic patients are vulnerable to overwhelming bacterial septicaemia. This can be serious or even fatal and should be considered a medical emergency. All patients undergoing chemotherapy should receive clear written instructions about how to seek help in the event of fever. At our institution, patients are given written fever rules printed on a red "Chemo Card" along with

a 24-hour emergency contact line, which allows emergency admission to the haematology unit (**Figure 4**).

Long-term complications of chemotherapy include peripheral neuropathy, which can occasionally be disabling. Cardiomyopathy is a specific complication of the anthracycline component of R-CHOP. Renal damage may result from nephrotoxic chemotherapy, such as the platinum-based drugs as well as from tumour lysis syndrome that may complicate the treatment of some high-grade lymphomas. Fertility may be reduced by chemotherapy. Where relevant, male patients are offered sperm banking and female patients should be offered urgent consultation with a fertility specialist. Both chemotherapy and radiotherapy may increase the risk of secondary malignancy.

What new treatments can we expect?

We are rapidly learning more about the molecular and genetic pathogenesis of lymphoma(4). This may allow future treatments to be targeted to genetic subtypes of lymphoma. It has also led to the development of novel, non-chemotherapy drugs that target pathways essential for tumour survival. Some show impressive response rates, such as Ibrutinib in relapsed mantle cell lymphoma. However, acquired resistance and unexpected toxicities are common and it is clear that there is still much to learn in terms of how these agents should be deployed. Other agents in clinical trials include T-cells from patients that have been genetically modified to recognise lymphoma cells and antibody-drug conjugates that deliver chemotherapy directly to lymphoma cells.

Patient support and education

Patients with lymphoma face particular challenges. Those with newly diagnosed indolent lymphoma frequently struggle with being told they have a malignant disease but that treatment will merely be observation alone. Patients in remission post-treatment frequently live in fear that each new symptom they develop could represent a recurrence of their disease. Both scenarios can be addressed by adequate patient education and emotional support. Trust in the whole multidisciplinary clinical team go a long way to easing patient concerns. Specialist nurses play an essential role in this aspect of care, both during clinic visits and as an essential point of contact should help or advice be needed between visits. Several patient groups and charities provide excellent, free of charge, educational and emotional support service for patients, carers and families.

BOX2

MAIN TEXT WORD COUNT TO HERE: 1998

BOX1

Typical criteria for urgent referral are:

- Persistent (>6 weeks) lymphadenopathy
- Lymph nodes greater than 2cm in size
- Rapidly increasing lymphadenopathy
- Generalised lymphadenopathy

NICE Guidance (2015):
*"Consider a suspected cancer pathway referral (appointment within 2 weeks) for non-Hodgkin lymphoma in adults presenting with **unexplained** lymphadenopathy or splenomegaly. When considering referral take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss".*

BOX 2

- Lymphoma Association (LA) produces extremely useful patient literature and has a "buddy" scheme that matches newly diagnosed patients with other who have been through a similar diagnosis. www.lymphomas.org.uk
- Macmillan offers medical, psychological and financial support to patients diagnosed with cancer. Tel. 0808 808 0000; website: www.macmillan.org.uk.
- There are several helpful patient groups, such as Facebook "Living with Follicular lymphoma" https://www.facebook.com/follicularlymphoma1/.
- **Cancer Research UK provides information about symptoms, risk factors, incidence statistics, treatment and trials for NHL. http://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma**

BOX 3

Outstanding questions and research priorities

- The management of patients who relapse early or fail to respond to chemotherapy.
- The management of older or comorbid patients who are unable to tolerate chemotherapy.
- How to prospectively identify and manage patients at high risk of treatment failure.
- How to identify and provide optimal prophylaxis against central nervous system relapse.
- The role of genomic medicine, novel antibodies and small molecules in the treatment of lymphoma.

BOX 4

What you need to know?

- NHL is the 6th commonest malignancy and covers a spectrum of histological subtypes.
- Lymphoma may be suspected based on clinical or radiological finding of enlarged lymph nodes but the diagnosis is made by tissue biopsy.

- The commonest high-grade lymphoma is Diffuse Large B Cell Lymphoma. It is an aggressive malignancy but is curable in 60-70% of patients with combined immunochemotherapy.
- The commonest indolent lymphoma is Follicular Lymphoma. It is generally considered incurable and follows a relapsing remitting course where intermittent treatment is required. Patients responding well to chemotherapy have a median survival of 20 years.
- The rapid increase in our understanding of lymphoma biology promises many new treatments that may further improve the outlook for patients with NHL.
- The relapsing and remitting nature of the indolent lymphomas in particular can present unique mental health challenges for patients that are managed by adequate patient education and emotional support.

BOX 5
Educational Resources

The following organisations produce and publish practice guidelines for the management of patients with lymphoma. The guidelines are available on online and can be accessed free of charge.

British Society for Haematology (BSH) Guidelines
http://www.b-s-h.org.uk/guidelines

EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (EMSO) Guidelines
http://www.esmo.org/Guidelines/Haematological-Malignancies

National Comprehensive Cancer Network, USA, Clinical Practice Guidelines
https://www.nccn.org/professionals/physician_gls/default.aspx

NICE Guidelines [NG52] Non-Hodgkin Lymphoma: diagnosis and management July 2016
https://www.nice.org.uk/guidance/ng52

How this article was created.

We searched Pubmed using the keywords “non-Hodgkin lymphoma”, “diffuse large B cell lymphoma” and “follicular lymphoma” to identify reviews and major studies published since 2000. This was supplemented by a review of the management guidelines listed in the Educational Resources section, by personal experience of the authors and feedback from patients.

Patient Involvement

When designing the content of this article we sought input from the patient group “Living with Follicular Lymphoma” and posed the question “what do doctors need to know about lymphoma?” Comments from patients, relatives, and carers influenced the structure of this article. The manuscript was reviewed by a patient who had received treatment for high-grade lymphoma and by a general practitioner. Their comments were incorporated into the final version, which also includes a case history as described by the patient.

Author contributions
All authors were involved in the design and writing of this manuscript.

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Competing Interests
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Lymphoma from the patient's perspective.

The story, written by a patient, demonstrates the diverse ways in which lymphoma can present, the relapsing remitting nature of indolent lymphoma, its propensity to transform into high grade lymphoma and the struggles patients face not only during treatment but also whilst in remission.

My lymphoma history.

It must have come to about 2 years of discomfort and lingering pain in my left side of my face and a hard swelling in my left groin when, finally I was referred to the hospital by my GP in May 2008. Subsequently two separate appointments with the ENT for the cheek and Ultra Sound for the groin swelling were booked. A biopsy of the swelling of my cheek was inconclusive a CT scan and a minor operation to remove the lump followed. Diagnosis: follicular lymphoma and immediate referral to the Oncology Clinic. Chemotherapy with R-CVP was recommended. The side effects of the chemo set in without hesitation - nausea, vomiting, constipation, weakness, hair loss etc. Hair loss was my least concern – it will grow again. Constipation was a pain with ten days without a stool movement. After six sessions of chemotherapy another CT scan showed clearance of the disease. I was in remission. It was November 2008.

From then on, I had regular checks and in 2011 the lymphoma returned. I had noticed for some time a swollen leg and pain with an occasional collapse of my right knee joint. I also had a skin rash on hands and lower arms. My GP had no explanation for it and suggested medication that might make me feel better. Since the next oncology check was due, I said that I would mention it to the doctor there. A CT scan and a biopsy were arranged. This time the diagnosis was high-grade lymphoma. My previous follicular lymphoma had now "transformed" into something more aggressive, a large mass in the right side of my pelvis near the uterus. A total of 6 cycles R-CHOP was prescribed. It was a severe treatment. I had to have two blood transfusions during the duration, followed by a course of radiotherapy. The side effects seemed to be worse than the ones that I had experienced after my previous chemo but I was in remission again. This time it lasted over five years. The consultant suggested discharge, which I declined. My paranoia set in, I was watching every slight difference in my body.

Then I detected a lump in my neck under my chin. Another CT scan and then another biopsy. This confirmed the original follicular lymphoma was back, but just in one place. This time I had radiotherapy. A shield was fitted for me and for 12 days running, except for Saturday and Sunday, I had treatment. After that I was very dehydrated due to lack of saliva and ulcers in my mouth. I was kept in hospital for 4 days. The lump had disappeared, but a new one on my upper gum then started to grow. It was cut out and now it was high-grade lymphoma again. One shot of radio seems to have done the trick. My last check seemed to be clear and I am in remission again and dealing with my paranoia.

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Figures

Figure 1. Age and gender-specific incidence of non-Hodgkin lymphoma in the UK. Data is modified from Cancer Research UK (CRUK) UK cancer incidence statistics 2014.

Figure 2. Relative incidence of the major subtypes of non-Hodgkin lymphoma based on data from Smith et al 2015, Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network.

Figure 3. PET-CT image of a patient with Diffuse Large B Cell Lymphoma (DLBCL) before (a) and after (b) treatment with 2 courses of R-CHOP chemotherapy. Areas of high intensity signal are seen in the left neck, mediastinum, para-aortic and iliac lymph nodes. Resolution is seen in the interim treatment scan. The high intensity seen in the right ureter and bladder represents normal excretion of the tracer.

Figure 4. Example of a "Chemo card" provided to patients undergoing chemotherapy. It includes emergency contact details and instructions to follow in the event of fever.

Table 1

Early stage	I	Single nodal area
	II	More than one nodal area, but does not cross the diaphragm
Advanced stage	III	Both sides of diaphragm involved
	IV	Extra nodal or bone marrow involvement
Suffix	A	No B symptoms
	B	B symptoms
	E	Extranodal disease (localised extranodal disease – Stage 1E)

Figure 1. Age and gender-specific incidence per 100,000 population

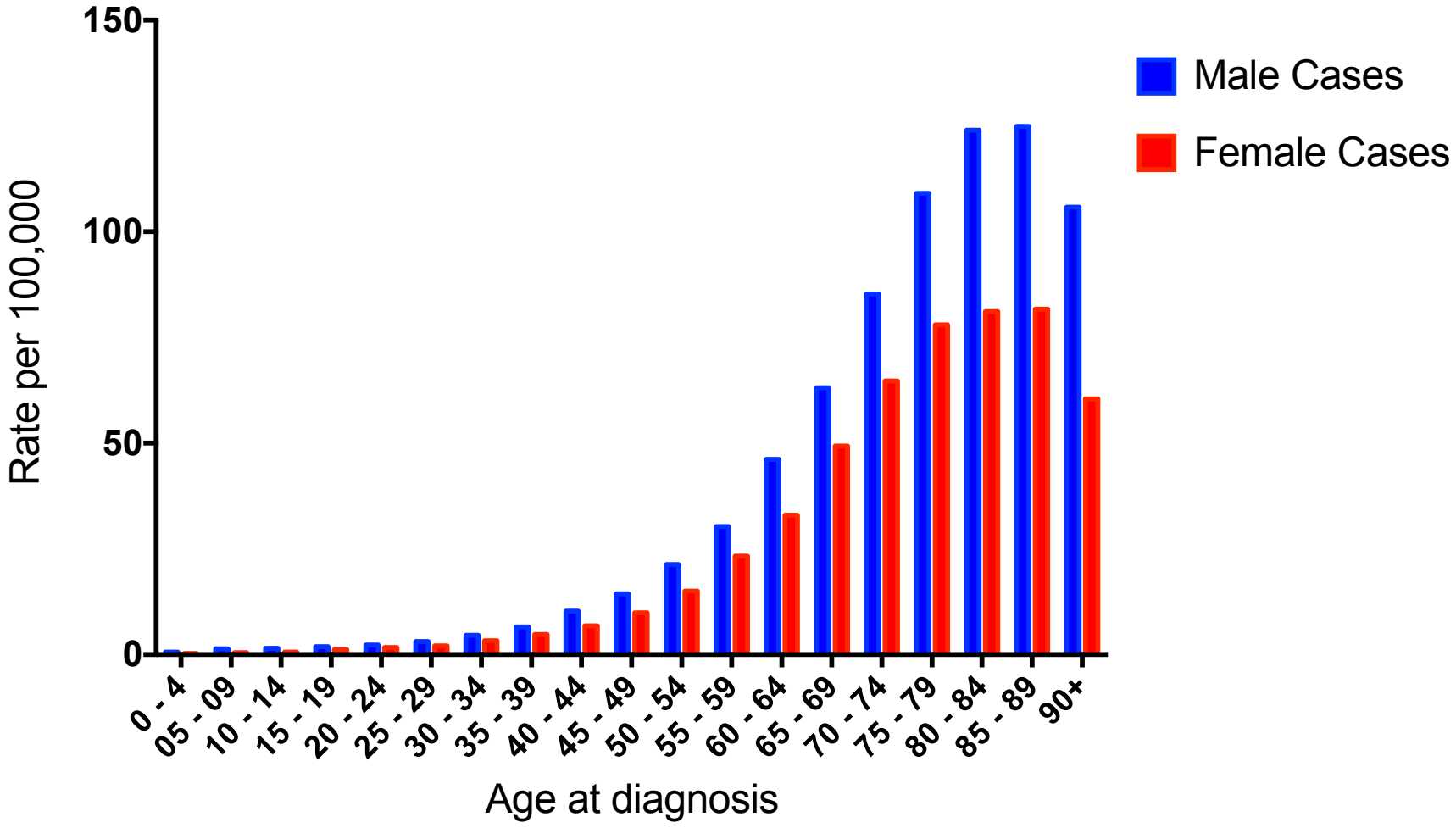
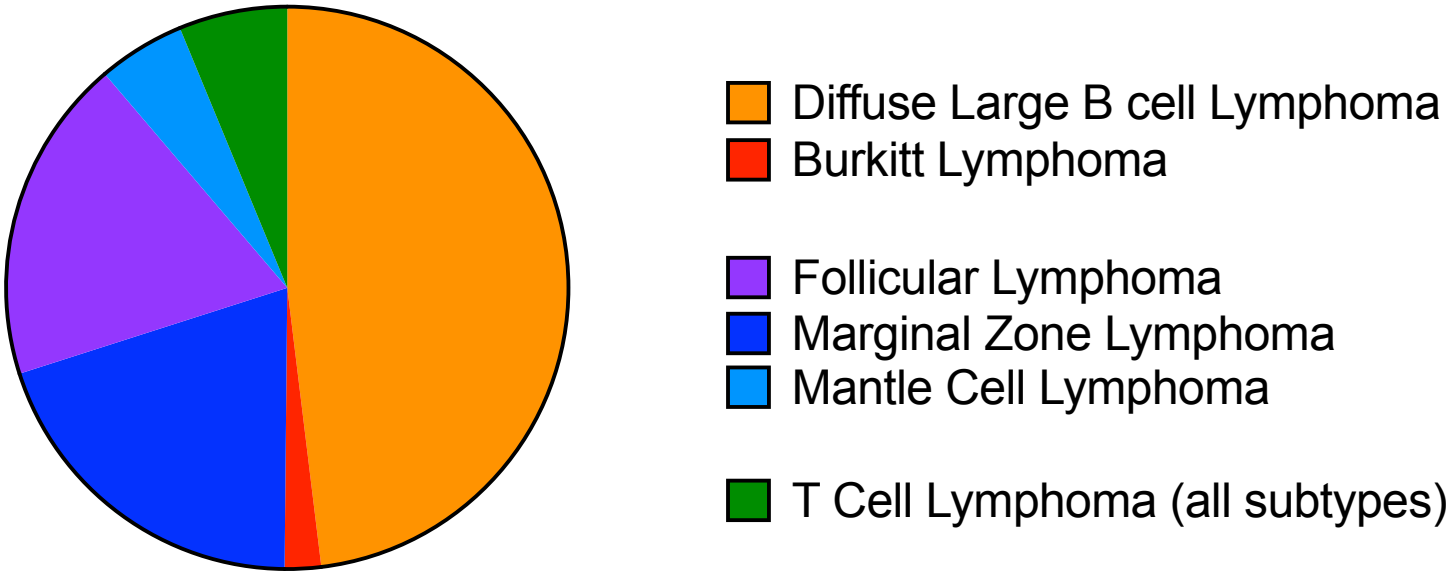


Figure 2. Relative incidence of non-Hodgkin lymphoma subtypes in UK



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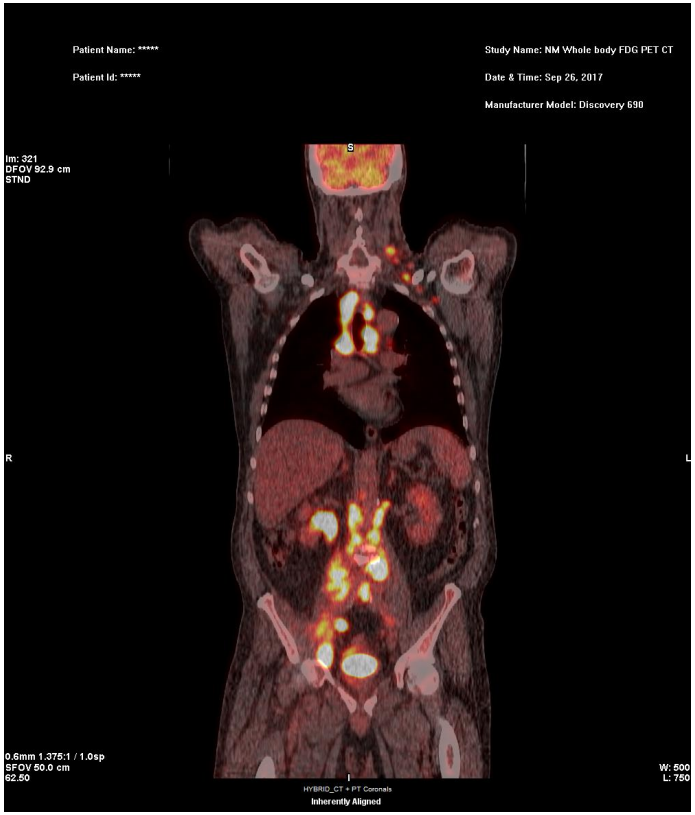
A



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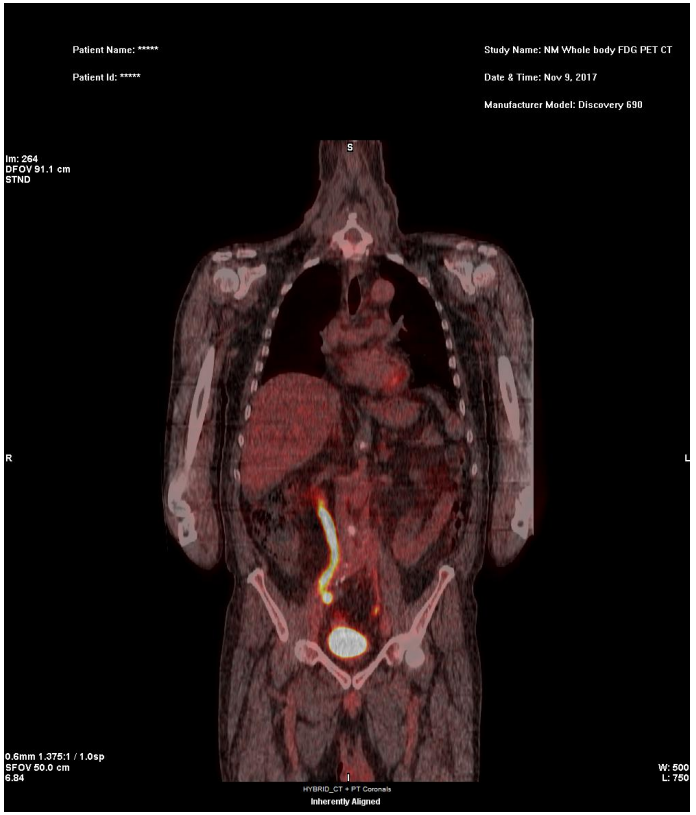

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