N. IRELAND Cancer Registry

Monitoring the care of leukaemia and lymphoma patients in Northern Ireland diagnosed in 2008

Leukaemia and Lymphoma **2008**

Queen's University Belfast

Monitoring the care of leukaemia and lymphoma patients in Northern Ireland diagnosed in 2008

Edited by: **Lisa Ranaghan and Anna Gavin**

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FOREWORD

This report is the first detailed study by the N. Ireland Cancer Registry of the pathway from referral through diagnosis, treatment and outcomes of treatment for patients with leukaemia and lymphoma in Northern Ireland.

This report shows that patients with leukaemia and lymphoma receive care from expert services and that survival rates are likely to be comparable to other populations. It provides valuable benchmarking information on leukaemia and lymphoma which is essential in helping us to track our progress. We are on a journey of continuous improvement in cancer care and this report also identifies those areas where change is still needed. This report is part of a series supported by the cancer network clinicians and the recommendations will be considered by the NICaN haematology group. Any future audit of leukaemia and lymphoma will hopefully demonstrate ongoing service improvements and enhanced experience of care for patients with haematological malignancies.

This series of reports highlights the importance of the Cancer Registry as a valuable public health tool which plays an important role in monitoring cancer care within Northern Ireland.

Dr Michael McBride
Chief Medical Officer

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The N. Ireland Cancer Registry (NICR) is funded by the Public Health Agency and the audit work is funded by grants from the Guideline and Audit Implementation Network (GAIN).
This report is the result of the work of the Registry Tumour Verification Officers, Donna Floyd and Jackie Kelly, who meticulously extracted detailed information from clinical records for analysis and presentation. Data were extracted by Colin Fox of the Registry's IT team.
The data cleaning was undertaken by Dr Patricia McDowell who with guidance from Dr Lisa Ranaghan (NICR Medical Advisor) undertook the statistical analysis. I am grateful to The N. Ireland Statistics and Research Agency (NISRA) for the secondment of Dr McDowell for this work. The content was written by Dr Lisa Ranaghan. A special word of gratitude to the Medical records departments in all Trusts who facilitated access to the clinical notes.

We acknowledge the excellent work of

- The haematologists, nurses and other health professionals who care for children and adults with leukaemia and lymphoma. In particular we recognise the many years of clinical expertise given by two recently retired haematologists, Dr Sid Dempsey and Professor Curly Morris.
- The Regional Haemato-oncology laboratory, Belfast City Hospital for provision of an excellent regional diagnostic service for patients with leukaemia and lymphoma.
- The Regional Cytogenetics laboratory, Belfast City Hospital for provision of an excellent regional cytogenetic service for patients with leukaemia.
- The N. Ireland Clinical Trials Centre (NICTC) who have accrued a high percentage of patients into national leukaemia trials.
- Our thanks also to the NICR Steering Group and Council who guide the work of the registry.

Anna Gavin .

A Gavin, Director NICR,
February, 2012

INTRODUCTION

The recording of leukaemia incidence and mortality is closely linked to the history of the Northern Ireland Cancer Registry. Indeed the need for accurate information on leukaemia incidence was a major factor in the decision to establish the Registry. In the 1970s and 1980s there was much public disquiet about the possible effects of the nuclear processing plant at Sellafield in Cumbria. In Ireland, it was feared that this was having a detrimental impact on the health of the population on the east coast, with rates and clustering of childhood leukaemia an issue of particular concern.

In Northern Ireland, swift investigation of patterns of disease in coastal compared to inland areas was hampered by the 'absence, incompleteness and poor quality of crucial information on leukaemia incidence' [(1)]. After a lengthy robust study it was concluded that there were no area differences in leukaemia incidence in Northern Ireland. One recommendation from the study report was that a properly organised registry should be set up to be responsible for rigorous, accurate and complete recording of all cancer incidence and mortality[(1)]. As a result the N. Ireland Cancer Registry was established in 1994.

This report is the first detailed study by this Registry into the incidence, outcomes and pathways of care of leukaemia and lymphoma patients in Northern Ireland.

SECTION I - LEUKAEMIA OVERVIEW

Leukaemia: Definition

Leukaemia is a cancer of the haematopoietic (blood-forming) cells which can be categorised as acute or chronic. There is a wide difference in the behaviour of the acute and chronic leukaemias. Leukaemia can arise in either of the two main types of white blood cells - lymphoid cells or myeloid cells. When leukaemia affects lymphoid cells, it is called lymphoblastic or lymphocytic leukaemia. When myeloid cells are affected, the disease is called myeloid leukaemia.

Acute leukaemia arises when immature lymphoid or myeloid cells fail to mature normally. These immature 'blast cells' increase in number in the bone marrow and eventually replace the bone marrow with the result that the production of normal functioning blood cells is markedly reduced. Leukaemia appears in one of four major forms:

- Acute lymphoblastic leukaemia (ALL).
- Acute myeloid leukaemia (AML).
- Chronic lymphocytic leukaemia (CLL).
- Chronic myeloid leukaemia (CML).

Leukaemia: Risk factors

Many studies have been devoted over the years to discovering the causes of leukaemia, and numerous factors have been implicated. As there is a wide range in the behaviour of the various subtypes of leukaemia it is unlikely that there is one common cause. Listed below are accepted risk factors for developing leukaemia:

- **Ionizing radiation:** exposure to very high levels of radiation, such as those caused by atomic explosions and nuclear power plant accidents has been shown to increase the risk of developing leukaemia[(2)]. An increased risk is also associated with radiotherapy treatment for cancer.
- **Chemical exposure:** An increased incidence of AML has been reported in persons with prolonged exposure to benzene and petroleum products[(3)]. Pesticide exposure has also been linked to some forms of AML[(4)].

- **Prior chemotherapy:** Use of chemotherapy drugs such as melphalan and cyclophosphamide (alkylating agents) in the treatment of lymphomas and myeloma, breast and ovarian cancers has been associated with the development of AML usually 3-5 years after exposure[5]. More recently topoisomerase II inhibitor drugs such as etoposide, doxorubicin and mitozantrone have been implicated in leukaemogenesis[6].
- **Smoking:** Cigarette smoking is associated with an increased risk of leukaemia. Benzene, an established cause of leukaemia, which is present in cigarette smoke is likely to be a contributory factor[7].
- **Genetic disorders:** An increased incidence of AML is seen in patients with Down's syndrome, Bloom syndrome, Fanconi's anaemia, Ataxia telangiectasia & Wiscott-Aldrich syndrome.
- **Socio-economic status:** Studies in the past consistently claimed that rates of childhood leukaemia were highest in more developed countries and in more privileged socio-economic groups[8,9]. However, recent research suggests that the evidence for this is far from conclusive, and that associations vary with time and place[10]. Some studies in the UK and elsewhere have found in fact that low socio-economic status not only fails to protect against leukaemia[10] but also is associated with reduced survival levels[10-13].
- **Viruses and infection:** The 'delayed infection' or 'hygiene' hypothesis arose partly as an attempt to explain the proposed link between childhood leukaemia and higher socio-economic status. This theory proposed that experience of infection early in life protected against leukaemia, whereas limited exposure resulted in a failure of the immune system so that susceptibility to the disease was increased[8]. Again however, recent research findings in this area are conflicting and contradictory, with some studies finding an inverse relationship between infection and leukaemia, some reporting no association, and some showing a positive relationship[9].

Acute Leukaemia: Clinical presentation

The symptoms and signs of acute leukaemia result from its effect on normal blood cell production (haematopoeisis) which results from the bone marrow being replaced with leukaemic cells.

- **Anaemia** will cause pallor, lethargy and breathlessness (symptoms of low haemoglobin (HB) level).
- **Bruising or bleeding** from mucosal surfaces is caused by a low platelet count (thrombocytopenia) causing petechiae (small red/purple spots on skin due to ruptured small blood vessels) and retinal haemorrhages.
- **Fever and persistent infections** due to a decrease in functioning neutrophils (white blood cells that fight infections).
- **Gingival (gum) hypertrophy** and skin involvement are more common with the monocytic subtypes of AML.
- **Bone pain** is common in children with acute lymphoblastic leukaemia but less common in adults.
- **Central nervous system (CNS) symptoms** although uncommon at presentation include headache, double vision and cranial nerve palsies.
- **Testicular enlargement** can occur in boys but more often during relapse.

Acute Leukaemia: Diagnosis

- **Blood tests** may reveal anaemia, thrombocytopenia and elevation of the white blood cell count (WBC). Panctyopenia (lowering of red and white blood cells and platelets) however is more common particularly in patients of all ages with ALL or in elderly patients with AML who may have a pre-existing bone marrow dysfunction (myelodysplasia). Approximately 10% of newly diagnosed patients with either ALL or AML present with markedly elevated WBC, greater than 100,000/µL. These patients constitute a poor prognostic group and are at increased risk of CNS involvement, tumour lysis syndrome (metabolic complications caused by breakdown products of dying cells) and leukostasis (clumping of leukaemic blast cells within blood vessels).
- **Bone marrow examination** will confirm pathologically the diagnosis. Immunocytochemical and immunophenotyping by flow cytometric analysis performed on the peripheral blood (PB) and bone marrow (BM) cells will further classify the type of leukaemia.

- **Cytogenetic analysis of the PB or BM blast cells** should be performed in all cases of acute leukaemia at diagnosis to identify the presence of any abnormal translocations or deletions of chromosomes.
- **Molecular studies (FISH and RT-PCR)** add sensitivity and precision to the detection of genetic events when conventional cytogenetics fails or gives normal results.
- **Coagulation screen** may identify abnormalities in the blood clotting process (coagulopathy) such as disseminated intravascular coagulopathy (DIC), most often seen in patients with acute promyeloctic leukaemia subtype.
- **Lumbar puncture** (necessary to detect occult CNS involvement) should be performed in all paediatric patients with ALL and in any patient with neurological symptoms. To prevent seeding of the CNS it may be necessary to postpone this until treatment has reduced the peripheral blood blast cell count.

Acute Leukaemia: Classification

The two main forms of acute leukaemia are acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML). Leukaemia classification is complex and specialised laboratory tests are used to identify the various subtypes, some of which are associated with specific damage to chromosomes. Details on the World Health Organisation (WHO) classification are shown in Appendix A.

Acute leukaemia : Treatment

The treatment for the different types of leukaemia although similar in their aim to induce remission differ in their detail. Where possible patients should be entered into national or international multicentre clinical trials. Details on the treatment of AML, ALL and CML are shown in Appendix A and B.

Acute leukaemia: Prognosis

Although 70-80% of children with ALL will achieve long-term remission with combination chemotherapy, the situation is less favourable for adults with only 35-50% achieving long-term remission due to a higher frequency of poor prognostic factors. For AML age is also an important prognostic factor with less than 10% of patients aged over 70 years surviving 5 years[14]. This is in part due to the increased frequency of poor prognostic factors at diagnosis. Patients with AML can be categorised into favourable, intermediate and poor risk groups (Table 2, Appendix A) and the 5-year overall survival for these groups varies significantly at 55%, 24% and 5% respectively for the favourable, intermediate and poor risk patients[15].

Chronic myeloid leukaemia (CML): Clinical Presentation

Chronic myeloid leukaemia is a rare disease accounting for 15% of adult leukaemias. It usually presents in the chronic phase and in asymptomatic patients (30%) it may be diagnosed on routine blood test showing a marked raised white blood cell count. As the disease progresses common symptoms are anaemia, weight loss, sweating and enlargement of the spleen. The natural history of the disease is the initial chronic phase lasting 3-6 years followed by an accelerated phase where the disease resembles acute leukaemia.

Chronic myeloid leukaemia (CML): Treatment and Prognosis

The treatment of the chronic phase of CML has been revolutionised by the use of the drug “Imatinib” (see Appendix B for details) with 89% of patients now surviving 5 years[16].

Survival

Survival from leukaemia has increased remarkably since the 1970s in the UK. Today over 80% of childhood leukaemia patients survive 5 years compared with only 33% in the 1970s.

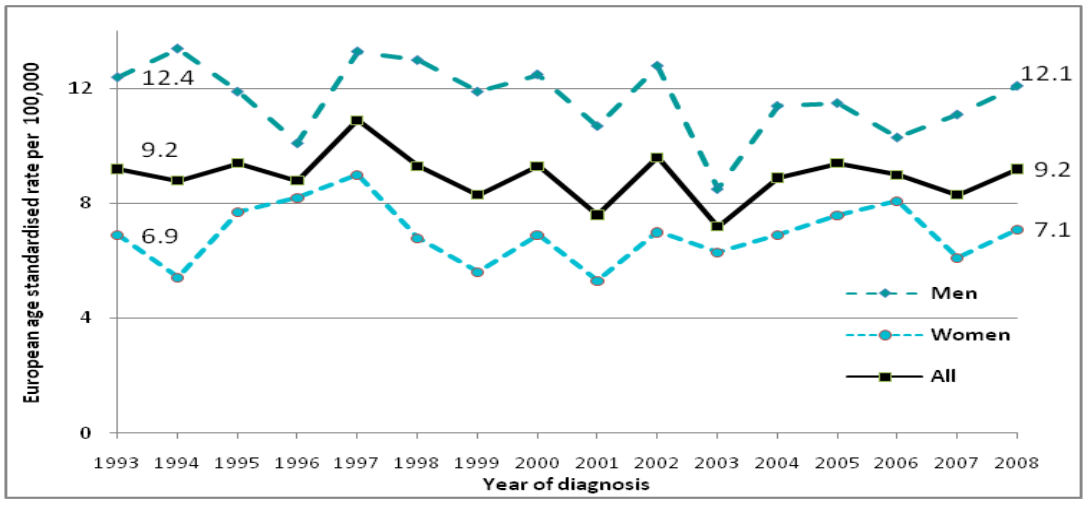
For adults, survival has also improved to 53% 1-year and 31% 5-year for Northern Ireland (Appendix C).

SECTION II - LEUKAEMIA IN N. IRELAND: THE PAST 16 YEARS

Leukaemia: Incidence (number of new cases diagnosed)

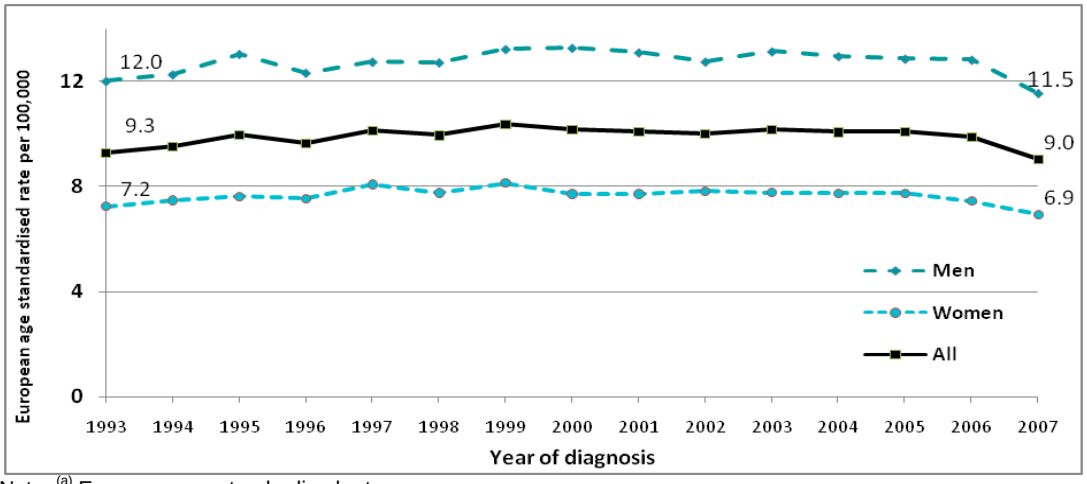
The incidence of all leukaemias in N. Ireland has largely remained steady over the years 1993-2008, with an average of 165 new cases diagnosed annually[17,18]. The European age standardised incidence rate[19] in N. Ireland in 2008 was 9.2 per 100,000 persons (Figure 1). These figures are similar to the UK (Figure 2). As occurs internationally, a higher incidence of leukaemia in males was observed across all age groups.

Figure 1. Leukaemia incidence N. Ireland 1993-2008[a,b]



Note: [a] European age standardised rates [b] Source N. Ireland Cancer Registry

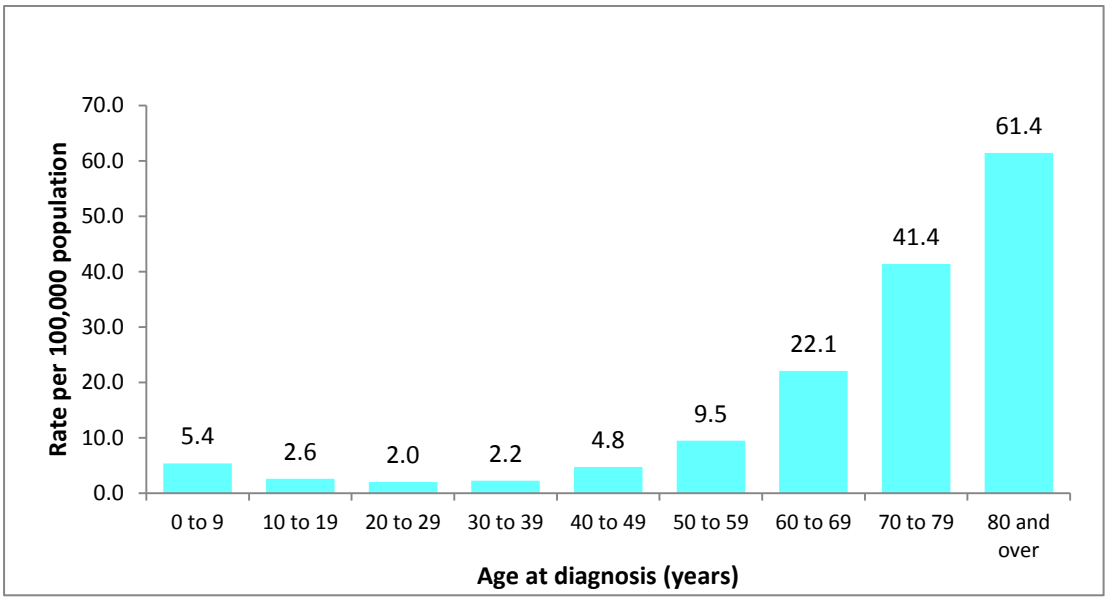
Figure 2. Leukaemia incidence UK 1993-2007[a,b]



Note: [a] European age standardised rates
[b] Source Cancer Research UKhttp://info.cancerresearchuk.org/cancerstats/types/leukaemia/incidence/

The risk of leukaemia rises with age. While only 8% occur in children and young people, 60% of cases of the acute lymphoblastic leukaemia subtype occur in children with a peak incidence in the first five years (Figure 3).

Figure 3. Leukaemia: Age specific incidence rates N. Ireland, 1993-2008[(a)]

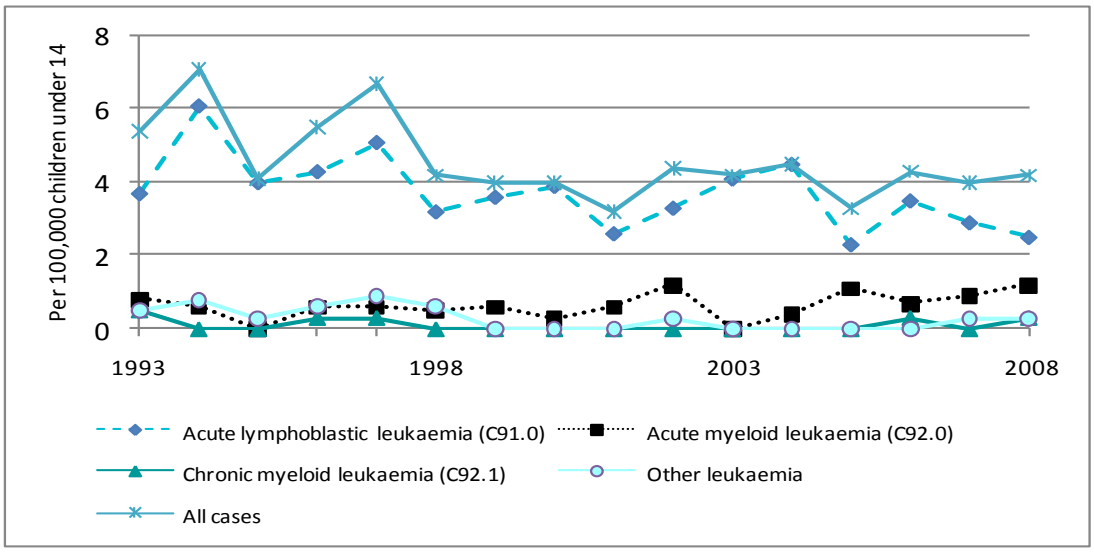


[(a)] Source N. Ireland Cancer Registry

Leukaemia: Trends in Children under 14 years

The incidence of leukaemia in children under 14 years old in N. Ireland is low and rates have remained largely steady, with minor fluctuations, since 1993 (Figure 4). The European age standardised rate was 4.2 per 100,000 for all cases of childhood leukaemia in 2008 which was similar to that of other countries.

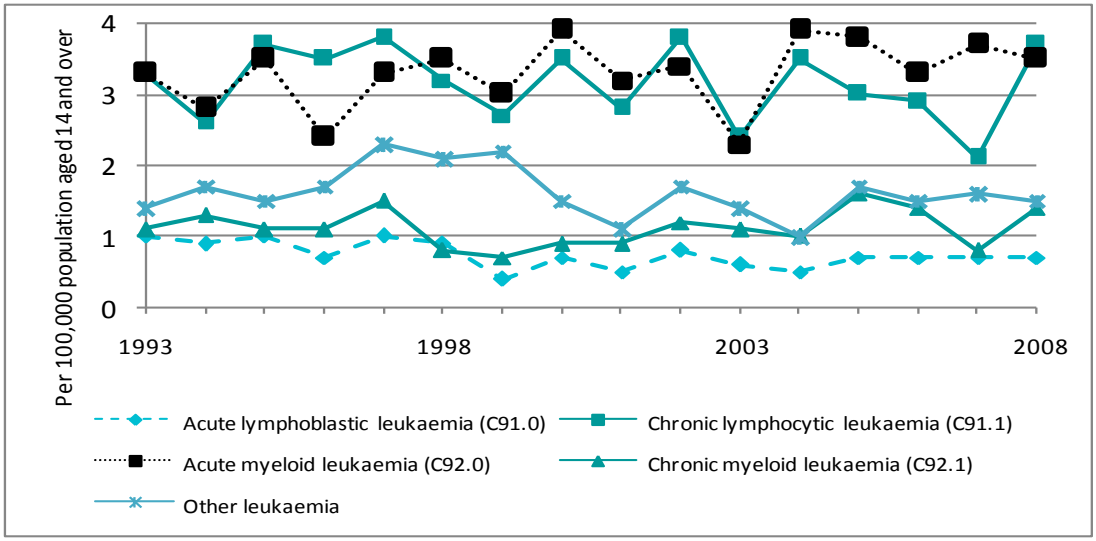
Figure 4. Childhood leukaemia[a] – Annual Incidence: N. Ireland 1993-2008[b]



[a] Less than 14 years [b] Source N. Ireland Cancer Registry

The pattern is very similar for the population aged 14 years and over (Figure 5). Although the incidence of leukaemia has fluctuated over the years, trends have generally remained steady.

Figure 5. All Leukaemia: Population aged 14 years and over in N. Ireland 1993-2008



Leukaemia: Prevalence

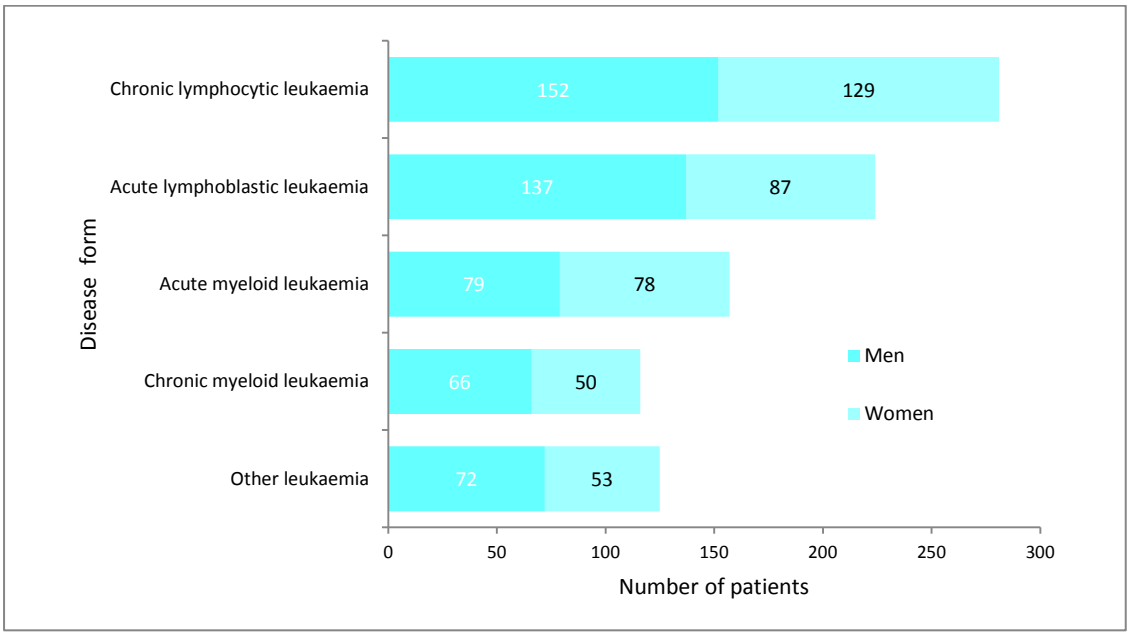
The prevalence of a disease is the number of people in the population with a history of diagnosis at a given point/period in time. By the end of 2008, there were 903 people in Northern Ireland alive with a history of leukaemia diagnosis since 1993 (Table 1, Figure 6). Chronic lymphatic leukaemia (CLL) was the most prevalent, followed by acute lymphoblastic leukaemia (ALL).

Table 1. Leukaemia prevalence by age, gender and type: N. Ireland by end of 2008[(a)]

Leukaemia Type	Under 14 years[b]		14 years and over[b]		
	Male	Female	Male	Female	All
Acute lymphoblastic leukaemia (C91.0)	48	35	89	52	224
Chronic lymphocytic leukaemia (C91.1)	0	0	152	129	281
Acute myeloid leukaemia (C92.0)	5	7	74	71	157
Chronic myeloid leukaemia (C92.1)	0	2	66	48	116
Other leukaemia	2	4	70	49	125
Total	55	48	451	349	903

Notes: (a) Diagnosed 1993-2008 and alive at the end of 2008 (b) Age at end of 2008

Figure 6. Leukaemia Prevalence by gender and type: N. Ireland by end of 2008



Leukaemia: Prevalence by age at diagnosis

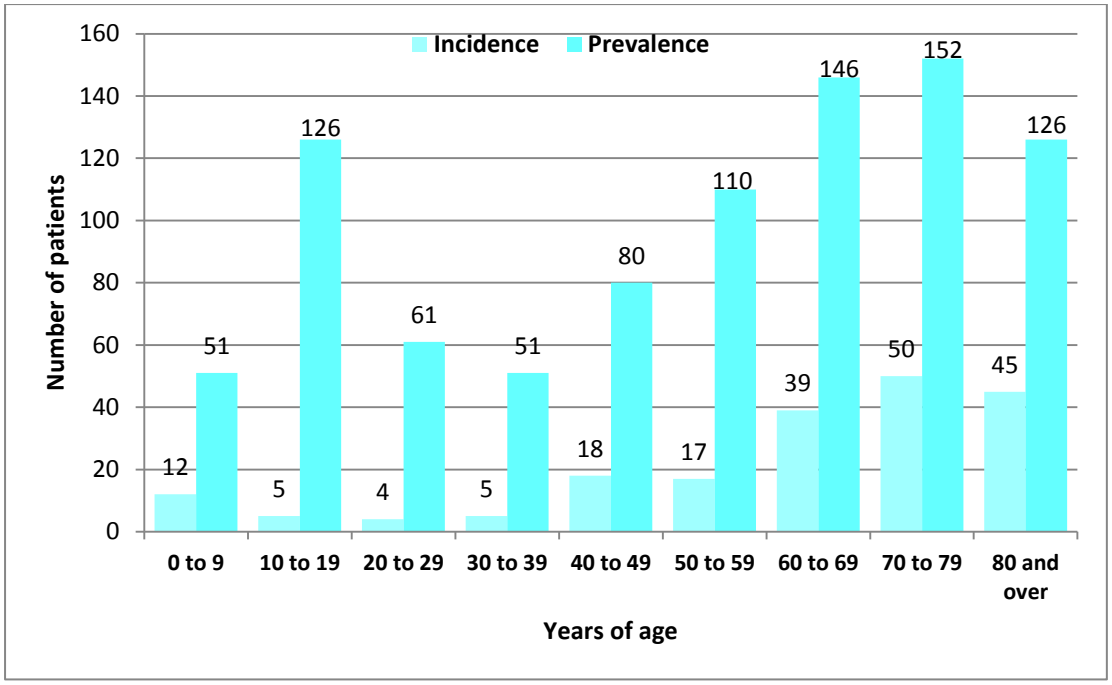
By the end of 2008 eight hundred patients with a history of leukaemia were aged 14 years and older and of these 98 (12%) had been diagnosed before the age of 14 (Table 2, Figure 7).

Table 2. Leukaemia prevalence by age at diagnosis[(a)] N. Ireland 2008

Age at diagnosis	Age at end of 2008	
	Age under 14	Age 14 and over
Under 14	103	98
Over 14	-	702

Note: (a) Diagnosed 1993-2008 and alive at the end of 2008

Figure 7. Leukaemia age specific incidence and prevalence: N. Ireland 1993-2008



Survivors of childhood leukaemia may require ongoing care and support in terms of their developmental, educational and psychosocial needs. Long-term follow-up studies have shown that a small proportion of patients may develop treatment-related side effects[(20)].

The relatively low number of people aged 14 and over who were diagnosed in childhood reflects the relatively new status of the N. Ireland Cancer Registry. The number of adult survivors of childhood leukaemia will increase with time reflecting the high cure rate in this disease.

SECTION III – BACKGROUND TO 2008 AUDIT

The Regional Cancer Services Framework which was published in 2008[21] outlined a cancer control programme for Northern Ireland. One of the recommendations was that the Northern Ireland Cancer Network (NICaN) and Northern Ireland Cancer Registry (NICR) should work with the Regional Multi-Professional Audit Group (RMAG) and the Northern Ireland Audit Advisory Committee (NIACC) to ensure the development of a regionally agreed programme of cancer audit, with methods and results to be shared throughout Northern Ireland. This report is the latest in the second series of such audits and the first on leukaemia and lymphoma. It is based on detailed information relating to patients receiving a first diagnosis of leukaemia or lymphoma in Northern Ireland in 2008.

Leukaemia and lymphoma are cancers of the haematopoietic (blood-forming) cells and lymphoid tissues respectively. They accounted for 7% of all cancers (excluding non-melanoma skin cancer) in Northern Ireland in 2008, with leukaemia accounting for 2.4% of cancers and lymphoma another 4.6%. Sections IV and IX of this report detail the diagnosis, treatment and outcomes of treatment for leukaemia and lymphoma patients respectively, diagnosed in 2008.

Current Guidance – Audit criteria

The Improving Outcomes in Haematological Cancers produced by the National Institute for Health and Clinical Excellence (NICE) in 2003[22] included the following among their recommendations:

- All patients with haematological cancer should be managed by multi-disciplinary haemato-oncology teams which serve populations of 500,000 or more (currently in N. Ireland there is one team for acute leukaemia and 5 teams which treat lymphoma, myeloma and the chronic leukaemias).
- In order to reduce errors, every diagnosis of possible haematological malignancy should be reviewed by specialists in diagnosis of haematological malignancy. Results of tests should be integrated and interpreted by experts who work with local haemato-oncology multi-disciplinary teams (MDTs) and provide a specialised service at network level. This is most easily achieved by locating all specialist haemato-pathology diagnostic services in a single laboratory.

- There should be rapid-access diagnostic services for patients with lymphadenopathy (chronically swollen lymph nodes or neck lumps).
- Clinical nurse and palliative care specialists are to have central roles in haemato-oncology teams, working closely with their medical colleagues. Clinical nurse specialists will arrange for patients and carers to receive multi-faceted support, coordinated care, and all the information they request, throughout the course of the illness.
- MDTs which manage patients with acute leukaemia and provide treatment intended to induce remission should have sufficient numbers of patients for the units concerned to develop and maintain expertise. Services are unlikely to be viable with five or fewer new patients per year. This treatment should be provided at a single facility within any one hospital site, in designated wards with continuous access to specialist nurses and haematologists.
- High dose therapy with progenitor cell transplantation is to be carried out only in centres which meet the Joint Accreditation Committee-International Society for Cellular Therapy (JACIE) accreditation standards, including the minimum case-load criterion of 10 procedures per annum.

Guidance for the management of haematological cancer was published by the Northern Ireland Regional Advisory Committee on Cancer Services (RACC) in 2006[23]. The recommendations included a number of proposals regarding funding and equipment, diagnosis and treatment, staffing levels and training. The guidance also recommended the facilitation of rapid referral and admission, the encouragement of multidisciplinary meetings and team working and, unless precluded by the urgent need for treatment, the offer of a review by a reproductive medicine physician prior to the commencement of treatment. Data on these issues are included in the audit.

The Northern Ireland Cancer Network (NICaN) Haematology Network guidelines for the Management of Leukaemia & Lymphoma are currently under development.

Methods

Data collection

Registry Tumour Verification Officers (TVOs) collected data by reviewing clinical notes of patients registered within the NICR database in 2008 with a diagnosis of:

- Acute myeloid leukaemia (C92.0).
- Acute lymphoblastic leukaemia (C91.0).
- Chronic myeloid leukaemia (C92.1).
- Hodgkin Lymphoma (C81.0).
- Non-Hodgkin lymphoma (C83-C85).

Multiple case notes from different hospitals were reviewed (where required) to collate the clinical information. Data were then entered into an electronic proforma, which had been developed with the guidance of clinicians; a copy is available at www.qub.ac.uk/nicr.

Exclusions & analyses

Patients were excluded if their records lacked sufficient information, or information was available only from a death certificate (DCO) or post-mortem.

Chronic lymphocytic leukaemia (CLL) was not included in this audit as there were potential issues of case ascertainment as cases diagnosed on blood samples only may not be registered within the NICR database. In addition there are well documented issues due to classification overlap with low grade Non-Hodgkin Lymphoma.

After cleaning and validation, data analysis was carried out using SPSS. Tests for statistical significance used in the report include Mantel-Cox log rank test. Survival was calculated using the Kaplan-Meier approach.

SECTION IVA – RESULTS OF THE 2008 AUDIT OF CHILDHOOD LEUKAEMIA

Study population

Leukaemia is one of the most common forms of childhood cancer accounting for almost one third of all cases. In 2008, twelve children under the age of 14 years were diagnosed with acute leukaemia. For the purposes of this audit children and young people age 14 and over are included in the adult leukaemia section as they are usually treated in adult units.

As expected ALL was more common than AML accounting for 75% of cases. The age at diagnosis was from under one year to 10 years of age, with a median age of 5 years. Numbers were too small to detect any pattern in incidence in terms of locality or deprivation.

Childhood leukaemia: Referral, presentation and diagnosis

Six children were referred by their GPs and 3 through Accident and Emergency departments. Five children presented first at the Royal Belfast Hospital for Sick Children (RBHSC) with the remainder presenting at other hospitals.

Symptoms at presentation

- The common presenting symptoms were lethargy, bruising/bleeding and/or recurrent infection.

Risk factors

- No family history of haematological cancer was recorded for any of the children.
- Co-morbidities were noted including other malignancy, cardiac problems and learning disability.

Diagnosis

The diagnosis and treatment of leukaemia was extremely prompt. Four children were first seen by a consultant haematologist and five by a consultant paediatrician. The majority of children were treated within a few days of referral.

Results of pre-treatment investigations are shown in Table 3.

Table 3. Childhood leukaemia: Results of pre-treatment investigations

Investigations					**Total available values in notes**
Category: White blood cell count (WBC) x10^9/L		*<10*	*10-99*	*>=100*	
Results	ALL	2	5	2	9
	AML	1	1	0	2
Category: Absolute Neutrophil count (ANC) x10^9/L		<0.5	0.5-2	>2	
Results	ALL	3	1	3	7
	AML	1	1		2
Category: % Bone marrow blast cells		*<20%*	*20-80%*	*>80%*	
Results	ALL			8	8
	AML	1		1	2
Category: Lumbar puncture result		Normal			
Results	ALL	8			8
	AML	2			2

- Two of the children had markedly elevated white blood cell counts (WBC> 100) which is known to be a poor prognostic feature in ALL.
- Four children presented with severe neutropenia (severely depressed neutrophil count) which can result in overwhelming infection.
- The majority of children had more than 80% blasts in the bone marrow at diagnosis.
- Ten children were recorded as having a normal lumbar puncture result at diagnosis.

Childhood leukaemia: Treatment

Clinical Trials

The Medical Research Council (MRC) childhood acute leukaemia trials, http://www.ctu.mrc.ac.uk, have led to major improvements in survival in the UK with 80% of children now achieving long term survival compared to 20% twenty five years ago[(24)].

- It is very encouraging that 78% of the children with ALL were enrolled in the MRC ALL 2003 trial (www.ctsu.ox.ac.uk) at diagnosis. The MRC ALL 2003 is a randomised trial to evaluate whether treatment intensity can be reduced without compromising the risk of cure in low risk patients who are negative for minimal residual disease (MRD) after various points in treatment. Patients in the low risk MRD group are randomised into one of the less intensive treatment protocols.
- In addition, another child with ALL was enrolled in the ALL R3 trial for relapsed disease.
- Three children had bone marrow transplants.

Multidisciplinary Team meetings and discussions with patients and parents

The Cancer Control Programme for Northern Ireland (2006) states that all patients with a new diagnosis of cancer should have their treatment plan agreed at an appropriately constituted and resourced Multidisciplinary Team Meeting (MDT). However as treatment for acute leukaemia is usually commenced as a matter of urgency it is generally not possible to discuss patients prior to commencing therapy.

- Review of the clinical notes did not provide details of MDT discussion in these cases as currently there is no formal multidisciplinary team meeting for childhood leukaemia. A children's cancer module however has now been developed within the Regional Cancer Patient Pathway system (CaPPS) which should facilitate recording of MDT discussions in future.
- Discussion of diagnosis, treatment options and likely treatment outcomes with parents and children (where appropriate) was well recorded in the clinical notes.

Dental assessment

Effective oral and dental care is critical for patients being treated for leukaemia, who may develop dental infection which can result in fatal sepsis in the immune-compromised. The UK Children's Cancer Study Group recommends that all children should undergo a dental assessment at the time of a cancer diagnosis, and if possible before treatment commences[25].

- A pre-treatment dental assessment was recorded for 6 children even though treatment commenced within a matter of days from diagnosis.

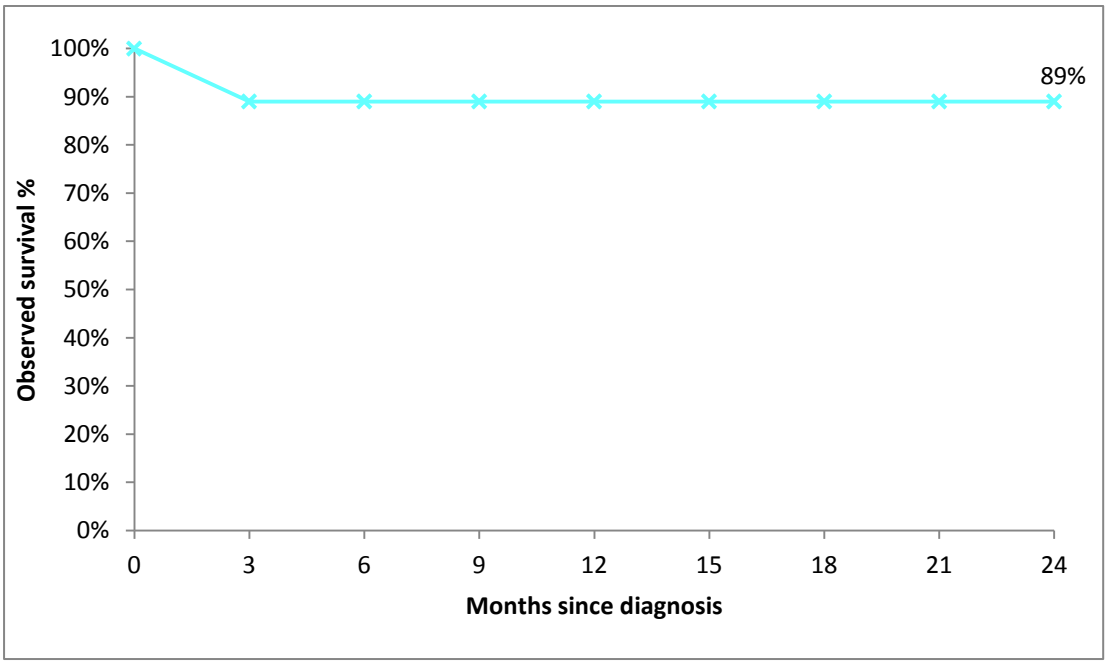
Childhood leukaemia: Survival

- Nine children remain in complete remission in 2010.

Childhood acute lymphoblastic leukaemia: Survival

Observed survival at two years was 89% for children with acute lymphoblastic leukaemia. Due to very small numbers of AML cases a survival analysis for AML was not performed.

Figure 8. Observed survival Childhood ALL 2008



SECTION IVB – RESULTS OF THE 2008 AUDIT OF ADULT LEUKAEMIA

Study Population

In 2008 there were 73 adult* patients with a new diagnosis of acute lymphoblastic leukaemia, acute myeloid leukaemia or chronic myeloid leukaemia in Northern Ireland (Table 4).

Table 4. Adult* leukaemia: Age, gender and diagnosis

Leukaemia type	Male	Female	Total
Acute lymphoblastic leukaemia	4	4	8
Acute myeloid leukaemia	26	24	50
Chronic myeloid leukaemia	8	7	15
Total	**38**	**35**	**73**

* Age 14 or over

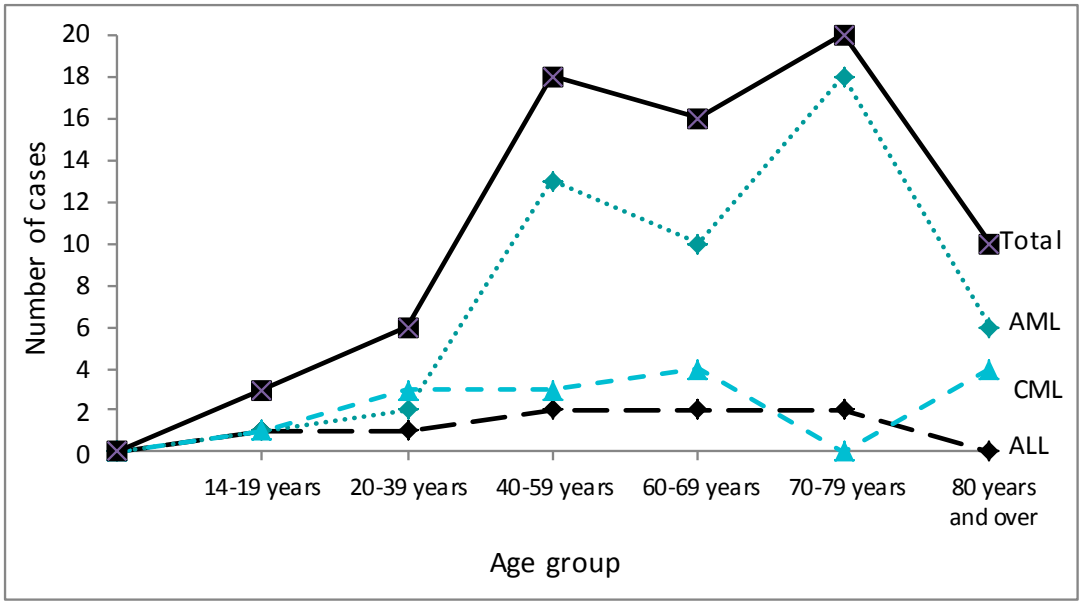
Table 5 and Figure 9 show the age bands and gender of the patients.

Table 5. Adult leukaemia: Age bands and gender of patients

Age band	Male	Female	All patients	
			Number	%
14-49 years	7	10	17	23%
50-59 years	5	5	10	14%
60-69 years	9	7	16	22%
70 years and over	17	13	30	41%
Median age in years	**68**	**62**	**67**	

- As expected, the majority of patients (63%) were aged 60 years or older with 41% aged 70 years or older.

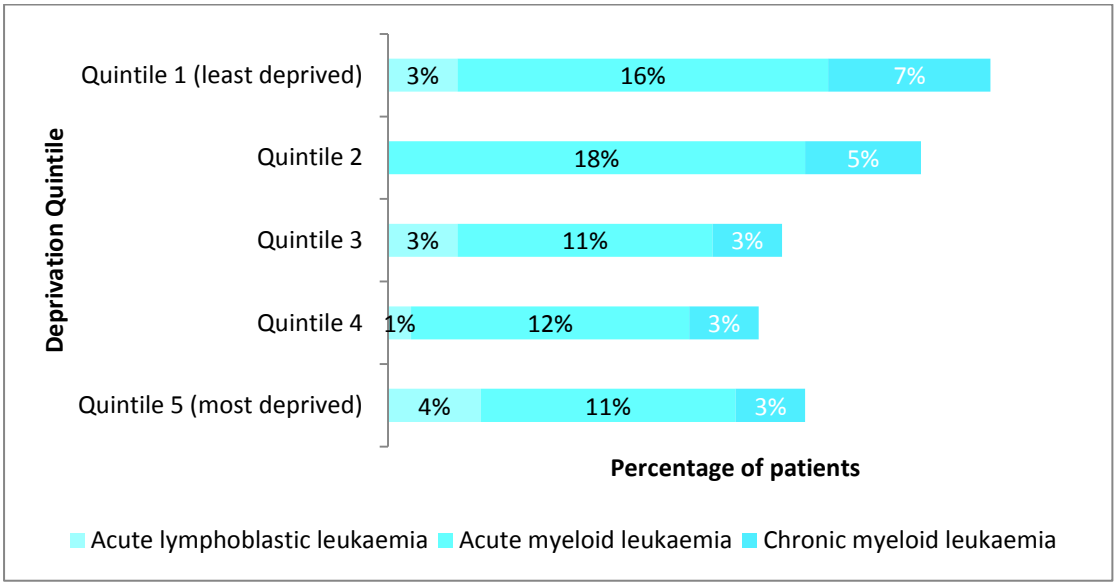
Figure 9. Adult leukaemia: Age bands of patients



Socio-economic residential area of patients

The population of N. Ireland can be divided into five equally sized quintiles ranked by socio-economic deprivation level of area of residence. If a disease is not related to deprivation, it is expected that 20% of cases of leukaemia would fall in each quintile.

Figure 10. Adult leukaemia: Socio-economic groups



- In the adult leukaemia study patients there were slightly greater numbers in quintiles 1 and 2, the least deprived quintiles (Figure 10). This was not however significant.

Referral, presentation and diagnosis

Referral source

Table 6. Adult leukaemia: Referral source

	All patients	
Source of referral	**Number**	**%**
General Practitioner	35	48%
Accident and Emergency	25	25%
Consultant	6	8%
Other	7	10%
Number	73	100%

- The majority of patients (73%) were referred by General Practitioners (48%) or via Accident and Emergency (25%).

Referral priority

Table 7. Adult leukaemia: Priority of referral

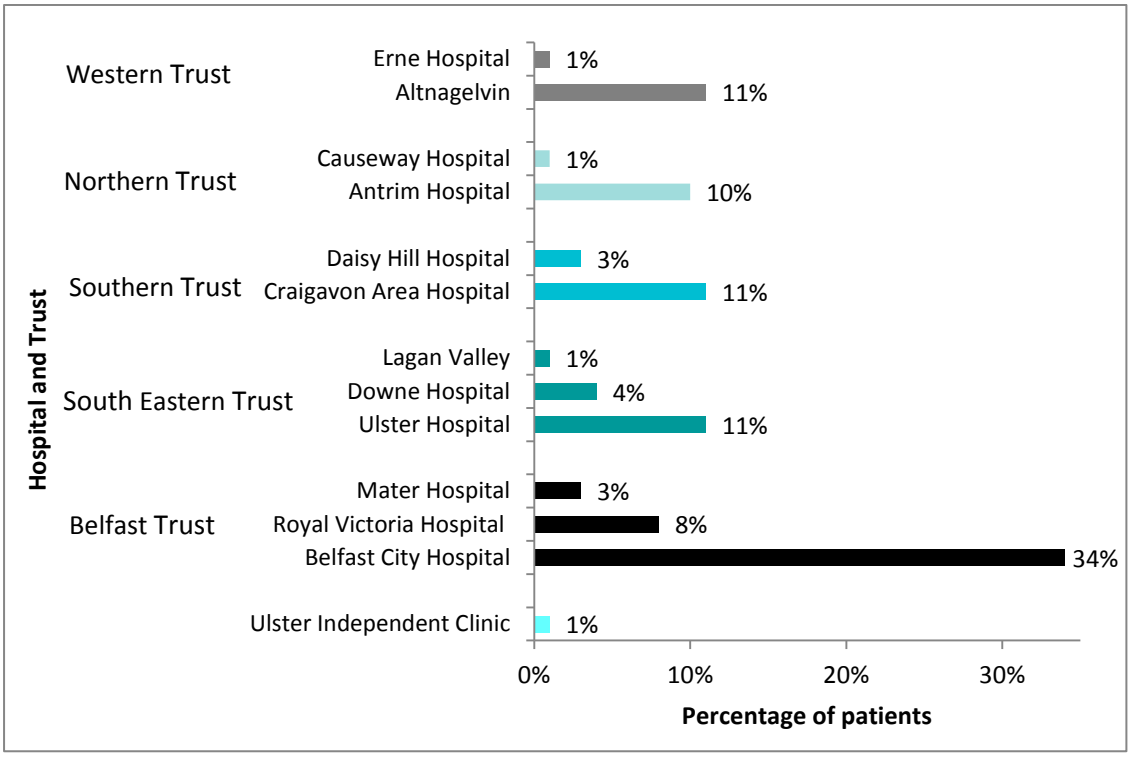
	All patients	
Priority of referral	**Number**	**%**
Emergency	34	47%
Urgent	16	22%
Routine	4	5%
GP red flag	1	1%
Other	6	8%
Not available in notes	12	16%
Number	73	100%

- 47% of patients were admitted as emergencies.
- 22 % were urgent referrals (mostly by GPs to outpatients).
- Only one referral was prioritised as a GP red flag suspect cancer referral.

Hospital/Trust of first presentation

- A third (34%) of patients first presented at Belfast City Hospital.
- The majority of the remaining patients first presented at Altnagelvin (11%), Craigavon (11%), Ulster (11%), Antrim (10%) and Royal Victoria Hospitals (8%).

Figure 11. Adult leukaemia: Hospital and Trust of presentation



Consultant specialty of first referral

Table 8. Adult leukaemia: Consultant specialty of first referral

	All patients	
Speciality	**Number**	%
Haematology	43	59%
General Medicine	13	18%
General Surgery	5	7%
Accident & Emergency	2	3%
Other*	7	10%
Not available in notes	3	4%
Number	**73**	**100%**

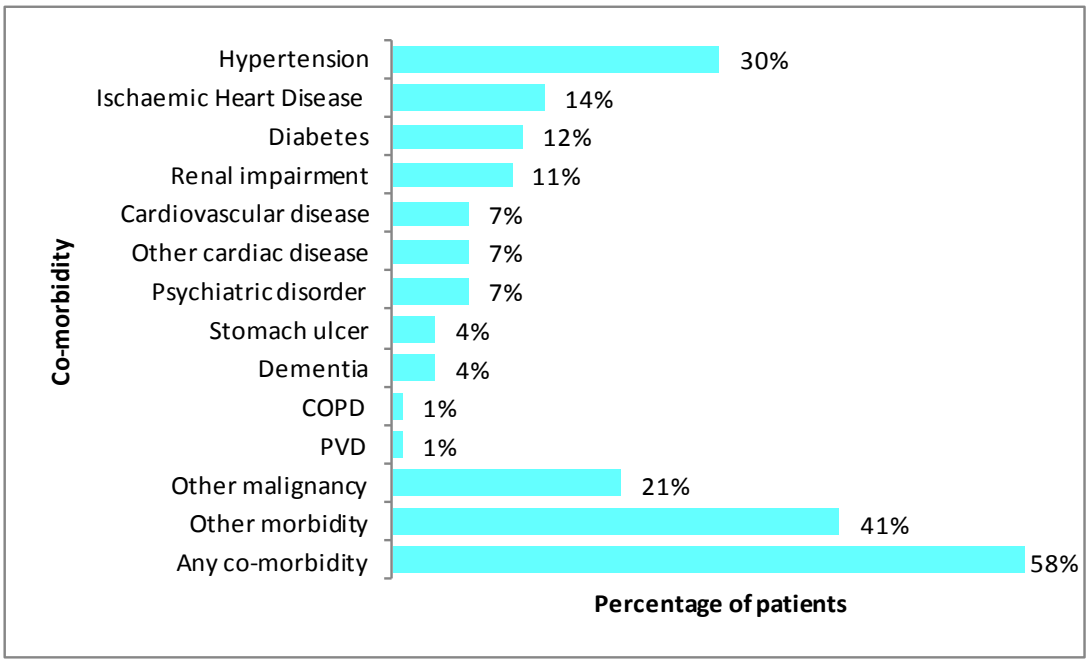
***** Other includes medical oncology, cardiology, endocrinology, gastroenterology, geriatric medicine and ophthalmology

- More than half (59%) of patients were referred directly to a Consultant Haematologist.
- 18% were first seen by a General Medicine Consultant.
- 7% were first seen by a General Surgery Consultant.

Co-morbidities

- 58% of patients were recorded as having some form of co-morbidity.
- As expected in a predominantly elderly group, hypertension, ischaemic heart disease /other cardiovascular disease and diabetes were the most commonly recorded co-morbidity.
- 21% of patients had a history of other malignancy.

Figure 12. Adult leukaemia: Co-morbidities*



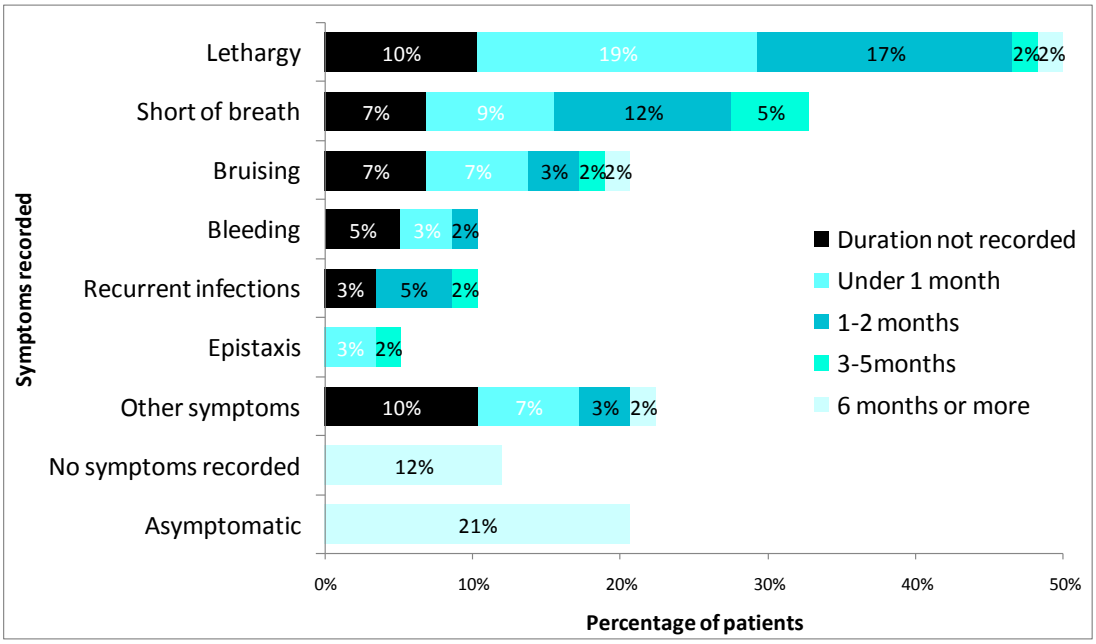
*Patients may have had more than one co-morbidity and/or malignancy

COPD= Chronic obstructive pulmonary disease, PVD= Peripheral vascular disease

Signs and symptoms

- As expected, the most common symptoms/signs recorded at presentation were lethargy (49%), shortness of breath (33%), easy bruising/bleeding (21%) and recurrent infection.
- 43% of patients with acute leukaemia had experienced at least one symptom for over a month.

Figure 13. Adult Leukaemia: Symptoms recorded by duration



- As expected, the majority of acute leukaemia patients reported short symptom duration.

Access to Haematology service

Table 9. Adult leukaemia: Referral to first seen by haematologist

Time	Acute lymphoblastic leukaemia	Acute myeloid leukaemia	Chronic myeloid leukaemia	All patients	
				Number	%
Same day	3	14	2	19	26%
1-7 days	2	22	8	32	44%
8-14 days	2	4	1	7	10%
More than 14 days	1	3	2	6	8%
Referral dates not available/Not applicable	0	7	2	9	12%
All patients*	8	50	15	73	100%

* Unavailable referral dates in 4 cases prevented inclusion in this analysis

- One third of acute leukaemia patients (for whom dates were available) were seen by a haematologist on the day of referral.

- The majority of patients (80%) were seen by a haematologist within one week.
- 5 patients who were under regular haematological review at the time of diagnosis of AML, with previous diagnoses of Myelodysplasia (3), Lymphoma (1) and neutropenia (1) were excluded from this analysis.

Method of diagnosis

Table 10. Adult leukaemia: Method of diagnosis

	All patients
Peripheral blood and bone marrow	62
Peripheral blood only	9
Not available in notes	2
All patients	**73**

- The diagnosis of leukaemia was confirmed by bone marrow aspirate in 62 patients (85%).
- 9 patients (12%) had a record of being diagnosed on peripheral blood only.

Results of pre-treatment investigations

Table 11. Adult leukaemia: Results of Investigations

						Total available values in notes
Category: White blood cell count (WBC) $x10^9/L$		***<4.0***	***4-10***	***10-99***	***>=100***	
Results	ALL	0	3	4	1	8
	AML	23	7	18	2	50
	CML			4	11	15
Category: Absolute Neutrophil count (ANC) $x10^9/L$		**<0.5**	**0.5-2**	**>2**		
Results	ALL	1	3	4		8
	AML	20	12	15		47*
	CML			15		15

Table 11. Adult leukaemia: Results of Investigations (continued)

						Total available values in notes
Category: % Bone marrow blast cells		**<20%**	**20-80%**	**>80%**		
Results	ALL		3	4		7*
	AML	9	27	5		41*
Category: % Bone Marrow Blast Cells		**<10**	**10-19**	**>20**		
Results	CML	9				9*

*Unavailable results in clinical notes prevented inclusion of all patients in this analysis.

- Three patients (AML 2, ALL 1) had markedly elevated WBC at presentation which is a recognised poor prognostic factor.
- Half of the AML patients presented with an elevated WBC which is the classic hallmark of acute leukaemia. However a significant proportion (23/50) presented with pancytopenia (low WBC, HB and platelet counts) which is commonly seen especially in elderly patients and those with pre-existing marrow dysfunction (Myelodysplasia).
- As expected the majority of acute leukaemia patients had more than 20% bone marrow blast cells which the WHO defines as the demarcation line between myelodysplasia and acute leukaemia.
- Nine CML patients (for whom results were available in the clinical notes) had bone marrow blast counts of less than 10% in keeping with chronic phase disease at diagnosis.

Cytogenetic analysis

Cytogenetic analysis of peripheral blood and bone marrow at diagnosis may identify the presence of any abnormal translocations or deletions of chromosomes.

Cytogenetic analysis: AML

In acute myeloid leukaemia the presence of specific cytogenetic abnormalities classifies patients into ‘favourable’, intermediate’ and ‘poor risk’ groups. The table below shows the cytogenetic profile of the 43/50 AML patients who had cytogenetic analysis performed.

Table 12. Adult AML: Cytogenetic analysis

Risk category	Number	%
Favourable	6	12%
Intermediate	28	56%
Poor	9	18%
No sample available	7	14%
All AML	50	100%

- The majority of patients for whom a result was available 28/43 (65%) fell into the 'intermediate risk' group.

Cytogenetic analysis: ALL

In ALL the presence of the Philadelphia chromosome t(9;22)(q34;q11) is a very strong adverse prognostic factor. It was present in 2 of the adult ALL patients.

Reproductive Health

NICE guidelines advise that prior to treatment men or adolescent boys should be offered the opportunity to store their sperm and women should be offered oocyte or embryo cryostorage as appropriate, provided that this will not worsen their condition and that sufficient time is available.

- Discussion of fertility preservation was recorded for five of the six (83%) men aged 16-45 included in the study (3 men accepted this offer).
- Discussion of fertility preservation was recorded for one of the six women in the age group (16-45 years). This procedure may have been deemed clinically inappropriate in the setting of acute leukaemia which is treated as a matter of urgency.

Dental assessment

Effective oral and dental care is critical for patients being treated for acute leukaemia, who may develop dental infection which can result in fatal sepsis in the immune-compromised.

- A pre-treatment dental assessment was recorded for only 5/46 (11%) of acute leukaemia patients who had active treatment.

Adult leukaemia: Treatment

Referral to treatment

Table 13. Adult leukaemia: Referral to active anti-leukaemia treatment

Time	Acute lymphoblastic leukaemia	Acute myeloid leukaemia	Chronic myeloid leukaemia	All patients	
				Number	%
Same day	0	2	0	2	4%
1-7 days	2	10	4	16	29%
8-14 days	5	7	4	16	29%
15-28 days	0	8	2	10	18%
More than 28 days	1	7	3	11	20%
All patients*	8	34	13	55	100%

*Unavailable referral dates in 2 AML and 1 CML case prevented inclusion in this analysis.

- 15 patients did not receive active anti-leukaemia treatment for clinical reasons.
- 42/58 of the acute leukaemia patients (72%) received active anti-leukaemia treatment.
- Of these, approximately 1/3 were treated within one week and over 60% within 2 weeks of 1st referral, however 1/5 waited over a month from referral to active treatment.

Acute lymphoblastic leukaemia: Treatment

- All 8 patients received active anti-leukaemia treatment in the Belfast City Hospital.
- Two patients (25%) were entered into clinical trials, MRC UKALL 12 (Appendix B) and UKALL 2003. The remaining patients were treated according to the standard MRC UKALL 12 chemotherapy protocol. In the UKALL 12 trial the role of the drug Imatinib and bone marrow transplant in patients with Philadephia positive ALL was investigated.
- One ALL patient subsequently underwent an allogeneic transplant.

Acute Myeloid leukaemia: Treatment

Table 14. Adult AML: Treatment

Treatment	Number	%
Active anti-leukaemia therapy	37	74%
Steroids only	2	4%
Supportive care	11	22%
All patients	50	100%

- Thirty seven of the 50 AML patients (74%) received active anti-leukaemia therapy.
- Thirty four of these patients (92%) received their treatment in the haematology unit in Belfast City Hospital. The remaining patients who underwent less intensive treatment received their chemotherapy in Altnagelvin Hospital haematology unit (2 patients) and the Ulster Hospital haematology unit (1 patient).

Clinical Trials

Table 15. Adult AML: Treatment

Leukaemia Trial	Number	%
AML 15	16	43%
AML 16	16	43%
No trial	5	14%
Total AML patients undergoing active treatment entered into leukaemia trial	32/37	86%

- It is very encouraging that 32 of the 37 patients (86%) receiving active treatment were entered into MRC acute leukaemia trials.
- Sixteen patients were entered into the MRC AML 15 trial (for patients aged under 60 years). In this trial (Appendix B) https://www.trials.bham.ac.uk/aml15patients were randomised to receive one of two standard induction chemotherapy regimens “ADE” or “DA”. In addition patients who have been identified as having a FLT3 gene mutation at diagnosis are randomized to receive a FLT3 inhibitor drug after each course of the allocated induction and consolidation chemotherapy. Patients not suitable for an allogeneic transplant were then randomized to receive one of three consolidation regimens.

The trial also evaluated the role of the monoclonal antibody drug Gemtuzumab and the role of allogeneic transplant, either standard or “mini”, in standard and poor risk patients. For adult patients with acute promyelocytic (APL) type AML the MRC intensive chemotherapy protocol was compared with the less intensive “Spanish” protocol.

- Sixteen patients were entered into the Leukaemia Research Fund (LRF) AML 16 trial (for patients aged 60 and over). Two patients were noted to have declined trial entry. Five AML patients subsequently underwent sibling donor allogeneic bone marrow transplants and 1 patient had an allogeneic transplant after reduced intensity conditioning (RIC) therapy.

Chronic myeloid leukaemia: Treatment

- The majority, 13/15 of CML patients were treated with Imatinib which is NICE- approved first line therapy for CML. One patient was treated with oral chemotherapy and one patient was unfit for treatment due to co-morbidity.
- 3 patients participated in the multicentre SPIRIT clinical trial comparing Imatinib alone with Imanitib in combination with Alpha Interferon.
- 4 patients declined trial entry.

Multidisciplinary Team discussions and Patient information

- Multidisciplinary team discussions were recorded in the clinical notes of 42 (58%) of patients. The remaining patients may have been discussed but the documentation may not have been filed in the notes.
- Discussion of the diagnosis with the patient was well recorded in the clinical notes (93%).
- Discussion of treatment options was also well recorded (89%).
- Recording of discussion of probable outcomes was found in the notes in 62% of cases.

Survival: Acute leukaemia 2008

Table 16 shows the observed survival for ALL, AML and CML at 1 and 2 years.

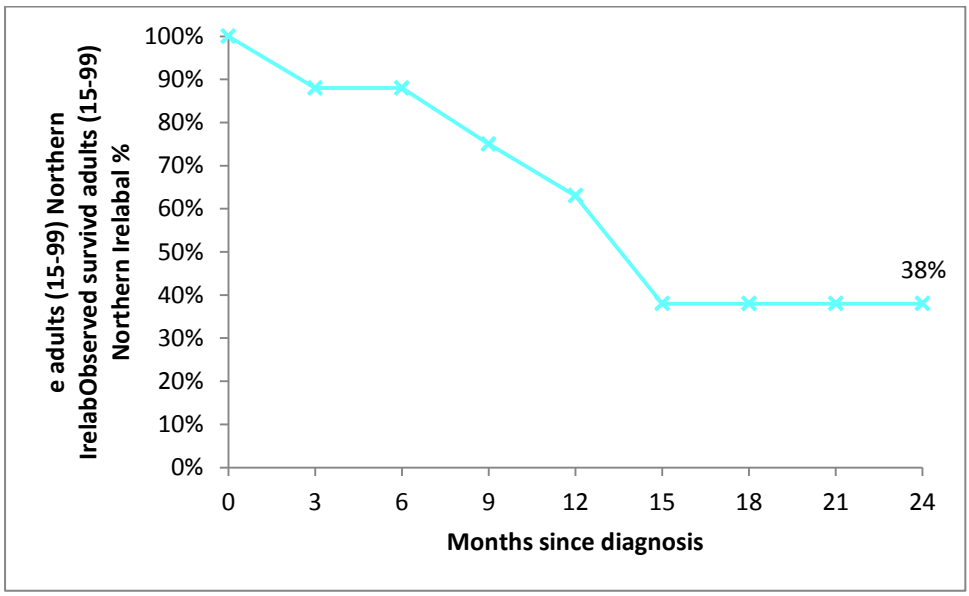
Table 16. Observed survival (% patients alive)

Time	Acute lymphoblastic leukaemia	Acute myeloid leukaemia	Chronic myeloid Leukaemia	All patients
1 month	100%	90%	93%	92%
6 months	88%	58%	93%	68%
1 year	63%	48%	87%	58%
2 years	38%	32%	87%	44%
All patients (number)	8	50	15	73

Survival: Acute lymphoblastic leukaemia

Figure 14 shows the observed survival for ALL which includes deaths from all causes.

Figure 14. Observed survival adult ALL



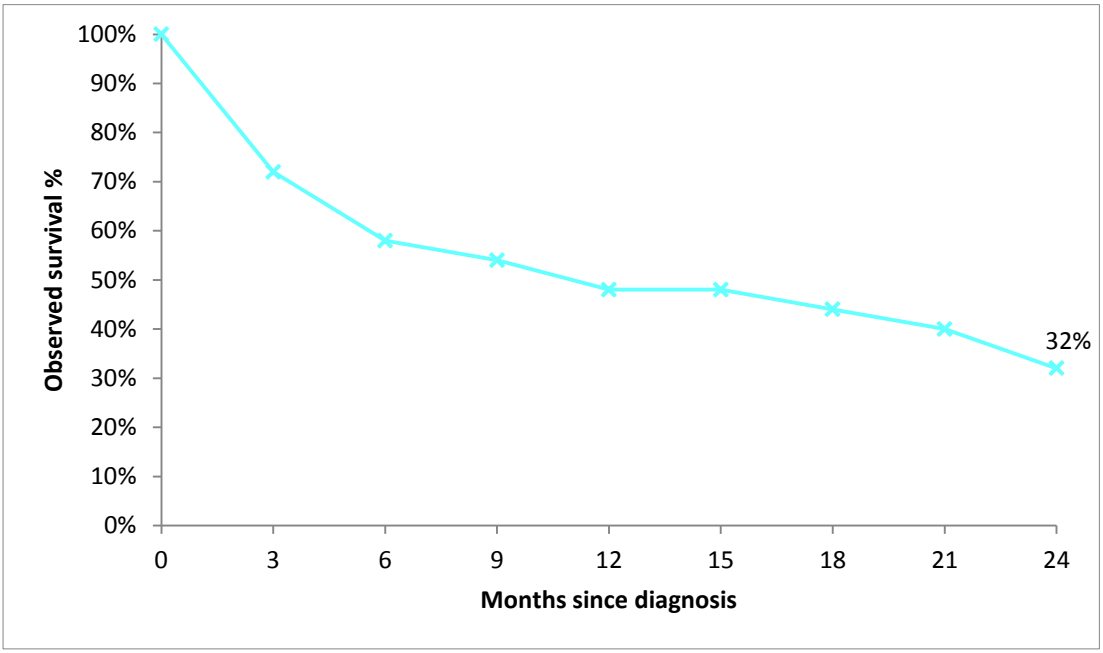
- As recognised the prognosis for adult ALL is much poorer than childhood ALL due to the higher frequency of poor prognostic features and treatment-related toxicity. Observed survival at 2 years was 38% in adults compared to 89% for children. It should be noted

that this is observed survival which includes death from causes other than leukaemia which will be lower in the adult population than among children.

Survival: Acute myeloid leukaemia

Figure 15 shows the observed survival for AML which includes deaths from all causes.

Figure 15. Observed survival AML



- Observed 2 year survival for AML (all ages) was 32%.

Survival: Acute myeloid leukaemia by age category

Table 17 and Figure 16 show the survival by age category less than 60 years compared to 60 years and over. Survival for those aged under 60 years was much better than for those aged sixty or over.

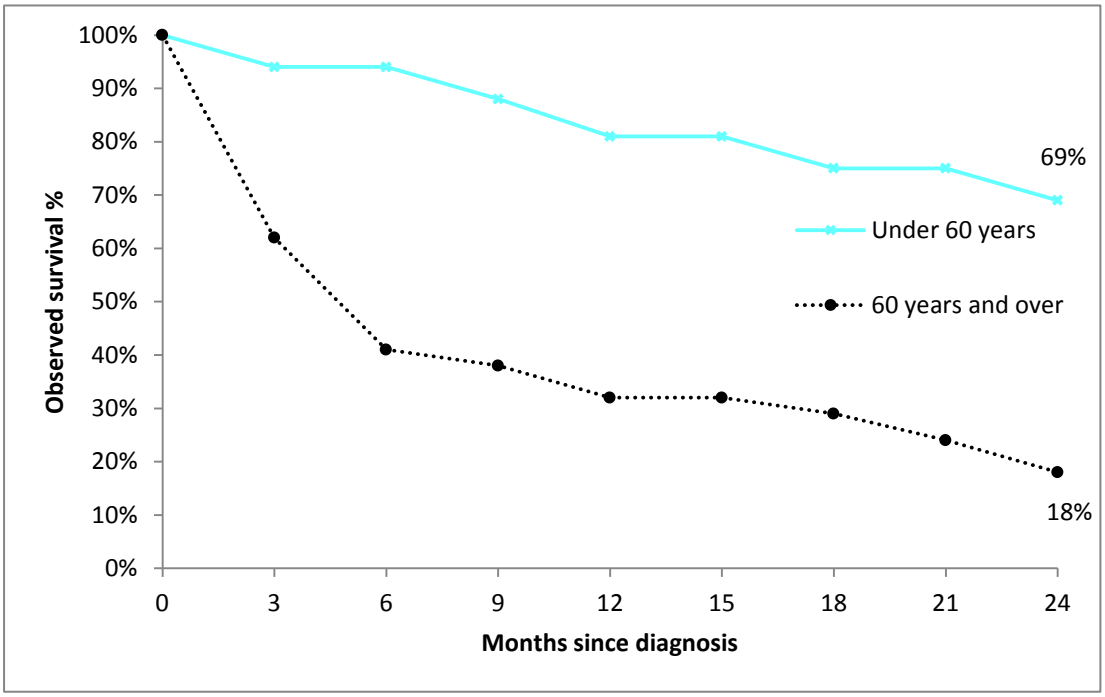
Table 17. Observed survival AML by age category

Time	Under 60 years old	60 years and over
1 month	94%	88%
6 months	94%	41%
1 year	81%	32%
2 years	69%	18%
All patients (number)	16	34

- The 2-year survival for AML was significantly lower for those aged 60 years and over (18% vs 69%, P<0.0001) as the result of higher incidence of poor prognostic factors, co-morbidities and chemotherapy resistance in elderly patients with AML.

Due to the small number of ALL cases analysis by age category was not performed.

Figure 16. Observed survival for AML by age



Survival by cytogenetic risk group: Acute myeloid leukaemia

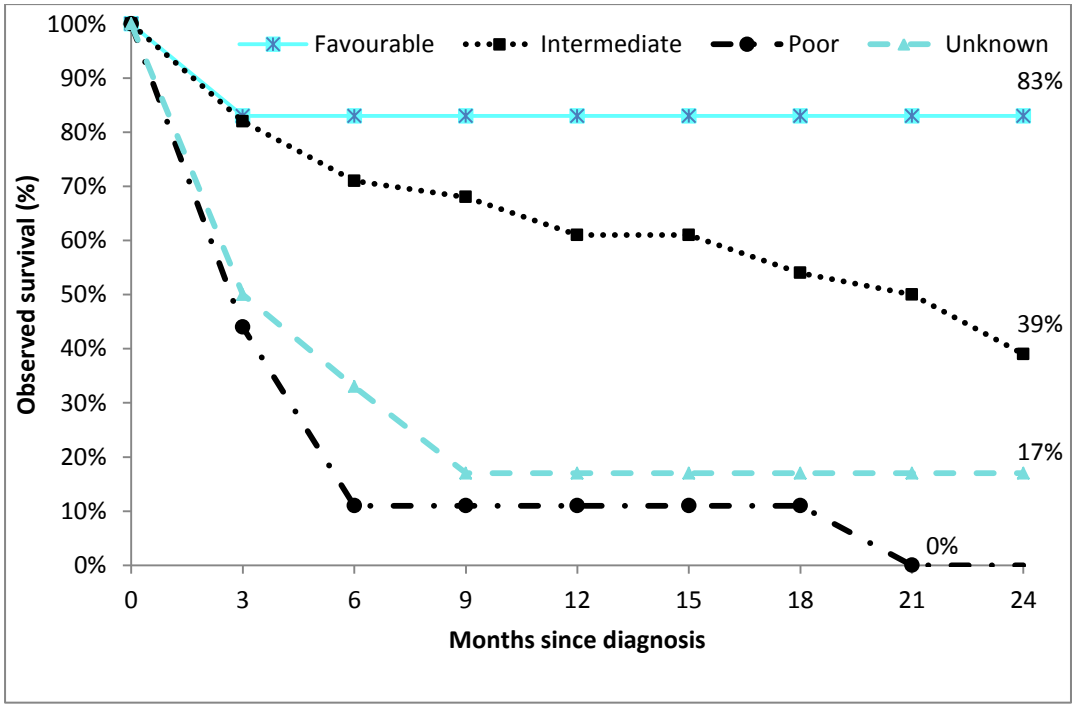
It was possible to categorise 43/50 AML patients according to their cytogenetic results into favourable, intermediate or poor risk (Table 18, Figure 17). The majority of patients fell into the intermediate risk category.

Table 18. Observed survival AML by cytogenetic risk category

Time	Poor	Intermediate	Favourable	Unknown
1 month	89%	89%	100%	83%
6 months	11%	71%	83%	33%
1 year	11%	61%	83%	17%
2 years	0%	39%	83%	17%
All patients (number)	9	28	6	6

- As expected survival rates were significantly higher for patients with a favourable (p=0.002) or intermediate (P=0.000) cytogenetic risk.

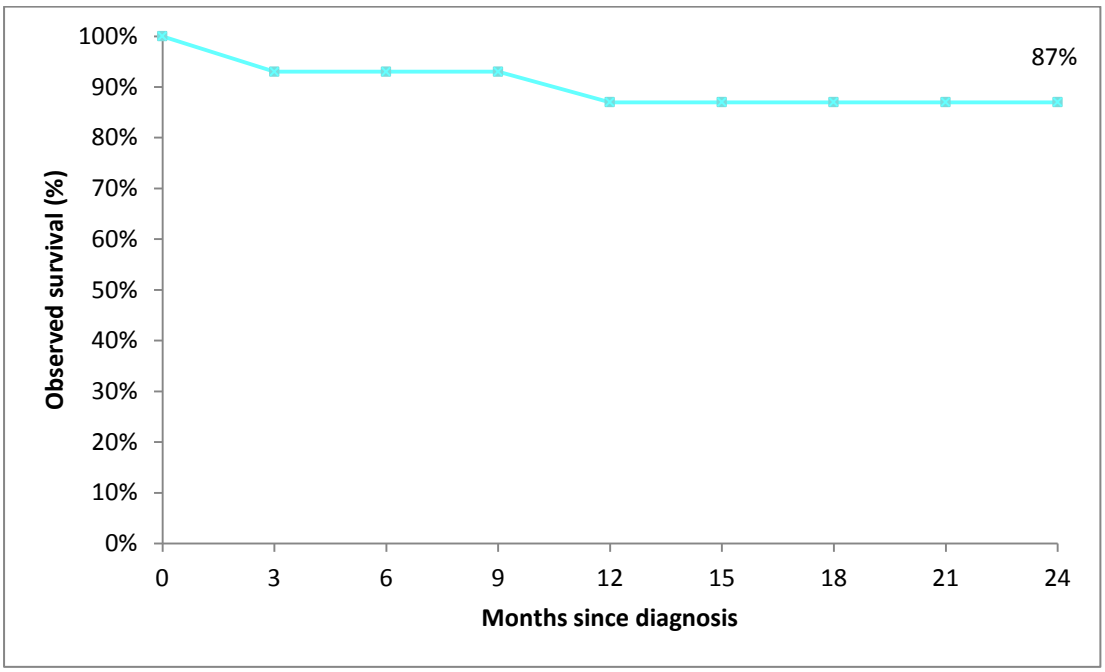
Figure 17. Observed survival AML by cytogenetic risk category



Survival: Chronic myeloid leukaemia

The 2 year observed survival of 87% (Figure 18) is very encouraging and it is likely that with further follow up to 5 years these patients will still be alive demonstrating the impact that targeted therapy with Imatinib has had in this disease.

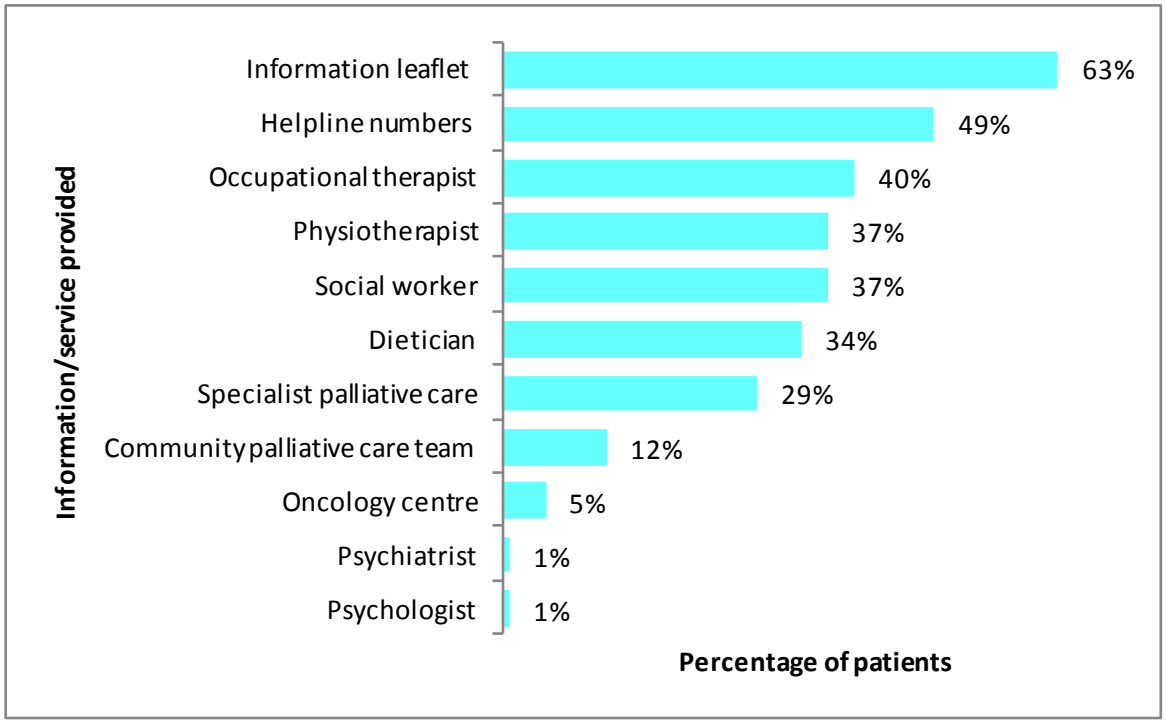
Figure 18. Observed survival (% patients alive) chronic myeloid leukaemia



Provision of patient information and referrals to other health professionals

- There was a record in the clinical notes of information leaflets being given to patients in 63% of cases and of helpline numbers being provided in 49%. It is likely however that all patients would have been given this information but that this was not recorded in the notes (Figure 19).
- Referral to other health professionals was common with patients often receiving input from several speciality services including occupational therapy (40%), physiotherapy (37%) and social work services (37%) respectively. Dietetics (34%), specialist palliative care (29%) and community palliative care (12%) (Figure 19).
- There was little variation in information provided by Trust (data not shown).

Figure 19. Adult leukaemia: Information provided and services of referral*



* Patients may have been given more than one type of information and/or referred to more than one service

Use of telephone helpline

- The helpline was used by almost half (47%) of patients with many patients calling on more than one occasion.
- In total, 101 calls to the helpline from the study patients were recorded in the notes.

SECTION VA -SUMMARY- CHILDHOOD LEUKAEMIA 2008

STUDY PATIENTS

- In 2008 there were 12 children with a new diagnosis of acute leukaemia.
- As expected ALL was the more common type with only 3 cases of childhood AML.
- Age at diagnosis was under one year to 10 years of age, with a median age of 5 years.

REFERRAL AND PRESENTATION

- Six children were referred by their GPs and 3 through Accident and Emergency departments. Five children presented first at the Royal Belfast Hospital for Sick Children (RBHSC) with the remainder presenting at other hospitals.

DIAGNOSIS

- The diagnosis and treatment of leukaemia was extremely prompt. Four children were first seen by a consultant haematologist and five by a consultant paediatrician.

TREATMENT

- Six children had a record of having had a pre-treatment dental assessment.
- The majority of children were treated within a few days of referral.
- 78% of the children with ALL were entered into MRC childhood leukaemia trials.
- Three children, two with AML and one with ALL subsequently had bone marrow transplants.

MULTIDISCIPLINARY CASE DISCUSSIONS

- In 2008 there was no formal Multidisciplinary meeting for childhood leukaemia.

PATIENT INFORMATION

- Discussion of diagnosis, treatment options and likely treatment outcomes with parents and children (where appropriate) was well recorded in the clinical notes.

SURVIVAL

- Observed survival at two years was very good (89%) for children with acute lymphoblastic leukaemia, the commonest type of leukaemia.

SECTION VB -SUMMARY- ADULT LEUKAEMIA 2008

STUDY PATIENTS

- In 2008 there were 73 adult patients with a new diagnosis of acute lymphoblastic leukaemia (8), acute myeloid leukaemia (50) or chronic myeloid leukaemia (15) in Northern Ireland.

REFERRAL AND PRESENTATION

- The majority of patients (73%) were referred by General Practitioners (48%) or via Accident and Emergency (25%).
- A third (34%) of patients first presented at Belfast City Hospital with the majority of the remaining patients first presenting at Altnagelvin (11%), Craigavon (11%), Ulster (11%), Antrim (10%) and Royal Victoria Hospitals (8%).
- More than half (59%) of patients were referred directly to a Consultant Haematologist.
- One third of patients were seen on the day of referral with the majority (80%) being seen by a haematologist within one week.
- The most common symptoms recorded at presentation were lethargy, dyspnoea (shortness of breath), easy bruising/bleeding and recurrent infection.
- 58% of patients were recorded as having at least one co-morbidity.

DIAGNOSIS

- Diagnosis of leukaemia was prompt and was confirmed by bone marrow aspirate in 62 patients (84%) with the remainder being diagnosed on peripheral blood sample only.
- Using cytogenetic analysis it was possible to categorise the majority of AML patients (43/50) into favourable (56%), intermediate (18%) or poor risk (14%) categories.

TREATMENT

- A pre-treatment dental assessment was recorded for only 11% of patients undergoing active treatment.
- 72% of leukaemia patients received active anti-leukaemia treatment, of these 1/3 were treated within one week and over 60% within 2 weeks, however 20% waited over one month from referral to active treatment.
- All 8 acute lymphoblastic leukaemia patients received active anti-leukaemia treatment with standard ALL chemotherapy protocols with 2/8 patients being treated in clinical trials.
- 37/50 of the AML patients (74%) received active anti-leukaemia treatment.

- 7 patients subsequently underwent allogeneic bone marrow transplant.
- 32 of the 37 AML patients (86%) receiving active treatment were entered into clinical trials.
- 87% of chronic myeloid leukaemia (CML) patients were treated with Imatinib which is NICE- approved first line therapy for CML. Three of these patients (23%) were entered into clinical trials.

MULTIDISCIPLINARY CASE DISCUSSIONS

- Multidisciplinary case discussions were recorded in the clinical notes of 42 (58%) of patients.

PATIENT INFORMATION

- Discussion of the diagnosis with the patient, discussion of treatment options and probable outcomes was well recorded in the clinical notes in 93%, 89% and 62% of cases.
- Recording of information leaflets being given to patients and of helpline numbers being provided was found in 63% and 49% of clinical notes respectively.
- Future fertility discussion was recorded for 83% of men and 16% of women aged 16-45 years.

SURVIVAL

- The 2 year observed survival for adult ALL patients was 38%.
- The 2 year observed survival for adult AML patients was 32%.
- The 2 year observed survival for adult AML patients was significantly worse for patients aged 60 years and over compared to those aged less than 60 years (18% vs 69%).
- The 2 year observed survival for adult AML patients was 83%, 39% and 0% for patients in the favourable, intermediate and poor cytogenetic risk categories.
- The 2 year observed survival for adult CML patients was 87%.

REFERRAL TO OTHER HEALTH PROFESSIONALS

- Referral to other health professionals was common with patients often receiving input from several speciality services including occupational therapy (40%), physiotherapy (37%) and social work services (37%) respectively. Dietetics (34%), specialist palliative care (29%) and community palliative care (12%).
- The helpline was used by almost half (47%) of patients with a total of 101 calls to the helpline from the study patients.

SECTION VI – LEUKAEMIA CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

- Patients with leukaemia in N. Ireland receive a very timely, expert and centralised service.
- Survival rates at two years suggest that with further follow up the 5 year survival rates will be comparable to other population-based data.
- High numbers of patients are entered into national leukaemia trials.
- Patients are provided with relevant information and have access to a well used helpline.

RECOMMENDATIONS

As with any service there are possibilities for improvement. The following recommendations stem from this audit.

- All patients should have their diagnosis and treatment plan discussed at an MDT (currently 58% for adults).
- The MDT discussion should be recorded in the Regional Cancer Patient Pathway System (CaPPS) which is now being used regionally for all cancers since 2009.
- All acute leukaemia patients should have access to a dental assessment (currently 11% for adults).
- The helpline facility is a well used resource that should be maintained.

SECTION VII - LYMPHOMA OVERVIEW

Lymphoma: Classification

Lymphoma is a cancer of lymphatic tissue. Lymphatic tissue which defends against infections is present in several organs in the body such as lymph nodes, the spleen, skin, gut and bone marrow.

The two main types of lymphoma are:

- Non-Hodgkin lymphoma (NHL).
- Hodgkin lymphoma (HL).

Non-Hodgkin lymphoma (NHL)

Non-Hodgkin lymphoma has more than twenty different subtypes which behave differently and require different treatment approaches. Specialised laboratory tests are used to identify the different subtypes, some of which are associated with specific damage to chromosomes. NHL can be broadly grouped into indolent/low grade NHL which develops slowly and high grade/aggressive NHL which develops more rapidly. Full detail on the World Health Organisation (WHO) classification of NHL can be found in Appendix D.

Hodgkin lymphoma (HL)

This was first described by Thomas Hodgkin in 1832. There are two main subtypes Classical Hodgkin lymphoma and Nodular lymphocyte predominant Hodgkin lymphoma. A more detailed classification is shown in Appendix D.

Lymphoma: Risk factors

The cause of most lymphomas is unknown however certain risk factors are associated with an increased risk of developing lymphoma such as:

- Weakening of the immune system (Immunodeficiency): Conditions such as HIV infection, immunosuppressant drugs used following organ transplant and rare congenital disorders such as Ataxia telangiectasia and Wiscott-Aldrich syndrome.

- Viruses: Several viruses such as the Ebstein Barr virus (EBV) and Human T-cell leukaemia/lymphoma virus (HTLV1) have been associated with a slightly increased risk of developing lymphoma.
- Familial Factors: In Hodgkin lymphoma (HL) same-sex siblings have a 10 times higher risk for the disease. The identical twin of a patient with HL has a 99 times higher risk of developing HL than a non-identical twin. In addition higher risk for HLis associated with fewer siblings and a higher socio-economic status in childhood. These associations suggest a genetic predisposition and/ or the role of an infectious/environmental agent during childhood or adolescence. In NHL there is a 2-3 fold increase in risk for close relatives which may be genetic/environmental.
- Exposure to environmental toxins**:** Chemicals have been linked to the development of NHL. Pesticides, herbicides, solvents, organic chemicals (eg.benzene, carbon tetrachloride), wood preservative and dusts (wood and cotton). A slightly increased risk is seen in the occupations that involve exposure to these agents.
- Chronic diseases: An increased incidence of gut lymphoma is seen in patients with Coeliac disease and inflammatory bowel disease, particularly Crohn's disease.

Lymphoma: Clinical presentation

Non-Hodgkin lymphoma (NHL)

The common presenting symptoms of the two main broad categories of NHL (indolent/low grade NHL and aggressive/high grade NHL) are shown below:

- Painless, swelling of lymph nodes (lymph glands).
- Fever, drenching night sweats and weight loss (more than 10% of body weight) referred to as B symptoms.
- Symptoms due to involvement of the other sites such as the gut, skin, bone marrow and central nervous systems.
- Fatigue and lethargy.

Although the symptoms are similar, in the indolent/low grade NHL they tend to develop and progress slowly while in the aggressive/high grade NHL symptoms develop and progress more rapidly requiring treatment within a short time of diagnosis. In addition indolent/low grade NHL is most common in middle and old age while the age distribution of the aggressive/high grade NHL is more varied.

Hodgkin lymphoma (HL)

Hodgkin lymphoma is more common in young adults age 20-29 who typically present with:

- Painless rubbery enlargement of lymph glands in the neck, armpit or groin.
- Fever, drenching night sweats and weight loss (more than 10% of body weight), referred to as B symptoms.
- Generalised itch.
- Cough and breathlessness.
- Fatigue and lethargy.

Although more common in young adults, HL can occur in older people typically from the 6th decade onwards.

Lymphoma: Diagnosis

Biopsy of a lymph node or other tissue is required. Additional laboratory tests are required to diagnose and classify the various subtypes of lymphoma as described in Appendix D.
Further tests are then required to determine the stage or extent of the lymphoma in particular to assess if the lymphoma has spread to other organs:

- CT scan of chest, abdomen & pelvis to define the number and location of involved sites.
- Blood tests should include serum lactate dehydrogenase (LDH) level as this is required to calculate lymphoma prognostic indices (Further detail in appendix D).
- Bone marrow biopsy.
- HIV serology.
- Lumbar puncture if there are neurological symptoms or in certain cases where the lymphoma is affecting the bone marrow, testis or breast.
- Sperm banking should be considered in young men with Hodgkin lymphoma prior to treatment.
- PET scan prior to treatment is useful in Hodgkin lymphoma as it helps in assessing response to treatment.

Lymphoma: Staging

Staging helps to define the extent of the lymphoma at diagnosis and is used to determine the most appropriate treatment. Details on the staging systems for the various types of lymphoma is shown in Appendix E.

Lymphoma: Treatment

There are significant differences in the approach to treatment for the different main types of lymphoma. Details on the specific treatments for each type are shown in Appendix F. In general the management of patients with indolent/low grade NHL usually involves the decision between 'Watch & Wait' or therapy in the form of chemotherapy and/or radiotherapy. Therapy may be deemed appropriate at diagnosis or after a period of Watch & Wait when clinical symptoms or complications have developed. For patients with aggressive/high grade NHL treatment is commenced soon after diagnosis and the majority of patients are treated with 6-8 courses of chemotherapy. Some patients however require radiotherapy only at diagnosis while others may require radiotherapy following chemotherapy. Similarly patients with HL depending on the stage are usually treated with chemotherapy followed by radiotherapy. Patients with aggressive/high grade NHL and HL who do not respond to initial treatment may require more intensive treatment with high dose chemotherapy followed by stem cell transplantation as detailed in Appendix F.

Lymphoma: Prognosis

The prognosis or outcome following treatment for the different types of lymphoma varies considerably. Various clinical indicators have been used to develop indices that predict the likely outcome from treatment for each of the lymphoma types. Details on prognostic indices can be found in Appendix G. In general the indolent/low grade NHL are responsive to radiotherapy and chemotherapy but tend to recur with a median survival of 8-10 years. For the aggressive/high grade NHL with current treatment protocols just over 50% of patients will survive 5 years or more while for patients with HL this figure is more than 80%. Survival for NHL has improved in Northern Ireland with 77% survival one year and 88% 5 years. Survival for HL remains steady at 89% one year and 79% 5 years (Appendix C).

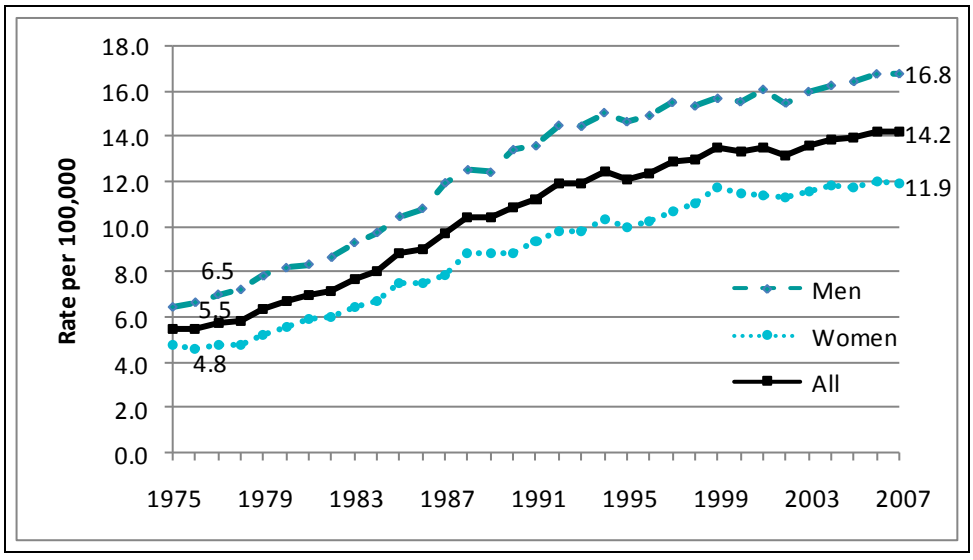
SECTION VIII - LYMPHOMA IN N. IRELAND: THE PAST 16 YEARS

Lymphoma: Incidence and trends

The annual incidence of NHL (world age-standardised) in N. Ireland at 10.4per 100,000 is similar to that of Northern Europe and North America[26]at 10 and 13.7 cases per 100,000 respectively. Non-Hodgkin lymphoma accounts for 3.7% of all cancers in N. Ireland (excluding non-melanoma skin cancers). Incidence increases with age with a male preponderance of 3:2. The incidence internationally has increased by 3-4% per annum in the last four decades. Some of this increase may be artefactual resulting from improved diagnostic techniques and access to medical care. Some is due to the rise in mean age of the population, the HIV pandemic and use of immunosuppressive therapy.

In Great Britain the incidence of NHL has almost tripled since 1975. Between 1993 and 2007 the rate increased from 5.5 to 14.2 per 100,000 while the incidence of Hodgkin lymphoma remained stable (Figure 20&21). In N. Ireland rates of NHL and HL have remained steady since the Cancer Registry started to record cases in 1993 (Figure 22).

Figure 20. Non-Hodgkin lymphoma Great Britain 1975-2007*

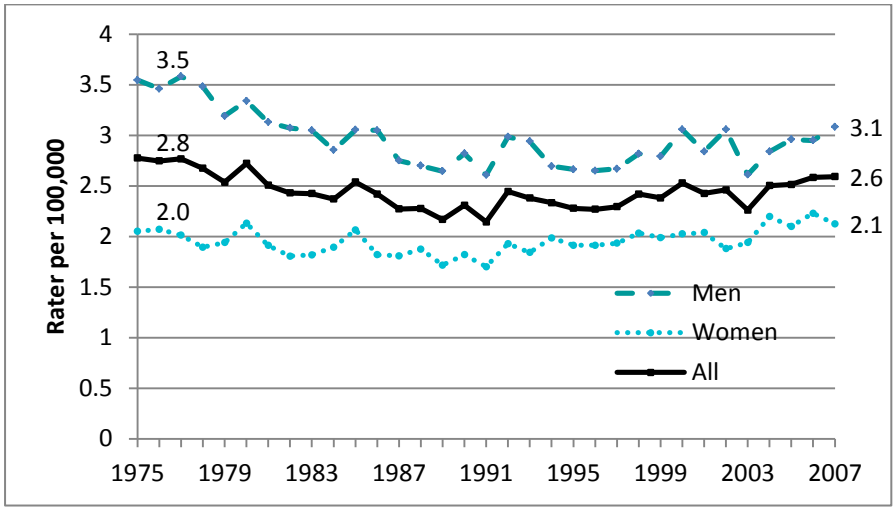


*European age-standardised rates

Source: Cancer Research UKhttp://info.cancerresearchuk.org/cancerstats/types/leukaemia/incidence/

Hodgkin lymphoma accounts for less than 1% of all cancers (excluding non-melanoma skin cancers) has a lower incidence of 2.8 per 100,000 in Northern Ireland, similar to levels in Europe and America but higher than the incidence in China and Japan[26] at 0.4 per 100,000.Similar to NHL it also has a male preponderance 1.3:1.0.

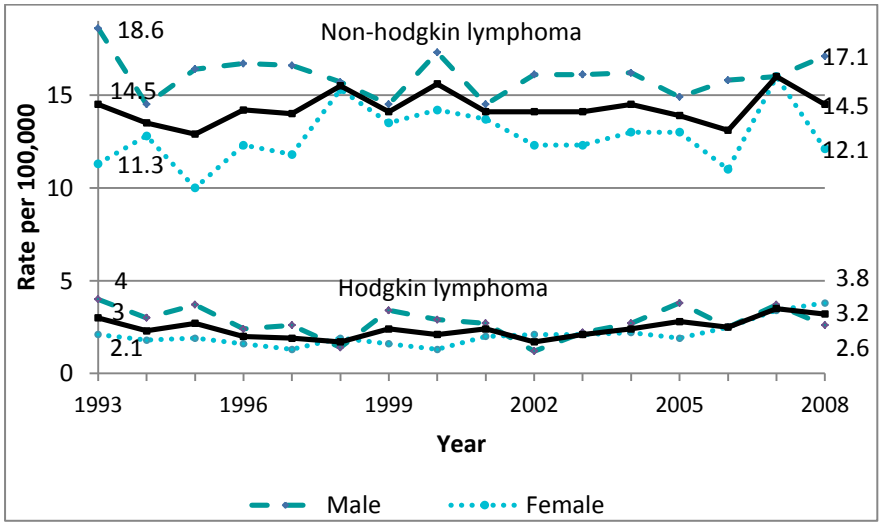
Figure 21. Hodgkin lymphoma Great Britain 1975-2007*



*Source: European age-standardised rates

- NHL is about four times more common than HL.
- The incidence of NHL & HL is higher among men.
- The incidence of NHL has increased in Great Britain while the incidence of HL has remained stable. In N. Ireland trend data is available only since 1993 and shows little variation over time.

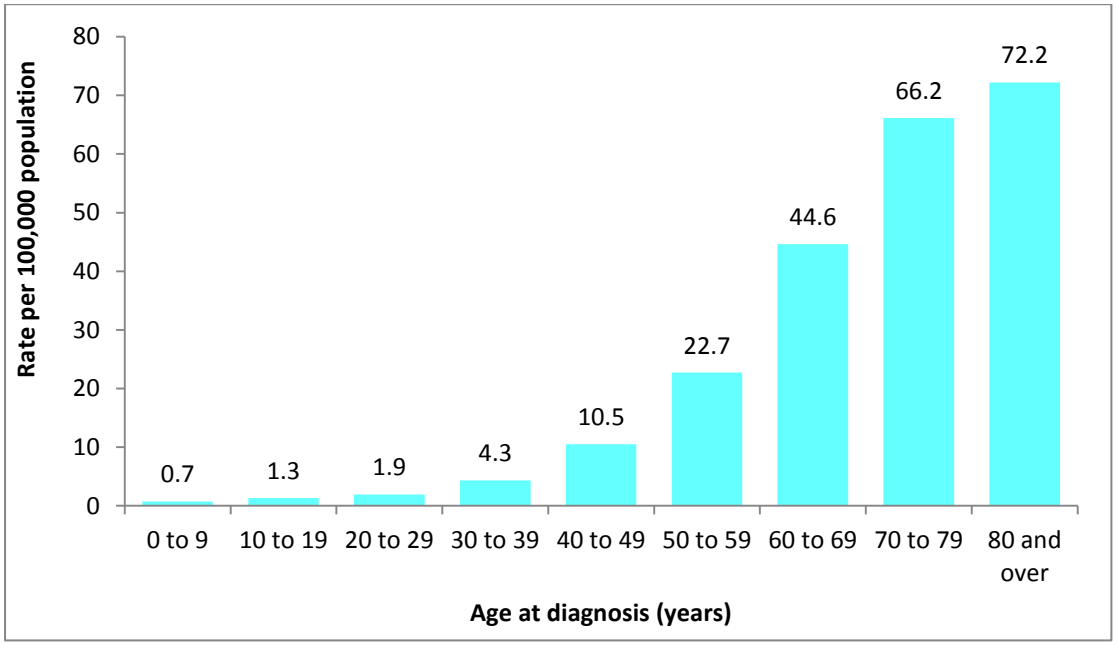
Figure 22. Hodgkin lymphoma and NHL rates Northern Ireland 1993-2008



Note: European age-standardised rates

Figure 23 below shows the incidence of NHL in N. Ireland by age category over the past 16 years clearly showing that NHL is predominantly a disease of patients aged 60 years and over.

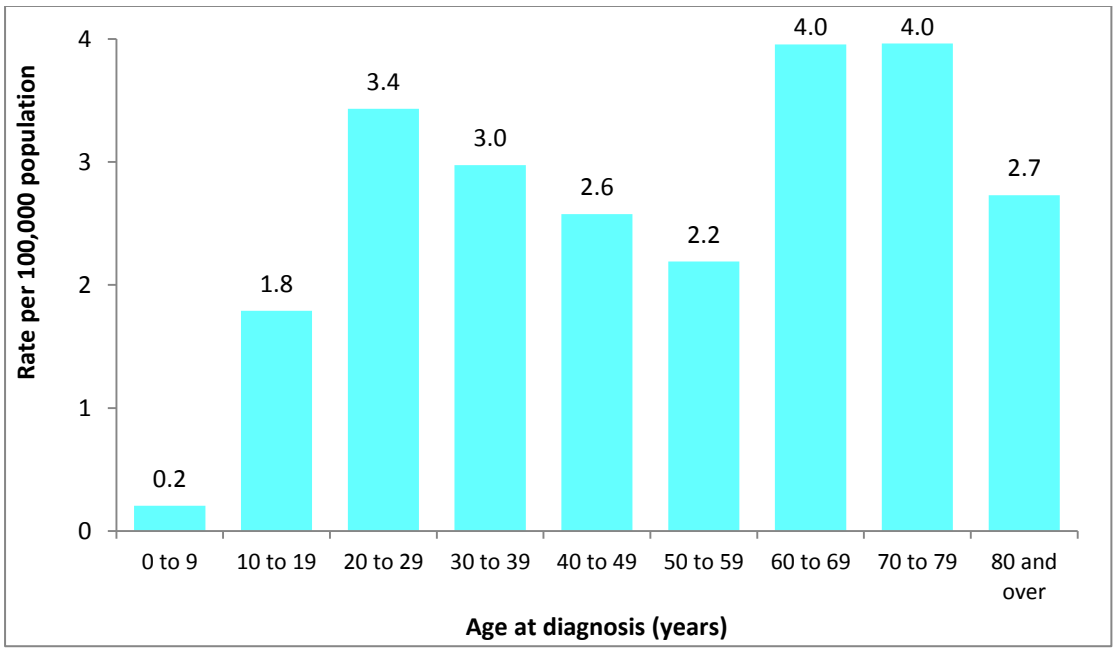
Figure 23. NHL Age-specific incidence rates Northern Ireland 1993-2008



Source: N. Ireland Cancer Registry

In contrast figure 24 below shows how the incidence of Hodgkin lymphoma, although much lower, peaks at age 20-30 and then has a second peak in the 60-80 age band.

Figure 24. HL: Age specific incidence rates Northern Ireland 1993-2008



Lymphoma: Prevalence

The prevalence of a disease is the number of people in the population with a history of diagnosis at a given point in time. By the end of 2008, there were 2,345 people living in Northern Ireland with a history of lymphoma diagnosis since 1993 (Table 19, Figure 25).

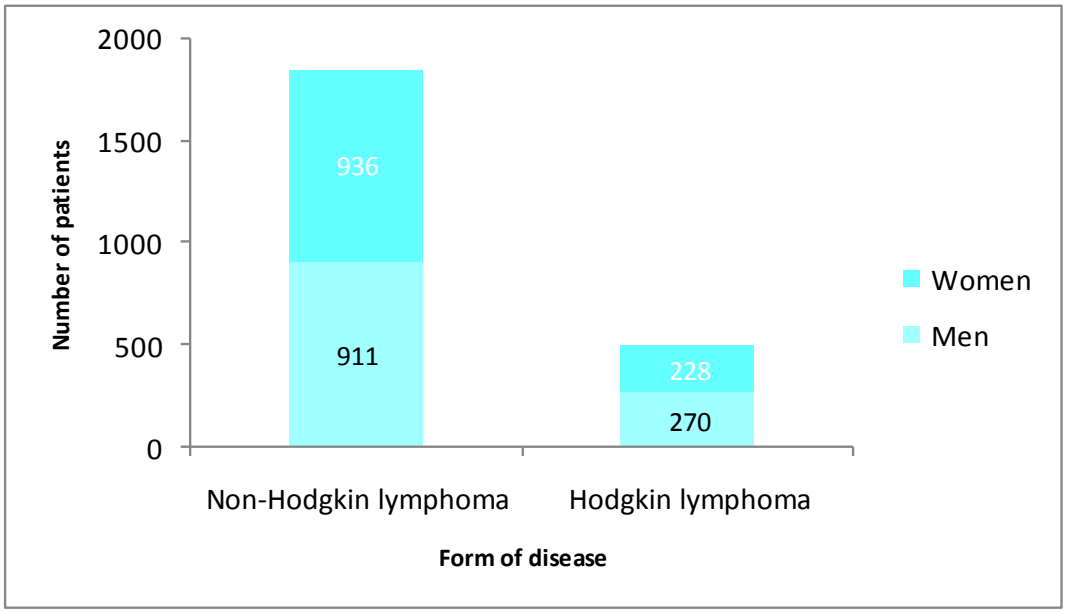
Table 19. Prevalence[(1)] of lymphoma by gender and type Northern Ireland by end of 2008

Lymphoma type	Male	Female	All
Non-Hodgkin lymphoma	911	936	1847
Hodgkin lymphoma	270	228	498
All lymphoma	1,181	1,164	2,345

Notes: (1) Diagnosed 1993-2008 and alive at the end of 2008

- The prevalence of NHL is more than 3 times that of HL.

Figure 25. Lymphoma Prevalence by gender and type Northern Ireland by end of 2008



SECTION IX - RESULTS OF 2008 AUDIT OF ADULT LYMPHOMA

For Methods See Page 18

Study population: Age, gender, histological type and socio-economic status

The study included 276 adult patients (age 14 and over) diagnosed in N. Ireland in 2008. There were 225 cases of Non-Hodgkin lymphoma (NHL) and 51 cases of Hodgkin lymphoma (HL). Childhood lymphoma is not included in this audit as the case numbers were very low (N=3).

Table 20. Adult Lymphoma by gender and diagnosis N. Ireland 2008

Lymphoma type	Male	Female	All patients
Non Hodgkin lymphoma	118	107	225
Hodgkin lymphoma	17	34	51
Number	**135**	**141**	**276**

In 2008 there was a slight excess of NHL in males, however the expected male:female 3:2 ratio was not observed. In addition, in 2008 there were more female cases of HL which was not seen in previous years and likely is an effect of small numbers.

Lymphoma: Age and gender

Table 21 below shows all cases of adult lymphoma by age band and gender.

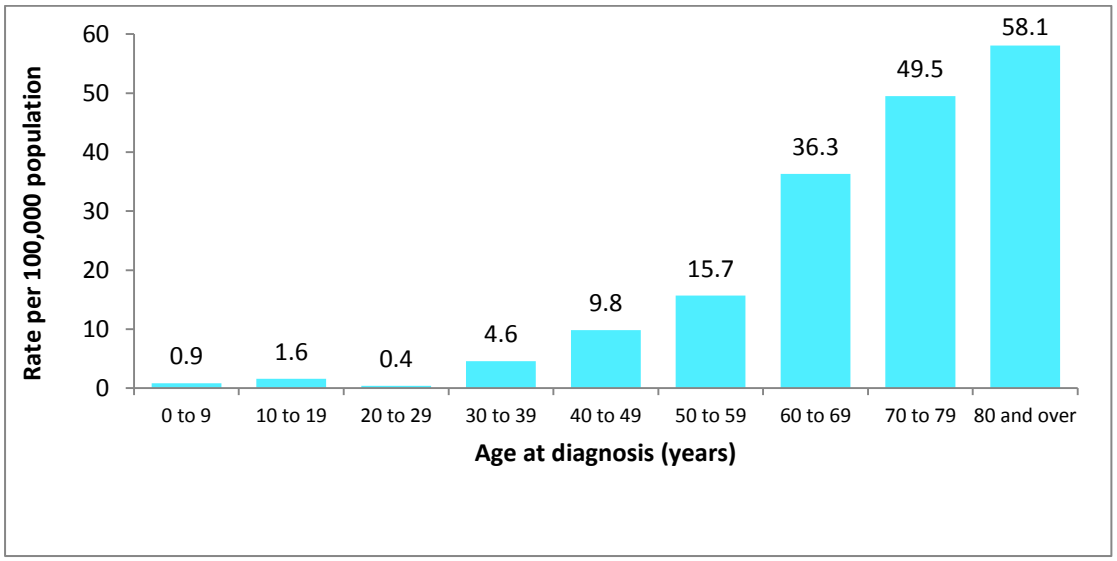
Table 21. Adult Lymphoma 2008: Age and gender of patients N. Ireland 2008

Age band	Male	Female	Number	%
14-19 years	3	4	7	3%
20-29 years	5	10	15	5%
30-39 years	10	6	16	6%
40-49 years	16	14	30	11%
50-59 years	19	20	39	14%
60-69 years	38	31	69	25%
70-79 years	29	32	61	22%
80 years and over	15	24	39	14%
Total	**135**	**141**	**276**	**100%**

As expected the majority (75%) of lymphoma patients were aged over 50 and 36% were age 70 or over.

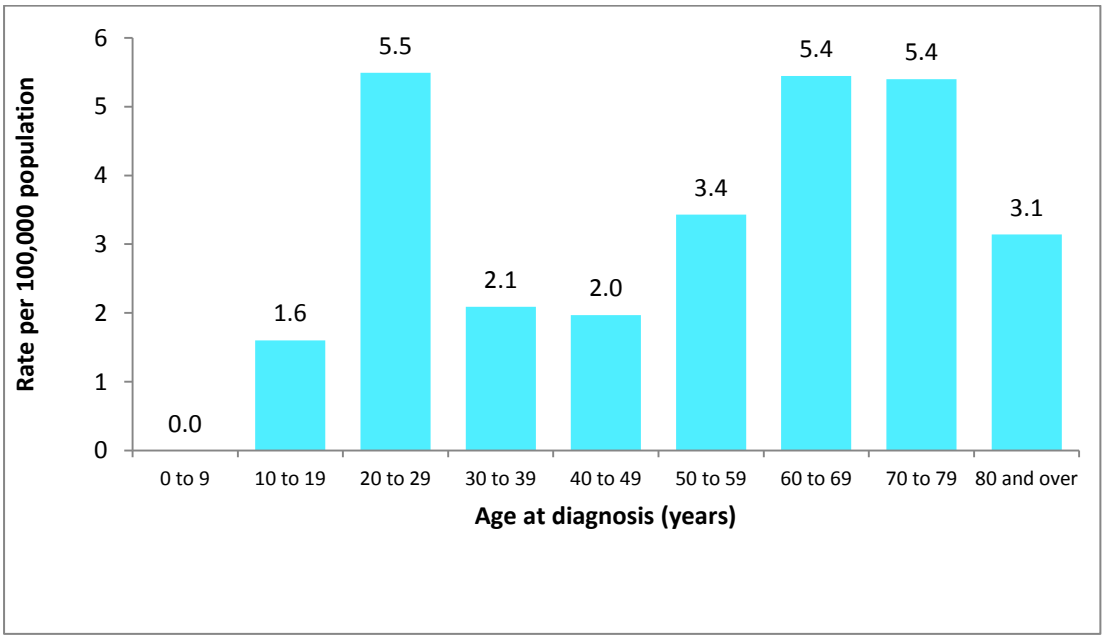
The increased incidence of Non-Hodgkin lymphoma (NHL) in middle and old age for patients diagnosed 2008 is clearly shown in Figure 26 below.

Figure 26. NHL Age-specific incidence rates N. Ireland 2008



For HL the established incidence peaks at age 20-30 years and age 60 to 80 years for patients diagnosed 2008 was clearly evident as shown below.

Figure 27. Hodgkin Lymphoma: Age specific incidence rates N. Ireland 2008



Lymphoma: Histological Type

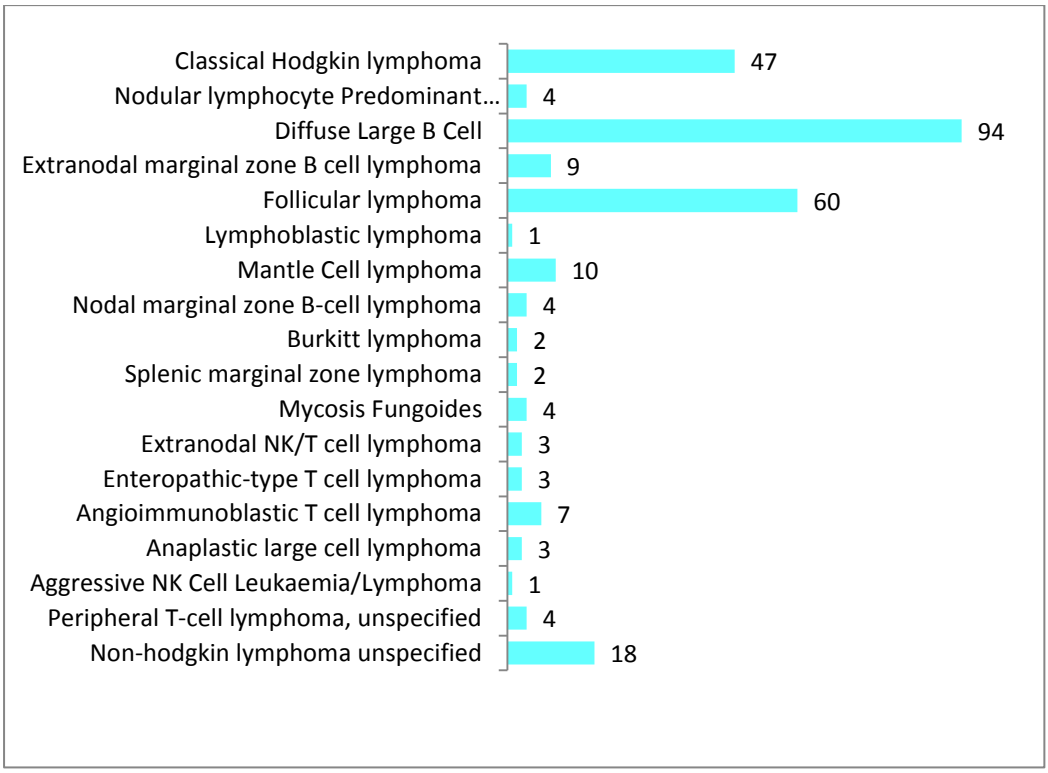
The frequency of the different subtypes of the adult lymphomas are shown in Table 22 below and Figure 28. Classical Hodgkin lymphoma was the most common type of HL.

Diffuse large B-cell lymphoma (DLBCL) was the most common of the Non-Hodgkin lymphomas (NHL) followed by Follicular lymphoma.

Table 22. Adult lymphoma: Histological type N. Ireland 2008

			Male	Female	All
Hodgkin lymphoma		Classical Hodgkin lymphoma	16	31	47
		Nodular lymphocyte predominant Hodgkin lymphoma	1	3	4
		All Hodgkin lymphomas	**17**	**34**	**51**
Non-Hodgkin lymphoma	**Mature B-cell neoplasms**	Diffuse Large B Cell	56	38	94
		Extranodal marginal zone B cell lymphoma	4	5	9
		Follicular lymphoma	24	36	60
		Lymphoblastic lymphoma	1	0	1
		Mantle Cell lymphoma	7	3	10
		Nodal marginal zone B-cell lymphoma	2	2	4
		Splenic marginal zone lymphoma	1	1	2
		Burkitt lymphoma	1	1	2
		All mature B-cell neoplasms	**96**	**86**	**182**
	Mature T-cell and NK-cell neoplasms	Aggressive NK Cell Leukaemia/Lymphoma	1	0	1
		Anaplastic large cell lymphoma	2	1	3
		Angioimmunoblastic T cell lymphoma	4	3	7
		Enteropathic-type T cell lymphoma	2	1	3
		Extranodal NK/T cell lymphoma	1	2	3
		Mycosis Fungoides	2	2	4
		Peripheral T-cell lymphoma, unspecified	3	1	4
		All mature T-cell and NK-cell neoplasms	**15**	**10**	**25**
	Unspecified lymphomas		**7**	**11**	**18**
		All non Hodgkin	**118**	**107**	**225**
	Total	**All lymphomas**	**135**	**141**	**276**

Figure 28. Lymphoma: Histological type frequency



Socio-economic residential area of patients

The population of N. Ireland can be divided into five equally sized quintiles ranked by socio-economic deprivation level of area of residence. If a disease is not related to deprivation, it is expected that 20% of all cases of lymphoma would fall in each quintile.

- There was no significant difference in the incidence of Non-Hodgkin or Hodgkin lymphoma across the different socio-economic groups.

Lymphoma pathway: First referral to diagnosis

Referral source

Table 23. Lymphoma pathway NHL and HL: Referral source

Referral source	Number	%
G.P.	161	58%
A&E	30	11%
Consultant	29	11%
Self	11	4%
Other	37	13%
Not available in notes	8	3%
Number	276	100%

- More than half (58%) of patients were referred by their GP.

Referral priority

Table 24. Lymphoma pathway NHL and HL: Priority of referral

Priority of referral	Number	%
Urgent	83	30%
Emergency admission	61	22%
GP red flag	36	13%
Routine	26	9%
Semi-urgent	3	1%
Other	25	9%
Not available in notes	42	15%
Number	276	100%

- Almost two-thirds of referrals were prioritised as either urgent (30%), emergency admissions (22%) or GP red flag suspect cancer referrals (13%).

Trust of first presentation

- Figure 29 and table 25 below show that in 2008 just under 1/3 of patients first presented to the Belfast Trust.

Figure 29. Lymphoma pathway NHL and HL: Trust of first presentation

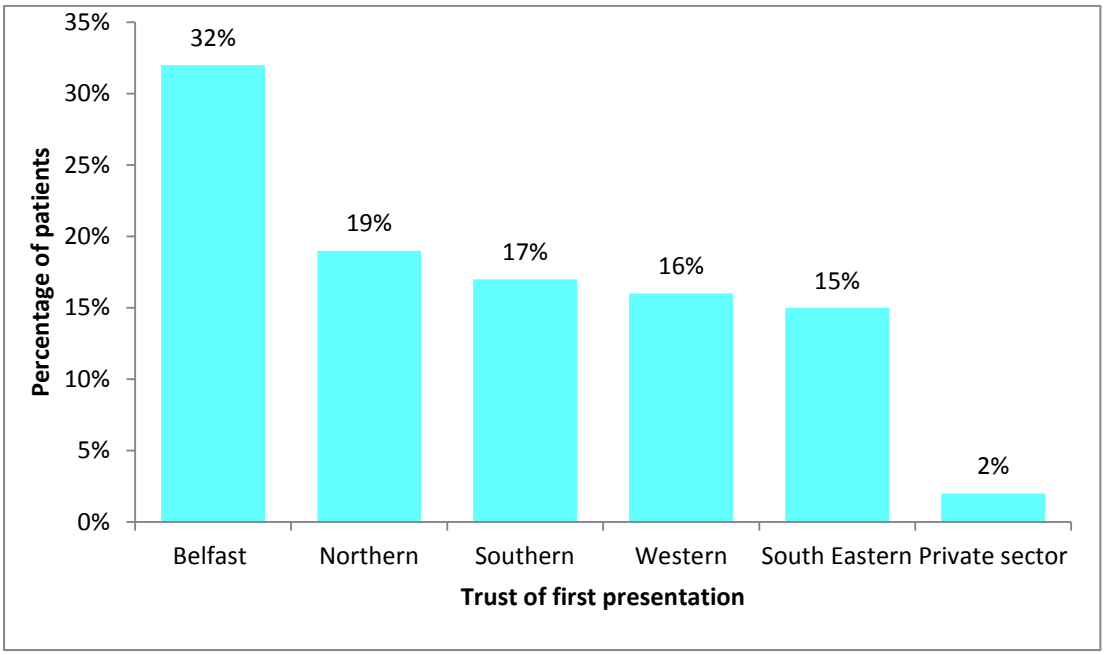


Table 25. Lymphoma pathway NHL and HL: Trust of first presentation

Trust	Number	%
Belfast	88	32%
Northern	53	19%
Southern	47	17%
Western	42	16%
South Eastern	41	15%
Private Sector	5	2%
Total	276	100%

Consultant specialty: First referral

Table 26 below shows the speciality of the consultant that first saw the patient in secondary care.

Table 26. Lymphoma pathway NHL and HL: First Consultant Specialty

Consultant speciality	Number	%
General Surgery	81	29%
General medicine	50	18%
Ear, nose & throat (ENT)	48	17%
Haematology	28	10%
Other	62	22%
Not available in notes	7	3%
All patients	**276**	**100%**

- 90% of lymphoma patients first presented to specialties other than haematology.
- Almost a third (29%) of patients were first seen by a General Surgeon.
- 18% were first seen by a General Medicine Consultant.
- 17% were first seen by an ENT surgeon.
- 10% were referred directly to a Haematologist.

Table 27 below shows the timeline for the minority of patients n=28 (10%) who were first referred directly to haematology:

- 46% are seen within 1 week of referral, 54% within 2 weeks and 85% within 4 weeks.

Table 27. Lymphoma pathway NHL and HL: Time to 1st seen when referred by Primary Care to a Haematologist

Time	Number	%
Same day	3	11%
1-7 days	9	35%
8-14 days	2	8%
15-28 days	8	31%
29-42 days	2	8%
More than 42 days	2	8%
Not available in notes	2	8%
Number	28	100%

,

Table 28 shows the timeline to diagnosis for the majority of patients n=248 (90%) who were first referred to other specialties.

Table 28. Lymphoma pathway NHL and HL: Time to diagnosis from date 1st seen by other specialty

Time	Number	%
0-7 days	79	32
8-14 days	39	16
15-21 days	27	11
22-28 days	14	6
29-42 days	20	8
> 42 days	59	24
Missing dates*	10	4
All patients	248	100

*Missing dates in clinical notes prevented inclusion in this analysis

- For patients first seen by other specialties confirmation of lymphoma diagnosis took more than 4 weeks for one third of patients and more than 6 weeks for one quarter of patients.

Table 29 below shows the timeline for accessing the haematology service for the majority of patients n=248 (90%) who were first referred to other specialties.

Table 29. Lymphoma pathway NHL and HL: Time to 1st seen by haematologist from date 1st seen by other speciality

Speciality 1st seen by	Same day	1-7 days	8-14 days	15-28 days	29-42 days	More than 42 days	Unavailable dates
ENT	0	4%	11%	19%	25%	40%	
General Surgery	0	7%	13%	20%	20%	41%	
General medicine	0	4%	18%	37%	16%	24%	
Other	2%	5%	17%	25%	15%	35%	
							7%
Total	**<1%**	**5%**	**14%**	**23%**	**18%**	**36%**	**33%**

* Missing dates in clinical notes in 17 cases (7%) prevented inclusion in this analysis.

- A significant proportion of patients for whom valid dates were available 83/248 (33%) waited more than 6 weeks before accessing the haematology service. As the date of onward referral to haematology was not well recorded in the notes it was not possible to further analyse the reasons for delay in the pathway at this point.
- Once a histological diagnosis of lymphoma was confirmed by other specialties just under half 94/198 (48%) of patients (for whom dates were available) were subsequently seen by haematology within 2 weeks of diagnostic biopsy. However a significant proportion of the remaining patients (31%) were not seen by haematology for 3 or more weeks. As the date of onward referral to haematology by other specialities was not well recorded in the notes it was not possible to further analyse the reasons for this delay.

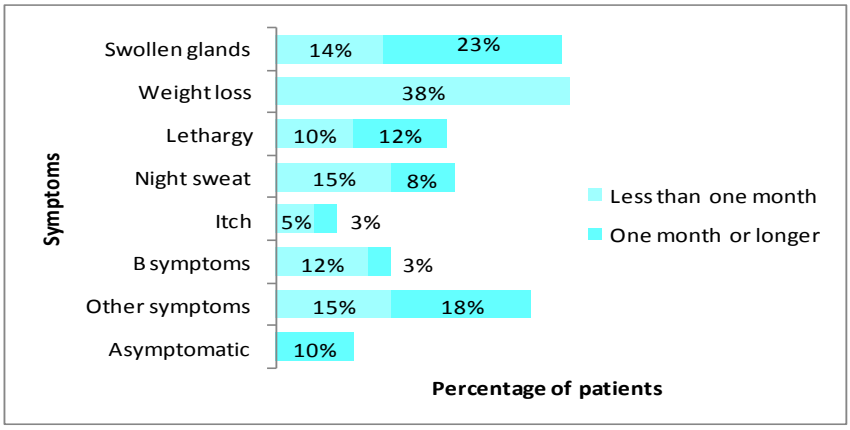
Table 30. Lymphoma pathway NHL and HL: Time from diagnostic biopsy to date 1st seen by Haematologist

Time	Number	%
0-7 days	43	22%
8-14 days	51	26%
15-21 days	42	21%
22-28 days	16	8%
29-42 days	31	16%
More than 42 days	15	8%
All patients*	198	

* Missing dates in clinical notes prevented inclusion of 34 patients in this analysis.

Signs and symptoms

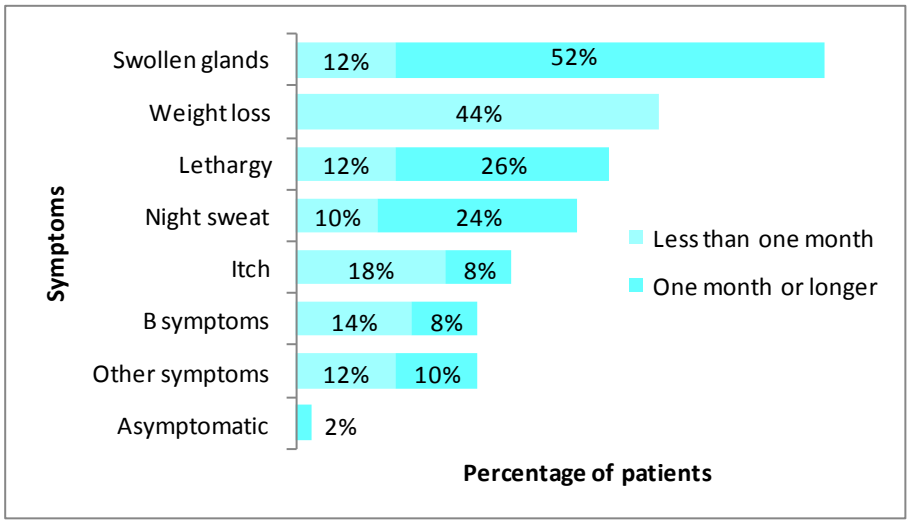
Figure 30. Non-Hodgkin lymphoma (NHL):Symptoms by duration



Notes: Some patients were recorded as having B symptoms (Fever, night sweats, weight loss) but the type of B symptom was not specified in the notes.

- For NHL patients, the most common symptoms at presentation were weight loss, lymphadenopathy (swollen glands), night sweats and lethargy.
- Recording of symptom duration was incomplete. However, at least half (50%) of patients had been symptomatic for more than a month.

Figure 31. Hodgkin lymphoma: Symptoms by duration

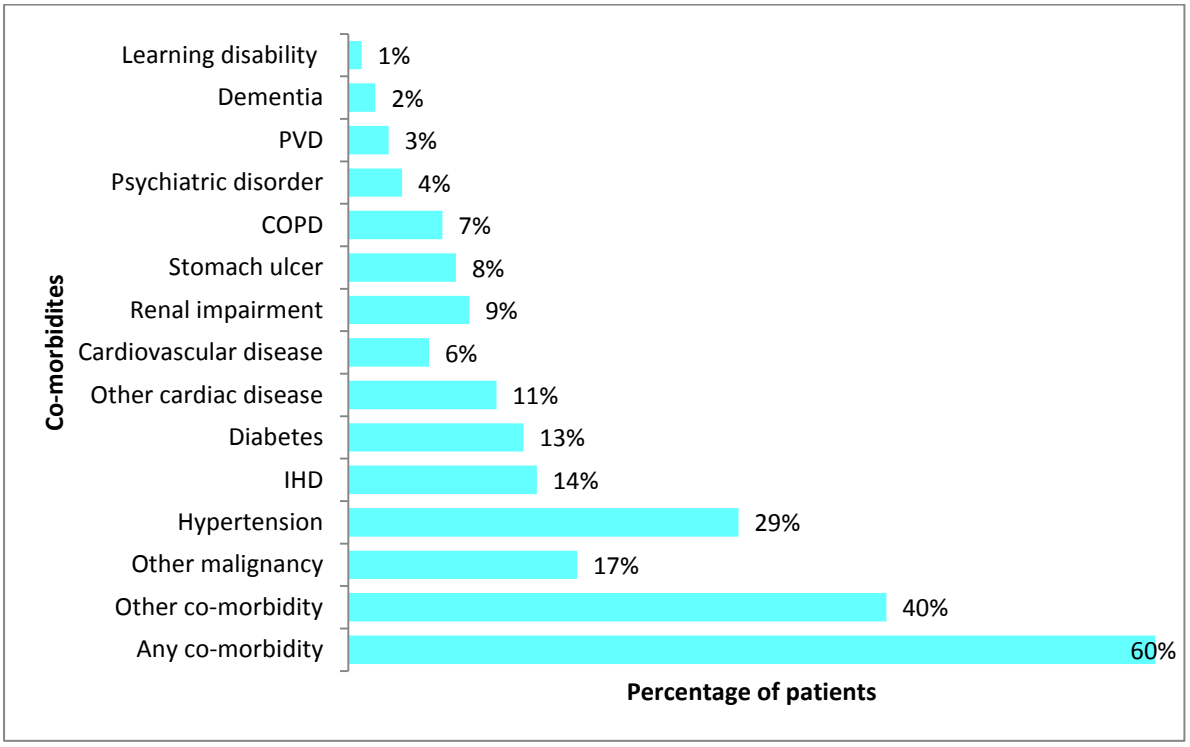


Notes: Some patients were recorded as having B symptoms (Fever, night sweats, weight loss) but the type of B symptom was not specified in the notes.

- As for NHL, the most common symptoms at presentation were weight loss, lymphadenopathy (swollen glands), night sweats and lethargy.
- Patients with HL tended to report longer symptom duration with almost three quarters (74%) experiencing at least one symptom for a month or longer.

Co-morbidities

Figure 32. Lymphoma: Co-morbidities



Notes: (1) PVD= peripheral vascular disease; COPD = chronic obstructive pulmonary disease; IHD = ischaemic heart disease.
(2) Patients may have had more than one co-morbidity and/or malignancy. (3) 'Other' includes asthma, arthritis, thyroid disorders, diverticular disease, high cholesterol and other morbidities

Figure 32 above shows the co-morbidities recorded for the lymphoma patients.

- A high proportion (60%) of patients were recorded as having some form of co-morbidity.
- Hypertension, ischaemic heart disease /other cardiovascular disease and diabetes were the most commonly recorded reflecting the age distribution of the patients.
- 17% of patients had a history of other malignancy.

Method of Diagnosis (Tables 31 & 32)

Table 31. NHL: Method of diagnosis

Method of diagnosis	Number	%
Lymph node excision	92	41%
Core needle biopsy	74	33%
Fine needle aspiration	3	1%
Peripheral blood and bone marrow samples	10	4%
Endoscopic biopsy	13	6%
Skin biopsy	7	3%
Bowel resection	3	1%
Other tissue	23	10%
All patients	**225**	**100%**

- The diagnosis of NHL was confirmed by lymph node excision in 41% of patients.
- One third of cases were diagnosed on core needle biopsy.

Table 32. HL: Method of diagnosis

Method of diagnosis	Number	%
Lymph node excision	38	74%
Core needle biopsy	13	26%
Total	51	

- The diagnosis of HL was confirmed by lymph node excision in the majority of patients (74%) with the remainder being diagnosed on core needle biopsy.

Stage recorded at diagnosis

Table 33. Stage recorded at diagnosis*

Stage	Non-Hodgkin Lymphoma		Hodgkin Lymphoma	
	Number	%	Number	%
Stage I [IA, IB, I]	26	12%	3	6%
Stage II [IIA, IIB, II]	20	9%	23	45%
Stage III [IIIA, IIIB, III]	39	17%	7	14%
Stage IV [IVA, IVB, IV]	25	11%	8	16%
Stage not recorded	115	51%	9	18%
All patients	**225**	**100%**	**51**	**100%**

* In clinical notes/GP letters/MDM database

- The stage at diagnosis was recorded in the clinical notes and/or multidisciplinary meeting (MDM) database in 49% of cases of NHL.
- Recording of stage was considerably better (82%) for patients with Hodgkin lymphoma.

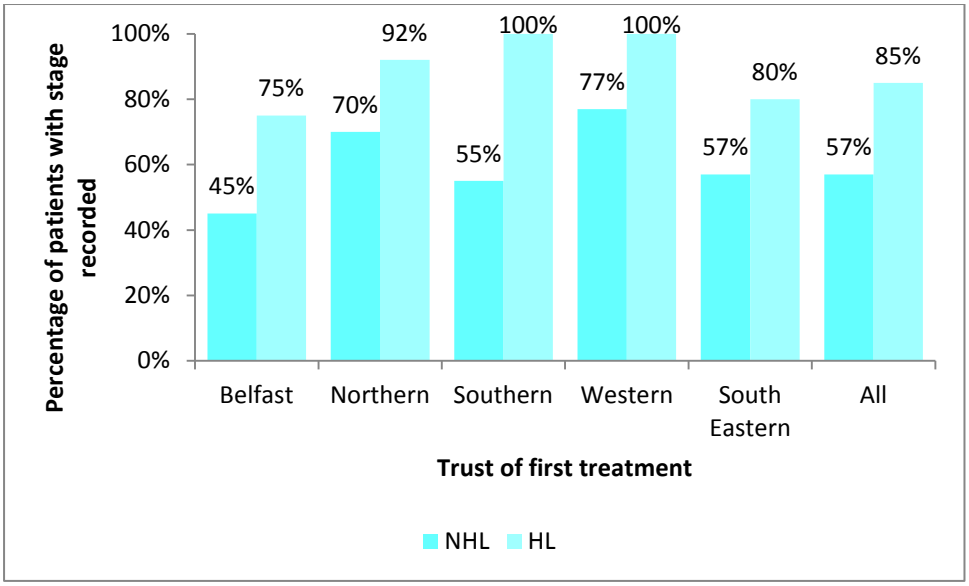
Stage recorded by Trust of first Treatment

Table 34. Stage recorded by Trust of 1st Treatment

Trust	Non- Hodgkin Lymphoma		Hodgkin Lymphoma	
	Stage (Total) recorded	% recorded	Stage (Total) recorded	% recorded
Belfast	26 (58)	45%	15 (20)	75%
Northern	16 (23)	70%	11 (12)	92%
Southern	12 (22)	55%	5 (5)	100%
Western	17 (22)	77%	5 (5)	100%
South Eastern	8 (14)	57%	4 (5)	80%
Total	79 (139)	57%	40 (47)	85%

- Recording of stage varied across Trusts with better recording of stage in the Western and Northern Trusts (Table 34 & Figure 33).

Figure 33. Stage Recorded by Trust of first treatment



Recording of prognostic index scores

Recording of the International Prognostic Index (IPI) and the Follicular Lymphoma International Prognostic Index (FLIPI) scores in the clinical notes or MDM database was poor. IPI was recorded in only 12% and FLIPI in 21% of relevant cases.

Treatment

Aggressive (Intermediate and high grade) NHL: 1st line treatment

The majority of patients with aggressive NHL received active chemotherapy and/or biological therapy, 103/130 (79%) most commonly receiving 6-8 cycles of R-CHOP regimen (see Appendix E). Three patients had radiotherapy as first treatment, one of whom subsequently required chemotherapy (Table 35).

Table 35. Aggressive NHL: 1st treatment modality

Treatment modality	Number	%
R-CHOP or similar regimen	103	79%
Supportive care*	23	21%
Involved field radiotherapy	4	3%
All patients	**130**	**100%**

* Includes patients who were not fit for active treatment, died before treatment could be commenced or declined active treatment.

Table 36 below shows the Trust where the 103 patients received chemotherapy as 1st line therapy.

Table 36. Aggressive NHL: Trust 1st line chemotherapy

Trust	Number	%
Belfast	46*	45%
Northern	19	18%
Southern	17	16%
Western	12	12%
South Eastern	9	9%
All patients	**103**	**100%**

*Includes 2 patients treated in the Children's hospital

- A high proportion of patients (45%) received their 1st line chemotherapy in the Belfast Trust.

Aggressive (Intermediate and high grade) NHL: Diagnosis to treatment

Table 37 below shows the time from diagnosis to first treatment for patients with Diffuse large B-cell lymphoma (DLBCL), the most common of the aggressive types of NHL.

- 76/92 (83%) of patients with DLBCL received active treatment with the majority receiving R-CHOP chemotherapy. Three patients had radiotherapy as first treatment one of whom required subsequent chemotherapy.

Table 37. DLBCL: Time from histological diagnosis to chemotherapy commenced

Time	Number	%
0-14 days	20	26%
15-21 days	15	20%
22-28 days	8	11%
More than 28 days	25	33%
Missing dates	8	11%
All patients	76	100%

- Just under half of the patients with DLBCL (for whom valid dates were available) commenced chemotherapy more than 3 weeks from histological diagnosis.

Aggressive (Intermediate and high grade) NHL: subsequent treatment

- Twenty seven of the 103 patients (26%) required 2nd line chemotherapy and 12 of these patients went on to receive 3rd line chemotherapy.
- Five patients subsequently underwent a bone marrow transplant, Autologous (4), Allogeneic (1).

Indolent/low grade lymphoma: treatment

Table 38 below shows the 1st treatment modality for the 72 patients with indolent/low grade lymphoma.

Table 38. Indolent/low grade NHL: 1st treatment modality

Treatment modality	Number	%
R-CVP* or similar regimen	35	49%
Watch & Wait	27	38%
Involved field radiotherapy	9	12%
Steroids alone	1	1%
All patients	72	100%

*R-CVP- see Appendix E for details.

- Just over one quarter of patients were initially managed by the 'Watch and Wait' approach and 8/27 (30%) of these patients subsequently required chemotherapy.
- The majority of patients 32/43 (74%) who required drug treatment received R-CVP (see Appendix E for details).
- Seven patients were treated with more intensive therapy R-CHOP which is the treatment of choice for the histological grade 3 follicular lymphomas that tend to behave more like DLBCL.

Table 39 below shows the Trust of treatment for the 43 patients who received chemotherapy either at diagnosis or after a period of 'Watch & Wait'.

Table 39. Indolent/low grade NHL: Trust 1st line chemotherapy

Trust	Number	%
Belfast	15	35%
Northern	5	12%
Southern	5	12%
Western	11	26%
South Eastern	7	16%
All patients	**43**	**100%**

- A higher proportion of patients (35%) received their 1st line chemotherapy in the Belfast Trust.

Hodgkin lymphoma: Treatment

Table 40. Hodgkin lymphoma: 1st treatment modality

Treatment modality	Number	%
Chemotherapy with ABVD or other regimen	47	92%
Supportive care	2	4%
Involved field radiotherapy	2	4%
All patients	**51**	**100%**

The majority of patients 33/47 (70%) with HL had combination chemotherapy (Table 40) most frequently with the ABVD regime (see Appendix E for details).

Table 41. Hodgkin lymphoma: Trust of 1st line chemotherapy

Trust	Number	%
Belfast	20*	42%
Northern	12	25%
Southern	5	10%
Western	5	10%
South Eastern	5	10%
All patients	**47**	**100%**

*Includes 1 patient treated in the Children's hospital

Table 41 above shows the Trust of treatment for the 47 patients who received 1st line chemotherapy.

- A high proportion of patients (40%) received their 1st line chemotherapy in the Belfast Trust.

Table 42. Hodgkin lymphoma: Time from histological diagnosis to chemotherapy commenced

Time	Number	%
0-14 days	13	25%
15-21 days	10	19%
22-28 days	7	14%
More than 28 days	11	22%
Missing dates/ not applicable	10	19%
All patients	51	100%

- Over half the patients with HL for whom valid dates were available had their chemotherapy commenced within 3 weeks of histological diagnosis (Table 42).

Hodgkin lymphoma: subsequent treatment

- Nine patients (18%) subsequently required high dose therapy with autologous* stem cell transplantation. One of these patients went on to have a second (Allogeneic**) transplant.

All lymphoma: Analysis of Trust of residence by Trust of 1st Treatment (Table 43)

Table 43. All lymphoma: Trust of Residence by Trust of 1st line Chemotherapy

Trust of treatment	Trust of residence				
	Belfast	Northern	South Eastern	Southern	Western
Belfast	31/37	13/49	27/44	4/29	3/31
	(84%)	(27%)	(61%)	(14%)	(10%)
Northern	1/37	33/49	1/44	0	1/31
	(3%)	(67%)	(2%)		(3%)
South-Eastern	5/37	0	16/44	0	0
	(14%)		(36%)		
Southern	0	2/49	0	25/29	0
		(4%)		(86%)	
Western	0	1/49	0	0	27/31
		(2%)			(87%)

Using the N. Ireland Statistics and Research Agency (NISRA) Central Postcode Directory http://www.nisra.gov.uk/geography/postcode.htman analysis of Trust of 1st line chemotherapy (Table 43) shows that in 2008 the majority of patients received their chemotherapy in their designated Trust of residence. However a proportion of patients from the South Eastern (61%) and Northern (27%) Trusts of residence received their chemotherapy in the Belfast Trust. Conversely, 14% and 3% of patients from the Belfast Trust of residence received their chemotherapy in the South Eastern Trust and Northern Trusts respectively.
Overall 78/190 (41%) of lymphoma patients who had chemotherapy received their chemotherapy in the Belfast Trust.

- The proportion of South Eastern Residents (36%) and Northern Trust Residents (67%) having 1st line chemotherapy within their Trusts was lower than expected.

* Autologous = patient's own stem cells, ** Allogeneic = stem cells from a donor

Multidisciplinary team discussions and patient information

- Multidisciplinary case discussions were recorded in the clinical notes or MDM database for 201/276 (73%) of patients. It is recognised that other patients may have been discussed at MDM but the documentation was not found in the clinical notes.

Multidisciplinary team discussions recorded by Trust

Table 44. All lymphoma: Multidisciplinary team discussions by Trust of Treatment

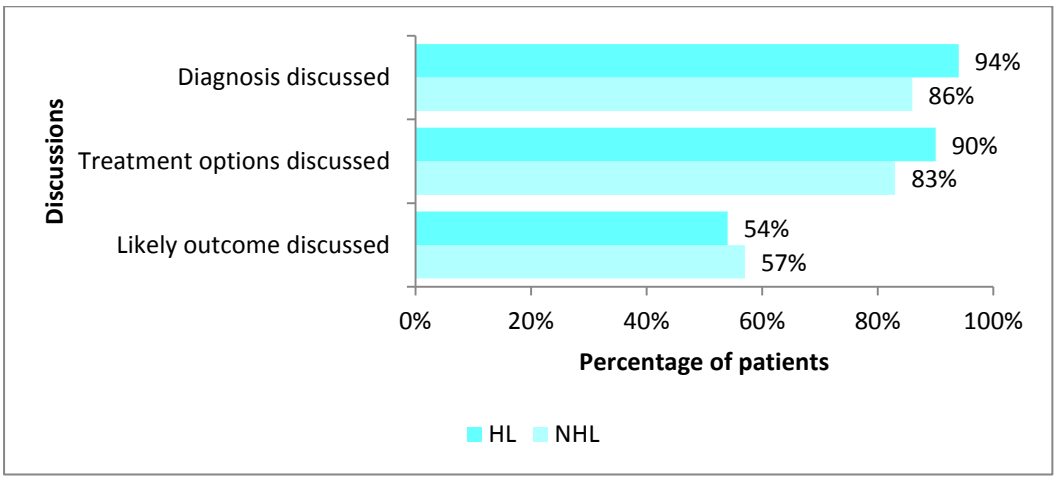
Trust	Number Discussed/Total	%
Belfast	84/109	77%
Northern	40/52	77%
Southern	34/45	76%
Western	28/39	72%
South Eastern	15/31	48%
Total	201/276	73%

- Overall 73% of lymphoma patients had a record of MDT discussion in the clinical notes or MDM database (Table 44) but less than half of patients in the South Eastern Trust had a record of MDT discussion.

Patient Information

- Discussion of the diagnosis with the patient was recorded in 86% of clinical notes, treatment options in 83% and likely outcomes in 57% (Figure 34).

Figure 34. Recording of discussions of diagnosis, treatment options and prognosis with patients



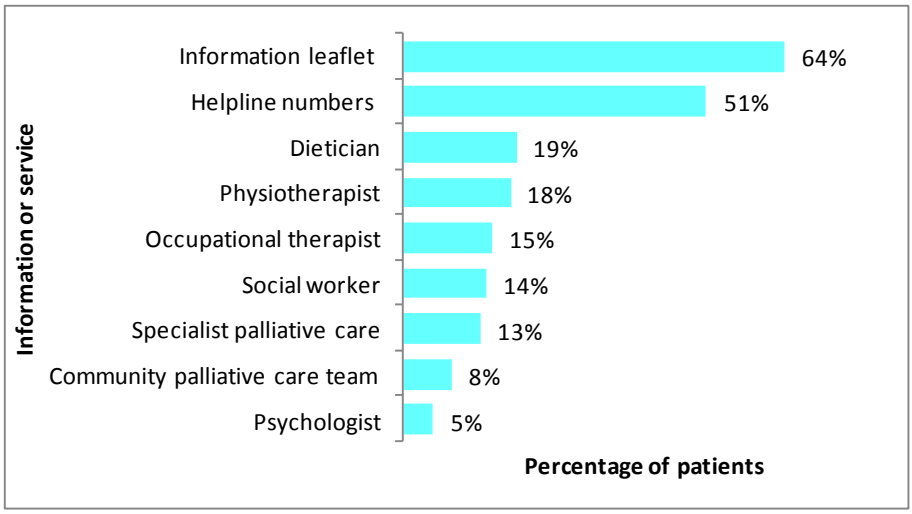
Reproductive health

- Discussion of fertility preservation was recorded for nine (50%) of the eighteen male NHL patients aged 16-45 included in the study.
- Discussion of fertility preservation was not recorded for any of the ten female NHL patients in this age group (16-45 years).

Provision of patient information leaflets and onward referrals to other health professionals

- Provision of information leaflets and helpline numbers were recorded for almost two-thirds (64%) and half (51%) of patients respectively (Figure 35).
- There was evidence of on-going support in a number of ways with 19% of patients referred to a dietician, 18% to physiotherapy, 15 % to occupational therapy and 14% to social work services.
- 13% of patients were referred to specialist palliative care, and 8% to community palliative care.

Figure 35. Percentage of patients receiving information or onward referrals*



* Patients may have been given more than one type of information and/or referred to more than one service

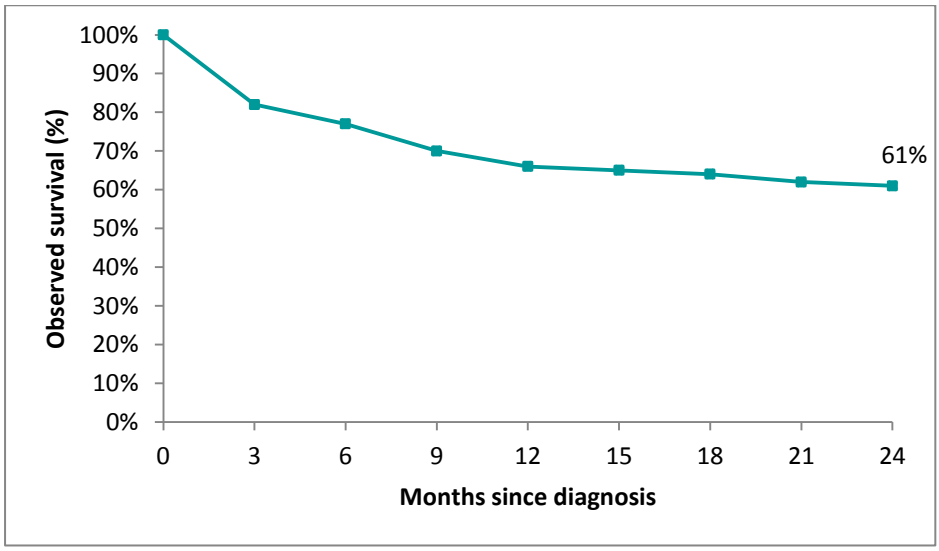
Use of patient helpline

- The helpline was used by almost a third (29%) of patients with many patients calling on more than one occasion. In total, 390 calls to the helpline were recorded in the clinical notes from the study patients.

Survival: Diffuse large B-cell Lymphoma (DLBCL)

Figure 36 and Table 45 below shows the 2 year observed survival for DLBCL (the most common type of the aggressive lymphomas).

Figure 36. Observed survival Diffuse Large B-cell Lymphoma (DLBCL)



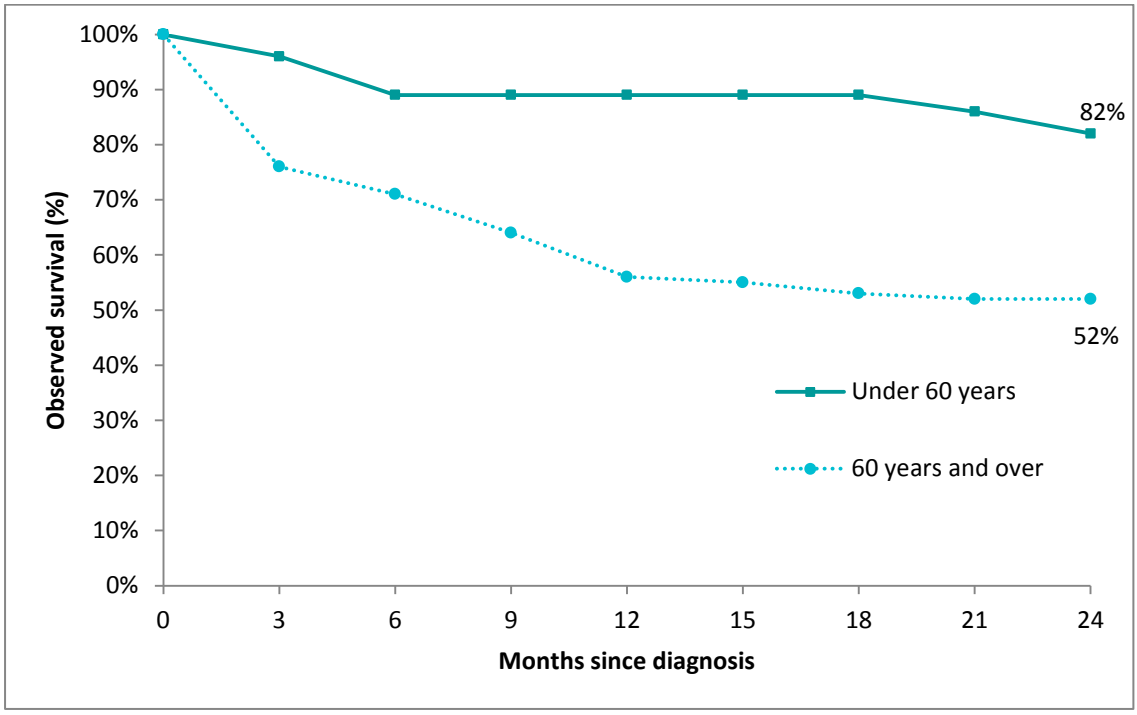
- 61% of patients were alive at 2 years.

Table 45. Observed survival DLBCL (% patients alive)

Survival	Diffuse Large B-cell Lymphoma
1 month	91%
6 months	77%
1 year	66%
2 years	61%
All patients (number)	94

The impact of age on the survival of patients with DLBCL is evident in Figure 37 below.

Figure 37. Observed survival Diffuse Large B-cell Lymphoma (DLBCL)



- Survival at 2 years for patients aged 60 years and over was significantly poorer (52% vs 82%).

Survival: Follicular lymphoma

As expected the observed survival for follicular lymphoma (the most common of the indolent/low grade lymphomas) was high at 93% at 2 years (Figure 38 & Table 46).

Figure 38. Observed survival Follicular lymphoma

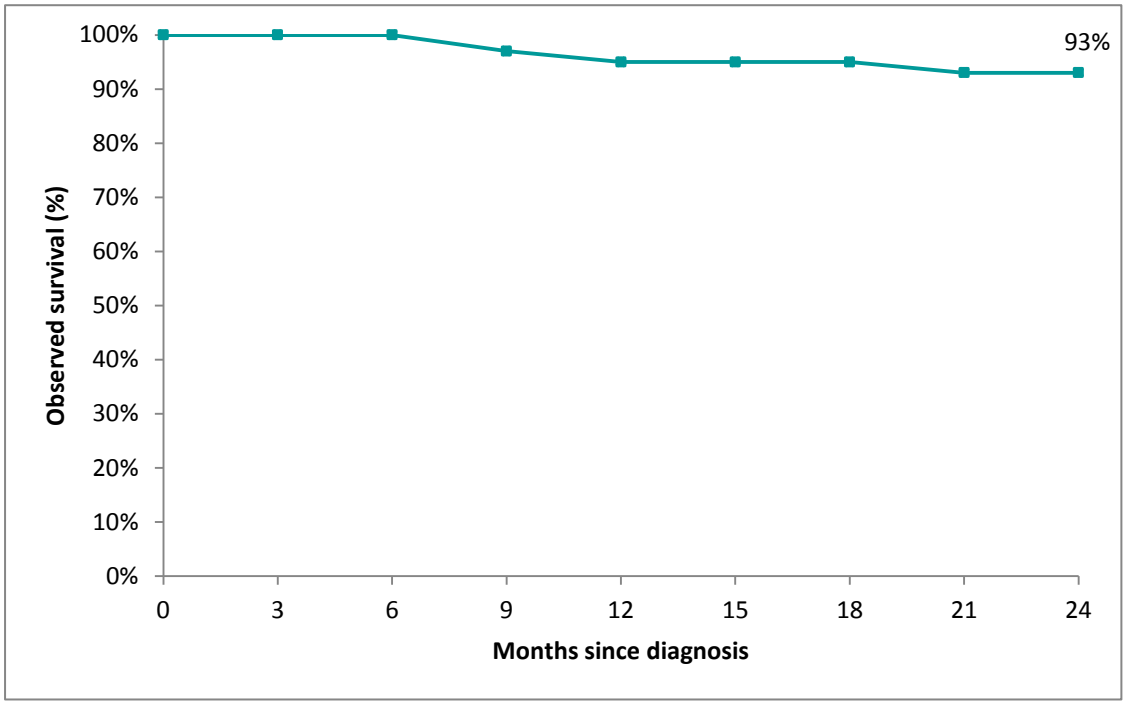


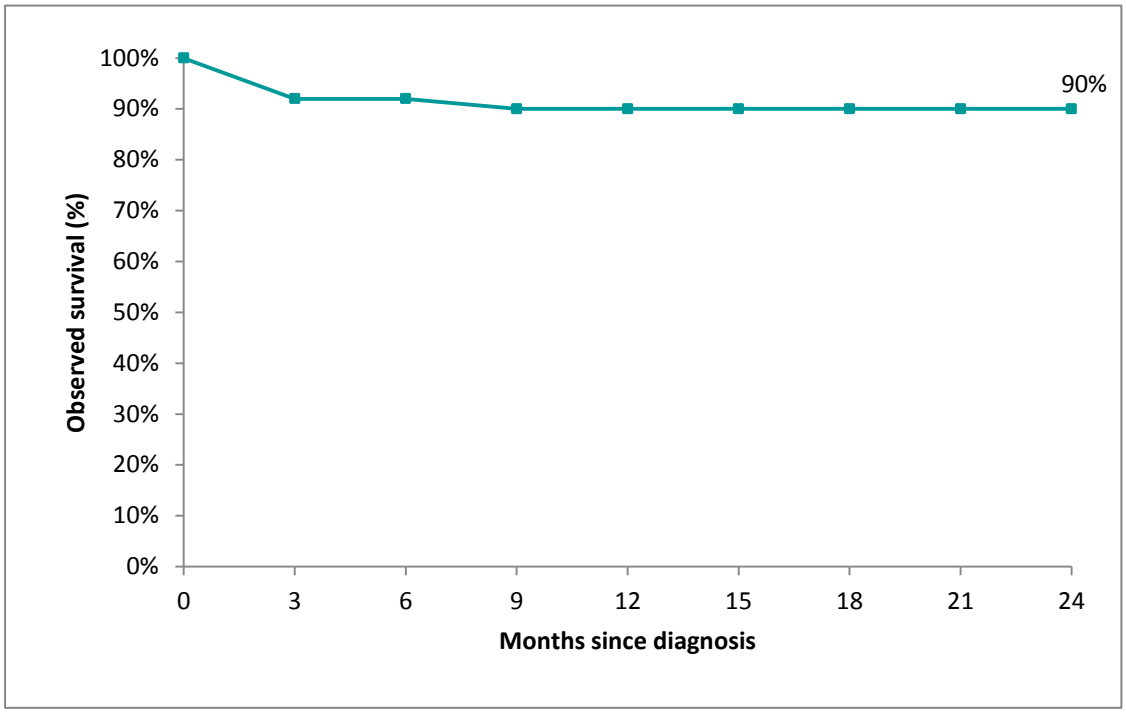
Table 46. Observed survival Follicular Lymphoma (% patients alive)

Survival	Follicular lymphoma
1 month	100%
6 months	100%
1 year	95%
2 years	93%
All patients (number)	60

Survival: Hodgkin lymphoma

Observed survival at 2 years for the patients with Hodgkin lymphoma was high at 90% (Figure 39 and Table 47).

Figure 39. Observed survival HL



- 90% of patients with HL were alive at 2 years.

Table 47. Observed survival HL (% patients alive)

Survival	Hodgkin lymphoma
1 month	96%
6 months	92%
1 year	90%
2 years	90%
All patients (number)	51

SECTION X –SUMMARY OF LYMPHOMA AUDIT

STUDY PATIENTS

- In 2008 there were 276 adult patients (age 14 and over) with a new diagnosis of lymphoma in Northern Ireland.
- There were 225 cases of Non-Hodgkin lymphoma (NHL) and 51 cases of Hodgkin lymphoma (HL).

LYMPHOMA PATHWAY: REFERRAL AND PRESENTATION

- Almost two-thirds of referrals were prioritised as either urgent (30%), emergency admissions (22%) or GP red flag suspect cancer referrals (13%).
- The majority of patients first presented to one of the cancer units.
- The majority (90%) of patients were 1st seen by non-haematology specialties: General Surgery (29%), General Medicine (18%), ENT (17%).
- Once a histological diagnosis of lymphoma was confirmed by other specialties a significant proportion of patients (22%) did not access the haematology service for 3 or more weeks. Just over one third of patients 83/231 (36%) were seen by haematology more than 6 weeks after 1st being seen by other specialties.
- A high proportion (60%) of patients were recorded as having some form of co-morbidity.
- 17% of patients had a history of other malignancy.

DIAGNOSIS AND STAGING

- The diagnosis of lymphoma was confirmed prior to onward referral to haematology in the majority of cases 199/233 (85%).
- Time to diagnosis from 1st seen by non-haematology specialty was more than 4 weeks for one third of patients and more than 6 weeks for one quarter of patients.
- The diagnosis of NHL and HL was confirmed by lymph node excision in 41% and 74% of patients respectively and core needle biopsy in 33% and 26% respectively.
- The stage at diagnosis was recorded in the clinical notes and/or multidisciplinary meeting (MDM) database in only 49% of cases of NHL.

- Recording of stage for NHL varied across Trusts with better recording of stage in the Western and Northern Trusts.
- Recording of stage was considerably better for patients with HL (82%).
- Stage for HL was generally well recorded. Recording was however lower in the Belfast and South Eastern Trusts.
- Recording of the prognostic scores (IPI and FLIPI) for NHL in the clinical notes or MDM database was generally poor.

TREATMENT

- The majority of patients with aggressive NHL received active chemotherapy and/or biological therapy 103/130 (79%).
- Just under half of the patients with DLBCL commenced chemotherapy more than 3 weeks from histological diagnosis.
- The majority of patients received their chemotherapy in their designated Trust of residence. However a proportion of patients from the South Eastern (61%) and Northern (27%) Trusts of residence received their chemotherapy in the Belfast Trust. Conversely, 14% and 3% of patients from the Belfast Trust of residence received their chemotherapy in the South Eastern Trust and Northern Trusts respectively.
- The proportion of South Eastern Residents (36%) and Northern Trust Residents (67%) having 1st line chemotherapy within their Trusts was lower than expected.

MULTIDISCIPLINARY CASE DISCUSSIONS

- Multidisciplinary case discussions were recorded in the clinical notes of 201/276 (73%) of patients, however only 48% of patients in the South Eastern Trust had a record of discussion.

SURVIVAL

- The 2 year observed survival for diffuse large B-cell lymphoma was 61%.
- The 2 year observed survival for diffuse large B-cell lymphoma was significantly worse for patients aged 60 years and over compared to those aged less than 60 years (52% vs 82%).
- The 2 year observed survival for follicular lymphoma was 93%.
- The 2 year observed survival for Hodgkin lymphoma was 90%.

PATIENT INFORMATION AND REFERRAL TO OTHER HEALTH PROFESSIONALS

- Discussion of the diagnosis with the patient (86%), discussion of treatment options (83%) and probable outcomes (57%) was well recorded in the clinical notes.
- Discussions regarding future fertility were recorded for 50% of men but none of the women in the 16-45 age group.
- Recording of information leaflets being given to patients and of helpline numbers being provided was found in 64% and 51% of clinical notes respectively.
- Referral to other health professionals was common with patients often receiving input from several speciality services including occupational therapy (15%), physiotherapy (18%), social work services (14%), dietetics (19%), specialist palliative care (13%) and community palliative care (8%).
- The helpline was used by almost a third of patients (29%) with a total of 390 calls to the helpline from the study patients.

SECTION XI–LYMPHOMA CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

- Patients with lymphoma in N. Ireland receive an expert specialist haematology service.
- More patients than expected 78/190 (41%) received their chemotherapy in the Belfast Trust.
- Survival rates at two years suggest that with further follow up the 5 year survival rates will be comparable to other population-based data.
- Patients are provided with relevant information and have access to a well used helpline.

RECOMMENDATIONS

As with any service there are possibilities for improvement. The following recommendations stem from this audit.

- Delay in the pathway from histological diagnosis (by other specialties) to accessing specialist haematology services should be further investigated.
- All patients should have their diagnosis and treatment plan discussed at an MDT.
- The MDT discussion should be recorded in the Regional Cancer Patient Pathway System (CaPPS) which is now being used regionally for all cancers since 2009.
- Recording of stage (currently 49% for NHL) and prognostic factors should be improved.
- The reasons for the higher number of patients receiving chemotherapy in the Belfast Trust merits further assessment.
- The helpline facility is a well used resource that should be maintained.
- Re-audit of the leukaemia and lymphoma pathway should be undertaken for more recently diagnosed patients.

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APPENDIX A -LEUKAEMIA CLASSIFICATION, TREATMENT AND PROGNOSIS

Acute Leukaemia: Classification

The two main forms of acute leukaemia are acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML). In 1997, a panel of haematopathologists recognising that in a proportion of patients cytogenetic testing of the blood and bone marrow cells at diagnosis revealed an abnormal cytogenetic profile such as translocations or deletions of chromosomes, proposed a new classification for haematopoietic and lymphoid neoplasms which was adopted by the World Health Organisation (WHO)[27]. The WHO classification recognises the importance of these cytogenetic events in the process of leukaemogenesis and is not only used to classify the different subtypes of acute leukaemia but also can predict response to therapeutic agents.

Acute lymphoblastic leukaemia (ALL): Classification

Acute lymphoblastic leukaemia is primarily a disease of children with 75% of cases occurring in children under six years of age. Lymphoblastic leukaemias can arise from either B-cells or T-cells. Approximately 85% are of the precursor B-cell type ‘B-ALL’ (Table 1). The bone marrow and blood are involved in all cases of B-ALL but other sites of involvement include the central nervous system, lymph nodes, spleen, liver, testes and ovaries. Cytogenetic abnormalities have a significant impact on the prognosis of patients with ALL. Up to 85% of patients have cytogenetic abnormalities which usually take the form of translocations of genetic information. The most ominous cytogenetic abnormality (known as the Philadelphia chromosome) is caused by the translocation of the *abl* gene from chromosome 9 to chromosome 22. Patients with Philadelphia chromosome positive ALL (Ph/BCR-ABL+) have a poor prognosis and require more intensive treatment.

Table 1. WHO classification of acute lymphoblastic leukaemia
B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL 1*
B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL* rearranged
B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22) *TEL-AML 1 (ETV6-RUNX1)*
B lymphoblastic leukaemia/lymphoma with hyperdiploidy
B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)
B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32) *IL 3-IGH*
B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PAX1*

Acute lymphoblastic leukaemia (ALL): Treatment

Where possible patients should be entered into national or international multicentre clinical trials. Patients ineligible/unwilling to participate in such clinical trials may receive the same or a modified version of the current chemotherapy protocol outside of clinical trial setting. The treatment of ALL can be subdivided into 4 phases.

- **Remission induction** chemotherapy is a combination of several chemotherapy drugs given to clear the bone marrow of overt leukaemia, a state known as 'complete remission'.
- **Consolidation therapy** which aims to further reduce or eliminate any residual disease and the development of drug-resistant cells consists of alternating cycles of cytoxic drugs and usually includes several intensification phases. The intensity of consolidation therapy varies, depending on the risk of relapse, age and cytogenetic profile.
- **CNS prophylaxis** reduces the risk of CNS relapse from 30% to 5%. It involves cranial irradiation with intrathecal chemotherapy. In children cranial irradiation is avoided due to side effects and high dose systemic therapy with intrathecal therapy is used as an alternative.
- **Maintenance therapy** consists of chemotherapy for 2-3 years or allogeneic (donor) stem cell transplantation (for high risk patients aged under 50 years with suitable donor). Alternatively autologous transplantation (using the patient's own stem cells) may be an option for high risk patients aged 60 years or under. **Allogeneic stem cell transplantation** is an alternative to maintenance therapy for high risk Philadelphia chromosome positive ALL (Ph/BCR-ABL+). This is an option for patients aged less than 50.

Acute lymphoblastic leukaemia (ALL): Prognosis

Although 70-80% of paediatric patients with ALL will achieve long-term remission with combination chemotherapy, the situation is less favourable for adults with only 35-50% achieving long-term remission due to a higher frequency of poor prognostic factors (i.e. age over 50 years, Ph/BCR-ABL+ disease, and time to achieving complete remission greater than 4 weeks).

Acute myeloid leukaemia (AML):Classification

Acute myeloid leukaemia is the most common acute leukaemia in adults, with an incidence of 3 per 100,000 annually. It is infrequent in children under 15 years and 66% of patients are older than 60 years. The French-American-British (FAB) classification [(28)] based on morphology and cytochemistry alone which defines 11 subtypes of AML has been superseded by the WHO classification which incorporates immunophenotyping and cytogenetics enabling categorization of cases into unique clinical and biological subgroups, Table 2 below.

Table 2. WHO classification of acute myeloid leukaemia
Acute myeloid leukaemia with recurrent genetic abnormalities
Acute myeloid leukaemia with t(8;21)(q22;q22),(AML1/ETO)
Acute myeloid leukaemia with abnormal BM eosinophils and inv(16)(p13.1q22) or t(16;16)(p13.1;p22); CBFB-MYH11
Acute promyelocytic leukaemia with t(15;17)(q22;q12);PML-RARA
Acute myeloid leukaemia with 11q23 (MLL) abnormalities
Acute myeloid leukaemia with multilineage dysplasia
Following MDS or MDS/MPD
Without antecedent MDS or MDS/MPD but with dysplasia in at least 50% of cells in 2 or more myeloid lineages.
Acute myeloid leukaemia with MDS therapy related
Alkylating agent/radiation-related type
Topoisomerase IIinhibitor related
Others
Acute myeloid leukaemia, not otherwise categorised
Acute myeloid leukaemia,minimally differentiated =FAB M0
Acute myeloid leukaemia, without maturation = FAB M1
Acute myeloid leukaemia, with maturation = FAB M2
Acute myelomonocytic leukaemia, without maturation = FAB M4
Acute myelomonocytic leukaemia = M5
Acute monoblastic and monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia
Acute basophilic leukaemia
Acute panmyelosis with myelofibrosis

Acute myeloid leukaemia (AML): Treatment

As for ALL, where possible patients should be entered into national or international multicentre clinical trials. AML treatment consists of two phases:

- **Remission induction** One or two courses of combination chemotherapy to achieve complete remission.
- **Consolidation therapy** Several cycles of chemotherapy using different combinations of agents. The number and intensity of these cycles varies according to age. Patients aged over 60 years will only tolerate less intensive treatments. Intense supportive therapy is essential to combat the major infective and haemorrhagic side effects of therapy.
- **Stem cell transplantation (SCT)** Allogeneic SCT should be offered to younger patients (under 45 years) with poor risk AML if they achieve complete remission following induction. For patients under 65 years autologous SCT is an option for intensive consolidation for those deemed to be intermediate to poor risk.

Acute myeloid leukaemia (AML): Prognosis

- Age is an important prognostic factor in AML with less than 10% of patients aged over 70 surviving 5 years[14]. This is in part due to the increased frequency of adverse cytogenetics features, secondary (treatment related AML) and chemotherapy drug resistance.
- Patients with AML can be categorised according to their cytogenetic profile into favourable, intermediate and poor risk groups (Table 3 below).

Table 3. Cytogenetic Risk Categories in AML

Risk Category	Abnormality
Good	t(8;21), t(15;17), inv(16)
Intermediate	Normal, +8, +21, +22, del(7q), del(9q), Abnormal 11q23, all other structural or numerical changes
Poor	-5, -7, del(5q), Abnormal 3q, Complex cytogenetics

- Cytogenetic risk category is a highly independent prognostic factor with 5 year overall survival of 55%, 24% and 5% respectively for the favourable, intermediate and poor risk patients[15].

Chronic Myeloid Leukaemia (CML): Treatment and prognosis

Chronic myeloid leukaemia is a rare disease with an incidence of 1.25 per 100,000. It accounts for 15% of adult leukaemias. It is characterized by a marked increase in granulocytes (a category of white blood cell) and the presence of the Philadelphia chromosome (a translocation between chromosomes 9 and 22 that forms a fusion gene BCR-ABL). 30% of patients are asymptomatic with diagnosis being made following routine blood test. As the disease progresses anaemia, weight loss, sweating and enlargement of the spleen are common. The natural history of the disease is classically either biphasic or triphasic with an initial chronic phase lasting 3-6 years followed by an accelerated phase then a blast crisis phase but 50% of patients transform directly from chronic phase to blast crisis.

The treatment of the chronic phase of CML has been revolutionised by the use of the drug "Imatinib" that specifically targets BCR-ABL, with 89% of patients now surviving 5 years[16].The ultimate goal of Imatinib therapy is to induce a complete molecular remission (BCR-ABL transcripts not detectable in peripheral blood). This requires close disease monitoring and modification of Imatinib dose. Patients whose disease progresses on Imatinib therapy may respond to an alternative drug such as Dasatinib or if eligible may be considered for stem cell transplantation.

APPENDIX B -LEUKAEMIA CLINICAL TRIAL PROTOCOLS

UKALL XII Protocol

UKALL XII Protocol Version 5.0

4. TRIAL DESIGN

4.1 Induction and high dose therapy with HSCT

All eligible patients will receive a uniform induction therapy based on the successful German protocol [1-10]. The modification is in accord with the risk-adapted German multicentre trial which has complete remission rates of over 85% even in patients with Ph+ disease.

All eligible patients will receive standard phase I induction therapy as specified in Section 8.4 Ph+ve ALL patients will then receive four weeks treatment with Imatinib combined with Phase II.

Following this, those patients with a sibling or MUD or related single haplotype match will go on to allogeneic transplantation, whilst those with no donor will have an autograft. After allograft or autograft patients will receive Imatinib as maintenance therapy.

4.2 Imatinib

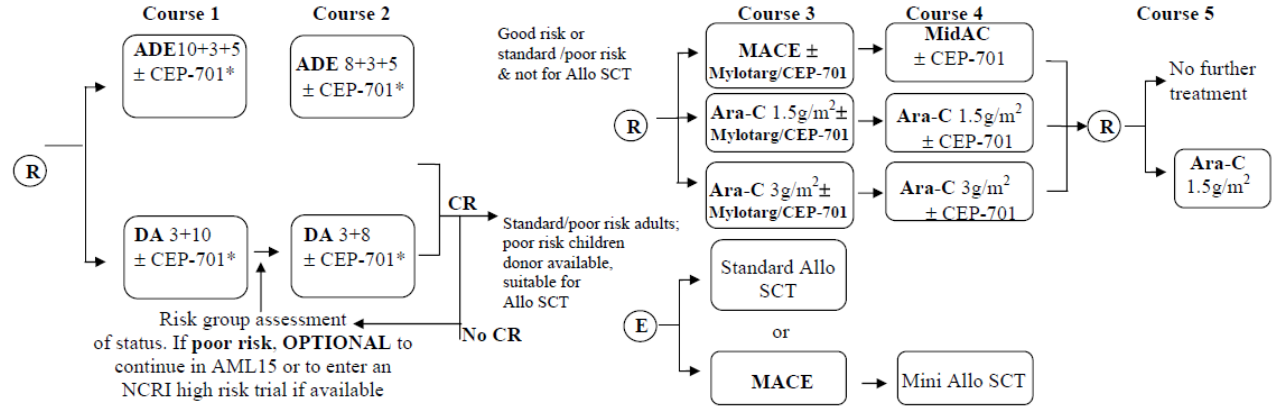
The molecular consequence of the t:9:22 translocation resulting in the Philadelphia chromosome is the creation of a fusion protein BCR-ABL. Patients with chronic phase CML express a 210 kDA BCR-ABL protein whereas patients with Ph+ve acute lymphoblastic leukaemia express either the 210 kDa BCR-ABL protein or the 185 kDa BCR-ABL protein. [31] These fusion proteins are constitutively activated tyrosine kinase with increased activity and the activity is required for the transforming abilities of the BCR-ABL oncoprotein. An inhibitor or the BCR-ABL protein tyrosine kinase could be a potentially useful therapeutic agent for CML and also for Ph+ve ALL. Knowledge of the structure of protein tyrosine kinase inhibitors has allowed for the synthesis of inhibitors with increased potency and specificity and one such class of compounds are the 2-phenylaminopyrimadine derivatives. One compound in this class, CGP 57148, is a potent inhibitor of the ABL protein kinase and is now known as Imatinib. [32] All ABL kinases including p210 BCR-ABL and p185 BCR-ABL are inhibited by similar concentrations of Imatinib. It is available as an oral formulation and phase I trials in CML patients were begun in June 1998. Results from those patients show that the drug is generally well tolerated Adequate bioavailability and pharmacokinetics have been observed with once daily administration. [33]

Accumulating evidence suggests that the earlier addition of Imatinib might increase the number of patients entering haematological CR and even molecular remission. This might increase the number of patients in whom first remission allografting is an option and might render autografting a more attractive approach for patients for whom no allogeneic donor is available. Furthermore, there appears to be little additional toxicity associated with the earlier use of Imatinib. The previous amendment introduced the Imatinib at the beginning of phase II of induction. By so doing, we aim to increase the overall CR rate and the rate of achievement of molecular remission at relapse.

AML 15 protocol

AML15 Protocol Flow Chart 1 - Trial Overview (Please refer to the back of the protocol for more detailed flow diagrams)

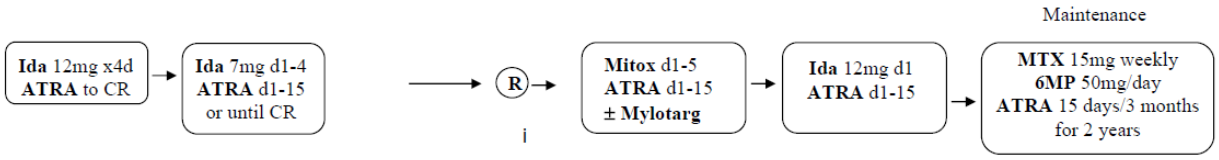
AML patients, other than APL



* Patients with a FLT3 mutation are eligible for the CEP-701 randomisation after course 1; patients who do not enter the CEP-701 randomisation after course 1 are eligible for the mylotarg consolidation randomisation.

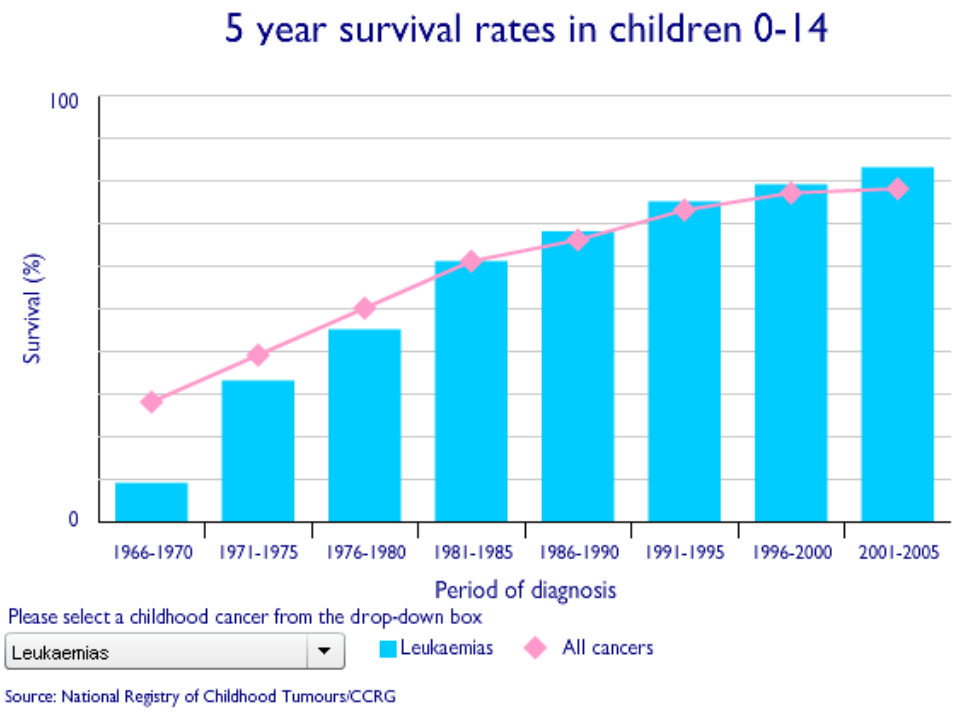
R Randomise
E Elect

Spanish Treatment



APPENDIX C – SURVIVAL FROM LEUKAEMIA AND LYMPHOMA

Figure 1. 5-year survival rates leukaemia in children 0-14 years 1966-2005



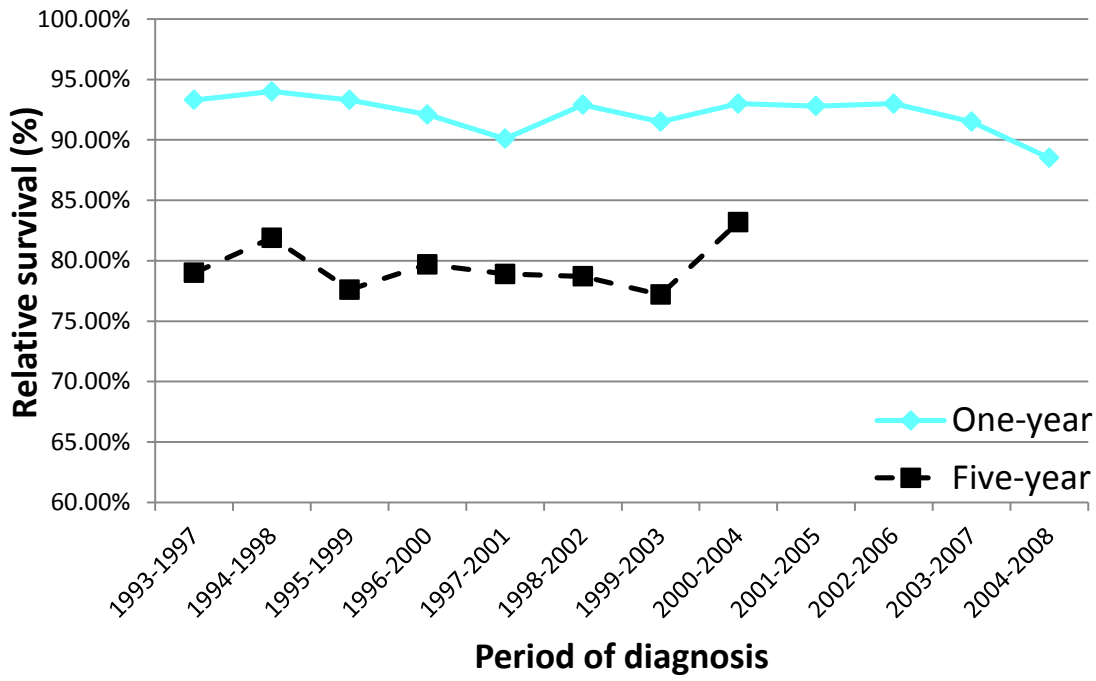
Source: CRUK Website

Leukaemia survival rates have increased markedly since the 1960s for children in the UK (Figure 1). Survival data are available in Northern Ireland since the 1990s and show similar high levels to those experienced in the rest of the UK with 89% relative survival at 1 year and 83% relative survival at 5 years (Table 1, Figure 2). (note: relative and observed survival for children is similar due to low numbers of deaths from other causes).

Table 1. Leukaemia survival children Northern Ireland 1993-2008

Period of diagnosis	Relative survival			
	One-year		Five-year	
1993-1997	93.30%	(86.5%,96.8%)	79.00%	(69.8%,85.6%)
1994-1998	94.00%	(87.1%,97.3%)	81.90%	(72.8%,88.2%)
1995-1999	93.30%	(85.7%,97.0%)	77.60%	(67.5%,85.0%)
1996-2000	92.10%	(84.1%,96.2%)	79.70%	(69.6%,86.7%)
1997-2001	90.10%	(81.1%,94.9%)	78.90%	(68.2%,86.3%)
1998-2002	92.90%	(83.7%,97.0%)	78.70%	(67.1%,86.6%)
1999-2003	91.50%	(81.9%,96.1%)	77.20%	(65.5%,85.4%)
2000-2004	93.00%	(83.9%,97.0%)	83.20%	(72.2%,90.1%)
2001-2005	92.80%	(83.5%,96.9%)		
2002-2006	93.00%	(83.9%,97.0%)		
2003-2007	91.50%	(82.0%,96.1%)		
2004-2008	88.50%	(78.2%,94.1%)		

Figure 2. Relative survival childhood* leukaemia Northern Ireland 1993-2008

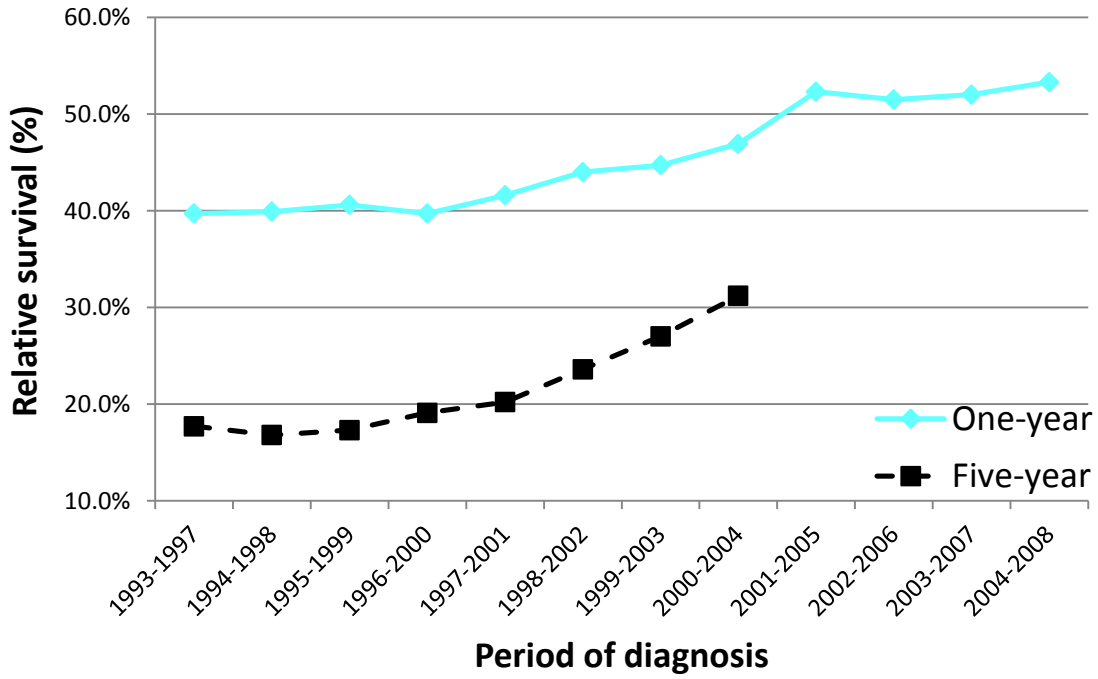


*Aged 0-14 years

Table 2. Adult leukaemia (excluding CLL) survival Northern Ireland 1993-2008

Period of diagnosis	Relative survival			
	One-year		Five-year	
1993-1997	39.7%	(35.1%,44.2%)	17.7%	(14.1%,21.6%)
1994-1998	39.9%	(35.4%,44.4%)	16.8%	(13.4%,20.6%)
1995-1999	40.6%	(36.1%,45.0%)	17.3%	(13.8%,21.1%)
1996-2000	39.7%	(35.3%,44.1%)	19.1%	(15.5%,23.0%)
1997-2001	41.6%	(37.1%,46.0%)	20.2%	(16.6%,24.2%)
1998-2002	44.0%	(39.4%,48.5%)	23.6%	(19.6%,27.7%)
1999-2003	44.7%	(40.0%,49.3%)	27.0%	(22.7%,31.4%)
2000-2004	46.9%	(42.1%,51.5%)	31.2%	(26.7%,35.8%)
2001-2005	52.3%	(47.6%,56.8%)		
2002-2006	51.5%	(46.9%,55.9%)		
2003-2007	52.0%	(47.5%,56.4%)		
2004-2008	53.3%	(48.9%,57.6%)		

Figure 3. Adult* leukaemia** survival Northern Ireland 1993-2008



*age 15 and over

**excludes chronic lymphatic leukaemia

1-year relative survival for adult leukaemia (excluding CLL) has improved in Northern Ireland from 40% to 53% between 1993/7 and 2004/8 while 5-year survival improved from 18% to 31%. 2004-2008 relative surival from adult chronic myeloid leukaemia was 78% 1-year, 61% 5-year in

Northern Ireland (Figure 4, Table 3). 2004-2008 relative survival for adult acute lymphoblastic leukaemia was 58% at 1-year, 43% at 5-years (Figure 5, Table 4). Relative survival for acute myeloid leukaemia has also improved but is lower at 40% 1-year, 18% 5-year (Figure 6, Table 5).

Table 3. Survival chronic myeloid leukaemia all adults (15-99) Northern Ireland 1993-2008

Period of diagnosis	Relative survival			
	One-year		Five-year	
1993-1997	60.20%	(48.6%,70.2%)	24.70%	(15.2%,35.9%)
1994-1998	59.10%	(47.4%,69.3%)	23.90%	(14.4%,35.2%)
1995-1999	66.40%	(54.1%,76.4%)	29.20%	(18.3%,41.5%)
1996-2000	67.10%	(54.5%,77.3%)	35.50%	(23.4%,48.6%)
1997-2001	74.30%	(61.9%,83.6%)	44.50%	(31.3%,57.6%)
1998-2002	77.40%	(64.9%,86.3%)	50.00%	(36.4%,62.8%)
1999-2003	80.60%	(68.7%,88.7%)	58.30%	(44.7%,70.3%)
2000-2004	78.80%	(67.2%,87.0%)	60.80%	(47.6%,72.2%)
2001-2005	82.40%	(72.1%,89.4%)		
2002-2006	77.90%	(67.8%,85.3%)		
2003-2007	77.40%	(66.9%,85.2%)		
2004-2008	77.80%	(67.5%,85.4%)		

Figure 4. Survival chronic myeloid leukaemia Northern Ireland 1993-2008

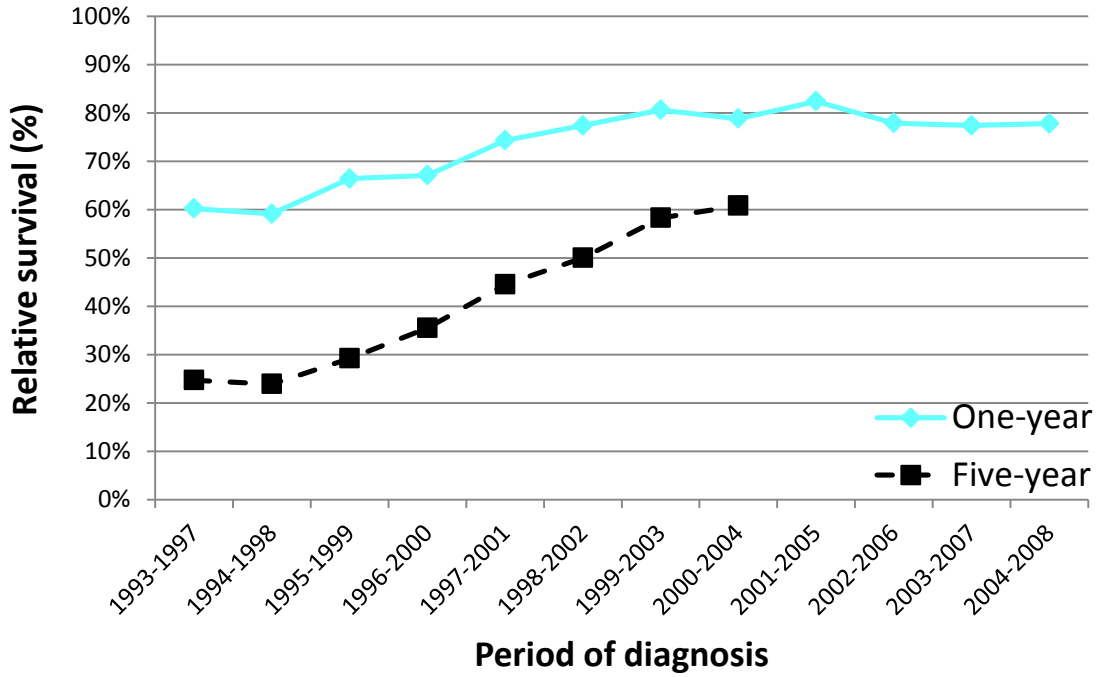


Table 4. Survival acute lymphoblastic leukaemia all adults (15-99) Northern Ireland 1993-2008

Period of diagnosis	Relative survival			
	One-year		Five-year	
1993-1997	52.90%	(39.6%,64.6%)	23.60%	(13.8%,35.1%)
1994-1998	52.10%	(38.6%,64.2%)	24.80%	(14.5%,36.7%)
1995-1999	50.40%	(35.8%,63.3%)	24.80%	(13.8%,37.7%)
1996-2000	49.20%	(34.3%,62.5%)	23.70%	(12.8%,36.7%)
1997-2001	47.00%	(31.9%,60.7%)	22.70%	(11.7%,35.9%)
1998-2002	58.90%	(42.3%,72.3%)	29.90%	(16.7%,44.4%)
1999-2003	64.60%	(47.4%,77.5%)	37.20%	(22.2%,52.5%)
2000-2004	65.70%	(48.7%,78.4%)	42.70%	(26.7%,58.3%)
2001-2005	70.60%	(53.8%,82.5%)		
2002-2006	64.30%	(48.1%,76.6%)		
2003-2007	58.10%	(42.6%,70.8%)		
2004-2008	58.10%	(42.6%,70.8%)		

Figure 5. Survival acute adult lymphoblastic leukaemia Northern Ireland 1993-2008

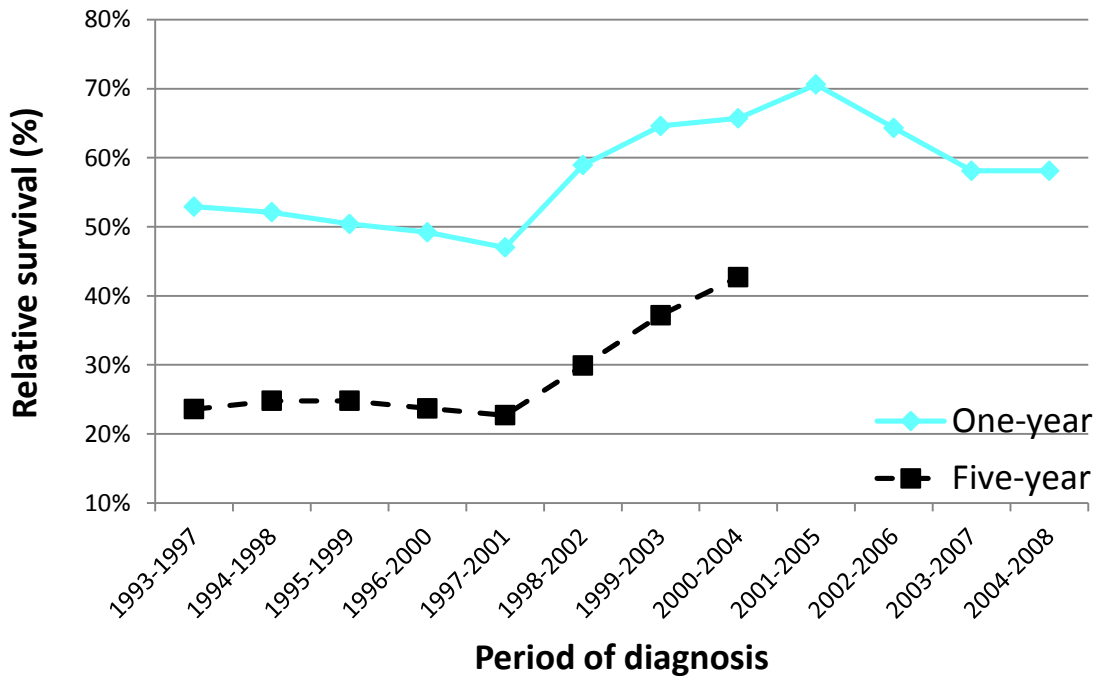


Table 5. Survival acute myeloid leukaemia all adults (15-99) Northern Ireland 1993-2008

Period of diagnosis	Relative survival			
	One-year		Five-year	
1993-1997	26.70%	(20.7%,33.1%)	9.20%	(5.6%,14.0%)
1994-1998	27.40%	(21.5%,33.7%)	7.80%	(4.6%,12.1%)
1995-1999	29.30%	(23.3%,35.6%)	8.50%	(5.2%,13.0%)
1996-2000	27.70%	(22.0%,33.7%)	9.50%	(6.0%,13.9%)
1997-2001	29.70%	(24.0%,35.6%)	10.60%	(7.0%,15.0%)
1998-2002	31.30%	(25.5%,37.2%)	13.40%	(9.4%,18.2%)
1999-2003	30.00%	(24.1%,36.1%)	13.90%	(9.7%,18.9%)
2000-2004	32.70%	(26.7%,38.7%)	18.30%	(13.6%,23.7%)
2001-2005	37.30%	(31.2%,43.5%)		
2002-2006	34.70%	(28.8%,40.7%)		
2003-2007	37.60%	(31.6%,43.6%)		
2004-2008	40.10%	(34.3%,46.0%)		

Figure 6. Survival acute adult myeloid leukaemia Northern Ireland 1993-2008

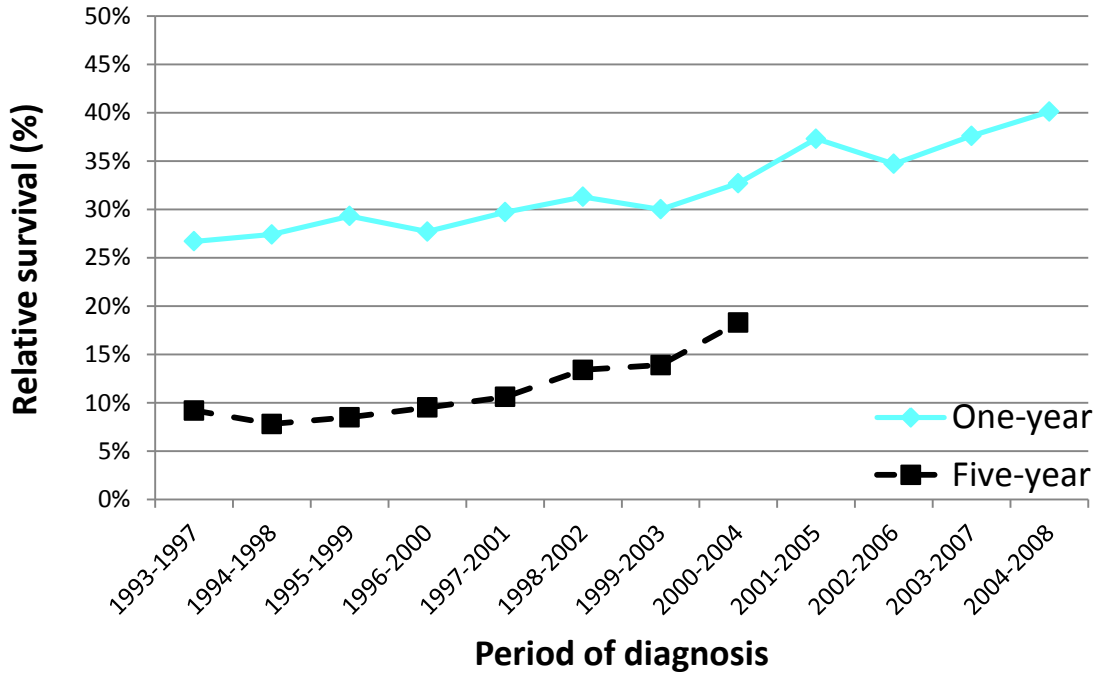
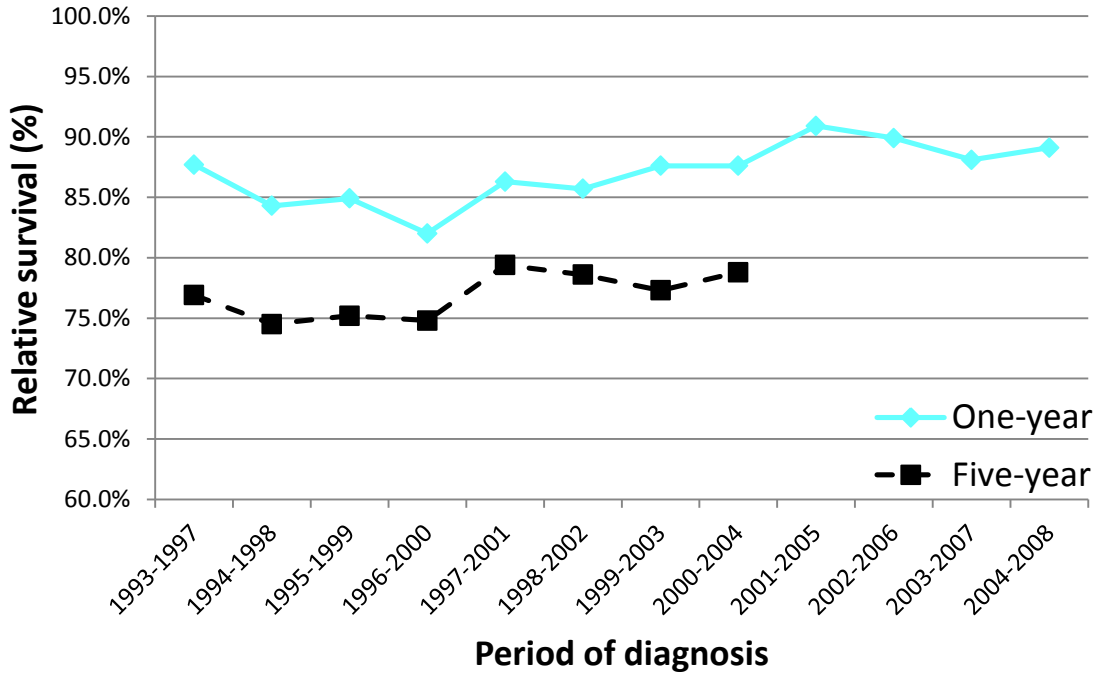


Table 6. Survival Hodgkin lymphoma adults (15-99) Northern Ireland 1993-2008

Period of diagnosis	Relative survival			
	One-year		Five-year	
1993-1997	87.7%	(81.9%,91.8%)	76.9%	(69.5%,83.0%)
1994-1998	84.3%	(77.7%,89.2%)	74.5%	(66.5%,81.1%)
1995-1999	84.9%	(78.4%,89.7%)	75.2%	(67.3%,81.6%)
1996-2000	82.0%	(75.0%,87.3%)	74.8%	(66.9%,81.3%)
1997-2001	86.3%	(79.9%,90.8%)	79.4%	(72.0%,85.3%)
1998-2002	85.7%	(79.1%,90.3%)	78.6%	(71.0%,84.6%)
1999-2003	87.6%	(81.5%,91.9%)	77.3%	(69.9%,83.3%)
2000-2004	87.6%	(81.4%,91.9%)	78.8%	(71.3%,84.7%)
2001-2005	90.9%	(85.5%,94.5%)		
2002-2006	89.9%	(84.3%,93.6%)		
2003-2007	88.1%	(82.9%,91.9%)		
2004-2008	89.1%	(84.3%,92.6%)		

Figure 7. Survival Hodgkin lymphoma Northern Ireland 1993-2008

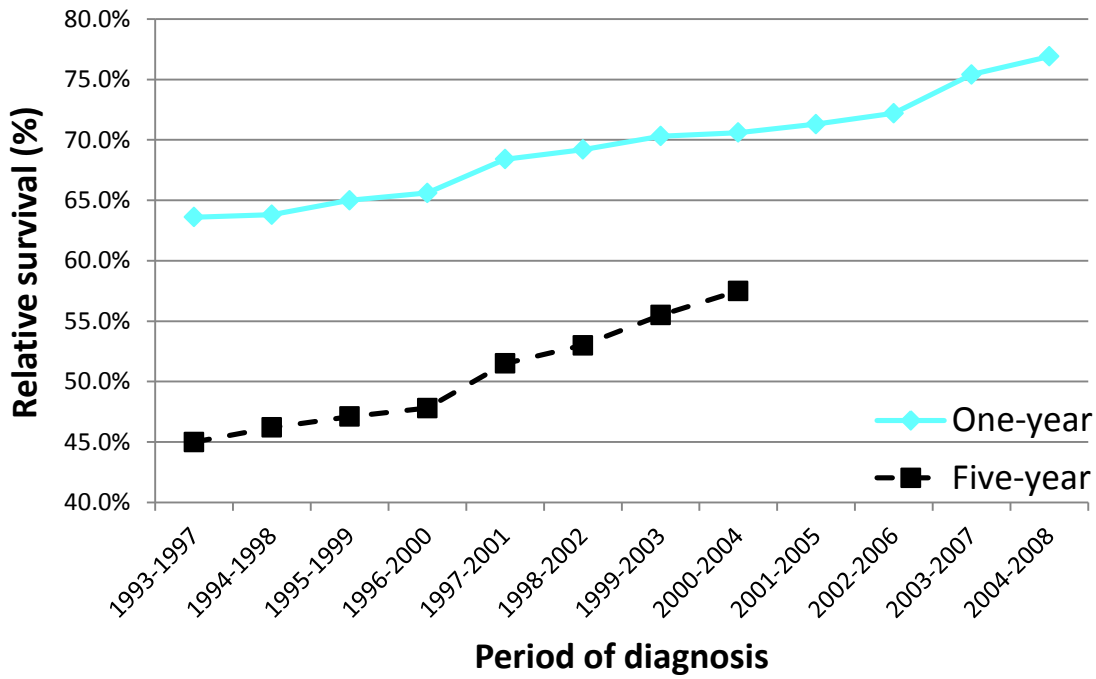


Survival from Hodgkin lymphoma remained high for patients diagnosed in Northern Ireland at 88% 1-year and 78% 5-year.

Table 7. Survival Non-Hodgkin lymphoma adults (15-99) Northern Ireland 1993-2008

Period of diagnosis	Relative survival			
	One-year		Five-year	
1993-1997	63.6%	(60.6%,66.4%)	45.0%	(41.7%,48.3%)
1994-1998	63.8%	(60.9%,66.6%)	46.2%	(42.9%,49.5%)
1995-1999	65.0%	(62.1%,67.7%)	47.1%	(43.8%,50.3%)
1996-2000	65.6%	(62.7%,68.3%)	47.8%	(44.6%,51.0%)
1997-2001	68.4%	(65.7%,71.1%)	51.5%	(48.3%,54.7%)
1998-2002	69.2%	(66.4%,71.7%)	53.0%	(49.8%,56.1%)
1999-2003	70.3%	(67.6%,72.9%)	55.5%	(52.3%,58.6%)
2000-2004	70.6%	(67.9%,73.1%)	57.5%	(54.3%,60.6%)
2001-2005	71.3%	(68.7%,73.8%)		
2002-2006	72.2%	(69.6%,74.7%)		
2003-2007	75.4%	(72.9%,77.8%)		
2004-2008	76.9%	(74.4%,79.2%)		

Figure 8. Survival Non-Hodgkin lymphoma Northern Ireland 1993-2008



Survival for Non-Hodgkin lymphoma improved from 64% 1-year and 45% 5-year in 1993/7 to 77% 1-year and 58% 5-year by 2004/8.

APPENDIX D - LYMPHOMA CLASSIFICATION

Non-Hodgkin lymphoma (NHL): Classification

Non-Hodgkin lymphoma is an overarching diagnosis applied to a group of malignant diseases that arise from the lymphoid system. The World Health Organisation (WHO) classification using morphology, immunophenotype and cytogenetics, defines a list of clinico-pathologically distinct types of lymphoma. Clinical management however is still largely based on the Revised European American Lymphoma (REAL) classification[29] which groups histological diagnosis into 3 main categories indolent (low grade), aggressive (intermediate and high grade) and very aggressive. The Clinical grade and frequency of the different Non-Hodgkin lymphomas in the REAL classification is shown in Table 1 below.

Table 1. REAL Classification of Non-Hodgkin lymphoma

Diagnosis	% of all lymphomas
Indolent lymphomas (Low grade)	
Follicular lymphoma (Grade I & II, grade III is intermediate)	22%
Marginal zone B-cell, MALT lymphoma	8%
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	7%
Nodal marginal zone B-cell lymphoma	2%
Lymphoplasmacytoid lymphoma	1%
Aggressive lymphomas (Intermediate/high grade)	
Diffuse large B-cell lymphoma	31%
Peripheral T-cell lymphoma	8%
Mantle cell lymphoma	7%
Mediastinal large B-cell lymphoma	2%
Anaplastic large cell lymphoma	2%
Very aggressive lymphoma	
Burkitt lymphoma	2%
Lymphoblastic lymphoma	2%
Other lymphomas	7%

Hodgkin lymphoma (HL): Classification

First described by Thomas Hodgkin in 1832.

The WHO classification defines 2 distinct clinical entities, Classical Hodgkin lymphoma and Nodular lymphocyte predominant Hodgkin lymphoma (Table 2).

Table 2. WHO Classification of Hodgkin lymphoma

Diagnosis	% of all Hodgkin lymphomas
Classical Hodgkin lymphoma (CHL)	92-97**%**
Nodular sclerosing Hodgkin lymphoma	
Mixed cellularity Hodgkin lymphoma	
Lymphocyte depleted Hodgkin lymphoma	
Lymphocyte rich Hodgkin lymphoma	
Nodular lymphocyte predominant (NLPHL)	3-8%

APPENDIX E - LYMPHOMA STAGING

Staging helps to define prognosis and select therapy and also helps assess response to therapy. The Ann Arbor staging system[30] originally developed for Hodgkin lymphoma (Table 1) has been historically used for the Non-Hodgkin lymphomas and has strong prognostic value determined by the number of lymph node regions involved and the presence or absence of B symptoms. The Cotswolds modification[31] of the Ann Arbor staging classification is now used for Hodgkin lymphoma which addresses disease distribution and bulk identified by modern imaging using CT and PET scanning.

Table 1. Ann Arbor Staging Classification for NHL

Stage	Area of involvement
I	One lymph node region
I_E	One extralymphatic organ or site
II	Two or more lymph node regions on same side of diaphragm
II_E	One extralymphatic organ or site (localized) in addition to criteria for stage II
III	Lymph node regions on both sides of diaphragm
III_E	One extralymphatic organ or site (localized) in addition to criteria for stage III
III_S	Spleen in addition to criteria for stage III
III_{SE}	Spleen andOne extralymphatic organ or site (localized) in addition to criteria for stage III
IV	One or more extralymphatic organs with or without associated lymph node involvement (diffuse or disseminated

APPENDIX F - LYMPHOMA TREATMENT

Lymphoma Treatment

Indolent/low grade lymphoma NHL

Traditional management of patients with low grade lymphomas of which follicular lymphoma is the most common type usually involves the decision between 'Watch & Wait' or conventional chemotherapy and/or radiotherapy. With the exception of grade III follicular lymphomas, which are usually treated like aggressive lymphomas, 'Watch & Wait' is the typical decision in asymptomatic patients with low bulk disease. Therapy may be initiated when clinical symptoms or complications develop. This approach has been shown to result in similar overall survival and better quality of life in asymptomatic patients. These patients require close monitoring usually every 3-6 months initially. Symptomatic patients however require treatment at diagnosis. These lymphomas are responsive to radiotherapy and chemotherapy but tend to recur with a median survival of 8-10 years. Chemotherapy with or without the addition of monoclonal antibody therapy Rituximab is generally 1st line treatment (and now NICE-approved) for symptomatic patients with more advanced stage disease III/IV.

Aggressive/high grade NHL

Diffuse large B-cell lymphoma (DLBCL) is the most common of the aggressive lymphomas. Patients with localised DLBCL lymphoma can be cured by combination chemotherapy and/or radiotherapy. Patients with more advanced stage disease require 6-8 courses of combination chemotherapy commonly R-CHOP regimen. The addition of the monoclonal antibody Rituximab (R) to standard CHOP regimen has resulted in significantly improved 5-year survival from 45% to 58% for these patients[(32)]. Patients with testicular, bone marrow, sinus or CNS involvement require additional intrathecal chemotherapy. Patients with bulk disease at diagnosis (disease site >10cm) should receive adjuvant radiotherapy. Response to initial therapy is assessed after 3-4 courses to identify early patients who are not responding or who may have progressed despite therapy. Following completion of 6-8 courses of R-CHOP response is reassessed with CT and PET scanning. PET scanning can help determine whether any residual masses identified on CT represent active disease. If positive on PET scan, biopsy to confirm the presence of disease is usually performed. High dose therapy and stem cell transplant (SCT) is used for patients who do not respond to this initial R-CHOP therapy or who relapse after achieving complete remission.

Stem cell transplantation can be curative for a significant proportion of patients DLBCL (the most common type of aggressive lymphoma), with 5-year survival rate of 53%[33].
Patients who achieve complete response to initial therapy require close follow-up usually every 3 months initially to detect any evidence of disease recurrence.

Hodgkin lymphoma (HL)

Therapy for HL has improved dramatically over the past 4 decades with patients aged less than 60 years having >80% chance of cure. Treatment is determined by stage, symptoms, disease bulk, age and co-morbidities with the aim of providing the best chance of cure while minimizing risk of treatment-related side effects (Risk-adapted therapy). Prognostic factors have been identified by European study groups[34] that enable patients to be classified into favourable and unfavourable groups which determine the treatment required. Patients are generally divided into 3 treatment groups:

- Stage I/II favourable (no risk factors).
- Stage I/II (presence of one or more risk factors).
- Advanced stage (Stage III/IV).

Where possible patients should be entered into multicentre randomized trials. Early favourable stage disease is usually treated with fewer (2-4 courses) of the established combination chemotherapy regimen ABVD followed by radiotherapy to sites of disease. Unfavourable disease requires 6 cycles of chemotherapy followed by radiotherapy to sites of disease with higher dose radiotherapy to sites of bulk disease. The International Prognostic Index (Tables 5 & 6, Appendix F) for patients with advanced HL has been developed to identify those patients that can be cured by standard chemotherapy and radiotherapy and those that will require more intensive therapy.

APPENDIX G - LYMPHOMA PROGNOSTIC INDICES

Prognostic indices have been developed which include clinical features that were independently predictive of survival. For the aggressive lymphomas (Table1&2) the International Prognostic Index (IPI) has been validated as a predictor of response to therapy, relapse and survival[35]. This has recently been revised to reflect the improved survival resulting from the inclusion of monoclonal antibody therapy in chemotherapy regimens[36]. For follicular lymphoma which is the most common of the indolent lymphomas (Table 3&4) the Follicular Lymphoma International Prognostic Index (FLIPI) may be used to assess the need for early treatment and its likely outcome[37]. For Hodgkin lymphoma the International Prognostic Score (IPS) for advanced Hodgkin lymphoma[34] has been developed to distinguish between patients who may be cured by standard therapy and those who will require more intensive therapy (Table 5&6).

Table 1. International Prognostic Index (IPI) for aggressive NHL.

Index	Risk factor
1	Age > 60y
1	PS 2-4
1	Stage III-IV
1	LDH elevated
1	Extra nodal >1 site
5	**Maximum Score**

Table 2. Risk groups of International Prognostic Index (IPI)

IPI Score	
0 - 1	low
2	low /intermediate
3	Iintermediate/high
4 - 5	High

Table 3. Follicular Lymphoma International Prognostic Index (FLIPI)

Index	Risk factor
1	Age > 60y
1	Haemoglobin < 12g/dL
1	Stage III-IV
1	LDH elevated
1	number nodal sites ≥5
5	**Maximum Score**

Table 4. Risk groups of Follicular Lymphoma International Prognostic Index (FLIPI)	
IPI Score	
0 - 1	low
2	intermediate
≥3	high

Table 5. International Prognostic Index for Advanced Hodgkin lymphoma (IPI)	
Index	**Risk factor**
1	Age ≥45
1	Haemoglobin < 10.5g/dL
1	StageIV
1	Albumin <40g/L
1	Male gender
1	WBC ≥15 $x10^9$/L
1	Lymphopenia <0.6 $x10^9$/L
7	**Maximum Score**

Table 6. Risk groups for Advanced Hodgkin lymphoma (IPI)	
IPI Score	
0 - 1	low
2-3	intermediate
4-7	high

CDS 73442

N.Ireland Cancer Registry
Centre for Public Health
Queen's University Belfast
Mulhouse Building
Grosvenor Road
Belfast BT12 6DP

T: +44 (0) 28 9063 2573
F: +44 (0) 28 9024 8017
W: www.qub.ac.uk/nicr

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