Get Data Out: haematological malignancies and transformations

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Introduction

The Get Data Out programme routinely publishes cancer statistics produced by NHS E (previously PHE and NHS D) in a consistent table, called the Get Data Out (GDO) table. This table collects patients into groups with common characteristics, and then publishes information such as incidence, treatment rates, survival and Routes to Diagnosis for these groups.

This document sets out the definitions of the cohort and groups for the Get Data Out tables for the 2023 release of data on haematological malignancies (HM) and haematological malignancy transformations.

Background

All cancer diagnoses are required to be registered in England. Patients of all ages, resident in England, diagnosed with histologically confirmed HM between January 1st 2013 and December 31st 2020 were included in the analysis. Diagnoses were made by pathologists and recorded by specialist clinical coders on the National Cancer Data Register with diagnostic data undergoing quality control within the National Disease Registration Service (NDRS).

Classification of disease

Haematopoiesis is the formation of blood cellular components within the bone marrow and occurs throughout life. All cellular blood components are derived from haematopoietic stem cells, and mature cells consist of myeloid cells including platelets, erythrocytes, granulocytes, monocytes and dendritic cells, and lymphoid cells such as T- and B-lymphocytes, NK-cells, and plasma cells. HM is a collective term used for neoplasms of the haematopoietic and lymphoid tissues. The World Health Organisation (WHO) classifies HM according to lineage e.g. myeloid, lymphoid, histiocytic, and a normal counterpart cell is thought to account for each neoplasm. As haematopoiesis is a complicated process there are over 150 subtypes of HM. Stem cell or precursor neoplasms such as acute leukaemia are considered separately from mature neoplasms such as lymphomas, myeloma. Leukaemias are cancers which circulate in blood or bone marrow and may be myeloid or lymphoid,

and can be acute or chronic. In acute disease, most of the abnormal cells don't mature and as such don't carry out normal cellular functions, these diseases tend to progress at a faster rate and are typically much more aggressive. Chronic disease on the other hand, occurs when there is a mix of normal cells alongside a population of immature cells and as such, these diseases tend to be slower growing. Lymphomas are cancer of mature lymphocytes (B-, T-, NKT- or NK- cells).

Disease groupings

In total, 157 distinct morphological entities of HM have been grouped to form 42 overarching subtypes, with further subclassification according to the cell lineage. In total, HM have been categorised in to 16 myeloid groupings and 23 lymphoid groupings for the purpose of Get Data Out and to avoid disclosing small numbers. Analysis includes patients of all ages, diagnosed in England between 2013 and 2020 and excludes patients diagnosed with monoclonal gammopathy of undetermined significance (9765/1). Further details on HM and how they have been grouped are included below.

Myeloid neoplasms

The GDO reports HM of the myeloid lineage according to 7 subtypes, with further information provided where cohorts are large enough that they are not deemed to be identifiable (>35-40 patients).

Cell lineage	Subgroup	Morphological description
Myeloid	Acute myeloid leukaemia (AML)	All
	Acute promyelocytic leukaemia (APL)	All
	Chronic myelomonocytic leukaemia (CMML)	All
	Mastocytosis	All
	Myelodysplastic syndromes (MDS)	Myelodysplastic syndromes (MDS) with isolated del(5q)
		Myelodysplastic syndromes (MDS) with excess blasts
		Myelodysplastic syndromes (MDS) with multilineage dysplasia
		Myelodysplastic syndromes (MDS) with single lineage dysplasia
		Myelodysplastic syndromes (MDS) with ringed sideroblasts
		Myelodysplastic syndromes (MDS) unclassifiable and NOS
	Myeloproliferative neoplasms (MPN)	Myelofibrosis
		Polycythaemia vera (PCV)
		Other myeloproliferative neoplasms (MPN)
		Chronic myeloid leukaemia (CML)
		Essential thrombocythemia (ET)
	Other myeloid neoplasms	All

Acute leukaemia:

Acute leukaemia emerges when some of your white blood cells do not develop properly. Instead of growing into fully functioning white blood cells, which are part of your immune system, they get stuck at an earlier stage of development and divide quickly. They build up in the blood and the bone marrow, leaving less room for healthy blood cells to develop causing low levels of normal blood cells. This is called bone marrow failure and means your body does not have enough white blood cells whose function is to fight infection, red blood cells which carry oxygen, or platelets whose function is stop bleeding. Patients usually present with tiredness, easy bruising or bleeding and recurrent unexplained infections.

Acute Myeloid Leukaemia (AML):

AML is an aggressive clonal disease of immature white cells of the myeloid lineage called granulocytes and monocytes, whereby the production of these immature cells leads to bone marrow failure. AML is diagnosed on the identification of excess immature myeloid cells called 'blasts' identified in the peripheral blood, bone marrow, and/or other tissues. The WHO currently describe 21 unique classifications of disease. As such, the number of possible classifications for disease means that there are small cohorts within the AML subgroup, which has meant that cases have been grouped together to avoid releasing potentially identifiable patient information.

Acute promyelocytic leukaemia (APL):

APL is a rare type of AML that emerges in the same way, but specifically affects promyelocyte cells (immature neutrophils/white cells) and has a very strong association with severe bleeding at presentation. Bleeding can be fatal in the first few weeks of diagnosis, but if controlled the overall cure rates are very high.

Myelodysplastic Syndromes (MDS):

MDS comprises a group of conditions whereby the bone marrow is unable to generate enough normal/healthy blood cells, and instead produces immature cells that are unable to carry out their normal function. These immature/abnormal blood cells either remain in the bone marrow space or end up being destroyed before they get into the bloodstream. As MDS progresses, the bone marrow starts to become full and immature blood cells begin circulating out into the bloodstream, generally resulting in patients who present with bone marrow failure. MDS can develop into AML over time. There are 6 main categories described for MDS which include:

- **Isolated del(5q):** characterised by a gene deletion which affects the development of red blood cells causing anaemia.
- **Excess blasts:** increased numbers of immature myeloid cells in the bone marrow or blood
- **Multilineage dysplasia:** at least 10% of two or more cells are abnormal i.e., red blood cells, white blood cells.
- **Single lineage dysplasia:** only one type of blood cell is abnormal.
- **Ringed sideroblasts:** at least 15% of immature red blood cells have developed a ring of iron around the nucleus.

- **Unclassifiable and not otherwise specified:** Used to define myelodysplastic syndromes that don't fit any of the defined above.

Myeloproliferative neoplasms (MPN):

MPN are chronic haem conditions characterised by clonal proliferation of one or more mature myeloid cells and include:

- **Myelofibrosis:** The bone marrow forms abnormal blood cells which causes scarring in the bone marrow, causing low blood counts and swelling of the liver and spleen.
- **Chronic myeloid leukaemia:** The bone marrow produces too many white blood cells, and the spleen can get very big
- **Polycythaemia vera:** The bone marrow produces too many red blood cells, with elevations in platelet and/or neutrophil counts also being relatively common. There is a risk of stroke as the blood becomes too thick to flow through blood vessels easily.
- **Essential thrombocythemia:** The bone marrow forms too many platelets, which increases the risk of stroke

A small number of which will transform to AML.

Chronic Myelomonocytic Leukaemia (CMML) and Juvenile Myelomonocytic Leukaemia (JMML): CMML and JMML are diseases characterised by development of abnormal monocytes and can express features of both MDS and MPN.

Mastocytosis

Mastocytosis are rare conditions caused by an excess number of mast cells gathering in the body's tissues. Mast cells are responsible for allergic reactions. There are two main types of mastocytosis. Cutaneous mastocytosis, which mainly affects children – where mast cells gather in the skin but are not found in large numbers elsewhere in the body. Systemic mastocytosis, which mainly affects adults – where mast cells gather in body tissues, such as the skin, internal organs and bones.

Lymphoid neoplasms

Lymphoid disease has been categorised in to 6 subgroups, defined as acute lymphoblastic leukaemia (ALL), Hodgkin lymphoma (HL), mature B-cell, mature T and NK cell neoplasm, plasma cell neoplasms and lymphoproliferative disorders and non-specific. All disease specific entities are included below along with their subtypes and cell lineage.

Cell lineage	Subgroup	Morphological description
Lymphoid	Acute lymphoblastic leukaemia (ALL)	Acute lymphoblastic leukaemia (ALL) NOS
		B-cell acute lymphoblastic leukaemia (B-cell ALL)
		T-cell acute lymphoblastic leukaemia (T-cell ALL)
	Hodgkin lymphoma	Classic Hodgkin lymphoma
		Nodular lymphocyte predominant Hodgkin lymphoma
	Lymphoproliferative disorders and non-specific*	Malignant lymphoma, NOS
		Immunoproliferative disease, NOS
		Leukaemia, NOS
		Lymphoid leukaemia, NOS
		Prolymphocytic leukaemia, NOS
		Lymphoproliferative disorder, NOS
		Post-transplant lymphoproliferative disorder, NOS
		Polymorphic post-transplant lymphoproliferative disorder
	Mature B-cell neoplasms	Burkitt lymphoma
		Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
		Diffuse large B-cell lymphoma (DLBCL) and other high grade
		Follicular grade 1 and 2
		Follicular grade 3
		Other follicular
		Hairy cell leukaemia
		Lymphoplasmacytic lymphoma (LPL) or Waldenstrom
		Mantle cell lymphoma (MCL)
		Marginal zone lymphoma (nodal, extranodal, MALT)
		Other mature B-cell neoplasms
		Splenic marginal
	Mature T-cell and NK-cell neoplasms*	Cutaneous T-cell lymphoma
		Other mature T-cell neoplasms
	Plasma cell neoplasms	Immunoglobulin deposition disease
		Myeloma
		Plasmacytoma

*Stubbed

Acute lymphoblastic leukaemia (ALL)

ALL is a clonal disease arising from lymphoid progenitors. These progenitors proliferate (multiply) a, causing bone marrow failure. Patients usually present with tiredness, easy bruising or bleeding and recurrent unexplained infections.

Hodgkin Lymphoma

HL are rare neoplasms of multinucleated Reed-Sternberg cells, which are derived from B-lymphocytes. Hodgkin lymphomas are sub-classified as either classical Hodgkin lymphoma (cHL; nodular, sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte-depleted) or nodular lymphocyte predominant Hodgkin lymphoma. Nodular lymphocyte predominant Hodgkin lymphoma has always been grouped with cHL but behaves more like an indolent lymphoma.

Mature B-cell lymphomas

Mature B-cell neoplasms are a group of highly heterogeneous diseases of B-lymphocytes, with 34 unique classifications described by the WHO and grouped according to 12 morphological subtypes for reporting, details of which are included below.

Burkitt lymphoma (BL):

BL is an extremely aggressive B-cell lymphoma originating from B-cells, is occasionally associated with the human immunodeficiency virus (HIV) and is associated with specific genetic abnormalities of the *C-MYC* gene.

Chronic lymphocytic leukaemia / small lymphocytic leukaemia (CLL/SLL):

CLL/SLL are slow growing diseases that affect lymphocytes. CLL/SLL are essentially the same disease, with one distinction, where the disease develops. When the majority of cancer cells appear in the bone marrow or peripheral blood then the disease is referred to as CLL, if however, the cells are mostly located in the lymph nodes then it is referred to as SLL.

Follicular lymphoma (FL):

FL is a relatively slow growing / indolent disease arising from B-lymphocytes which are a type of white blood cell that cluster together to form lumps in the lymph nodes or organs. Most present with advanced stage disease but are only treated if they are symptomatic as patients may live with FL for many years.

Mantle cell lymphoma (MCL):

MCL is a B-cell lymphoma with unique biological, pathological and clinical features. Most present with advanced stage disease with lymphadenopathy as well as splenomegaly and bone marrow infiltration. Most patients require treatment at diagnosis, but there is a marked variation as to how well patients respond.

Marginal zone:

Marginal zone lymphomas are types of slow growing (low-grade) non-Hodgkin lymphomas that develop from B cells. They are called marginal zone lymphomas because they develop in a particular region found at the edge of normal lymphoid tissues (collections of lymphocytes) called the marginal zone. There are three types of marginal zone lymphoma:

- MALT lymphoma (also known as extranodal marginal zone lymphoma) is the most common form of MZL and develops in lymphoid tissue outside lymph nodes, such as the parotid glands, stomach or lungs.
- Nodal marginal zone lymphoma (often called nodal MZL or NMZL) develops when abnormal B cells collect in lymph nodes, and is often treated in the same way as FL.
- Splenic marginal zone lymphoma occurs most often in the spleen and blood. It has been associated with hepatitis C virus infection.

Hairy cell leukaemia (HCL):

HCL develops because of too many B lymphocytes and is recognised by the cytoplasmic projections resembling hair (‘hairy cells’), disease involves the spleen, bone marrow, and peripheral blood. Patients often present with low blood counts and splenomegaly.

Waldenström's Macroglobulinaemia (WM) / Lymphoplasmacytic lymphoma:

WM Is a rare disease that affects the bone marrow and lymphatic tissue. WM has features of plasma cells and lymphocytes which is why is it also referred to as lymphoplasmacytic lymphoma. WM is defined by the overproduction of a paraprotein, or m – protein by B-lymphocytes, which can cause the blood to become thick and impair circulation.

Plasma cell neoplasms

Plasma cell neoplasms are diseases in which abnormal plasma cells form tumours in the bones or soft tissues of the body. Plasma cells develop from B lymphocytes (B cells), a type of white blood cell that is made in the bone marrow. Plasma cells make antibodies to fight bacteria and viruses, to stop infection and disease. When a single plasma cell becomes cancerous and divides, they continue to over-produce their own antibody, far more than normal plasma cells. This high level of antibody is called a paraprotein, or M - protein.

The following types of plasma cell neoplasms are:

- Immunoglobulin deposition disease
- Plasmacytoma – a single 'lump' of cells
- Multiple myeloma

Other haematological malignancies

Other HM are composed of Langerhans cell histiocytosis (LCH), histiocytic and dendritic cell neoplasms and neoplasms and leukaemias of ambiguous lineage. LCH cells are a type of dendritic cell that normally helps the body fight infection. Sometimes mutations develop in genes that control how dendritic cells function. These mutations may cause too many LCH cells to grow and build up in certain parts of the body, where they can damage tissue. There are other histiocytic and dendritic cell neoplasms also characterised by the accumulation of cells originating from dendritic cells or macrophages (immune cells). Neoplasms and leukaemias of ambiguous lineage are those diseases which fail to show commitment to either the myeloid, B-, or T-lymphoid lineages.

Transformations

Historically, it has been challenging for cancer registries to systematically capture the registration of multiple tumours, which is particularly true for haematological malignancies (HM) where patients may have relapsed disease, developed a secondary neoplasm or their disease has undergone progression or transformation.

To date there is no uniform definition of the transformation of haematological malignancies[1]. However, the basic principle of a transformation is that a tumour cell, subject to a complex combination of genetic mutations, can undergo a process of clonal evolution that profoundly changes the architecture of the cell and results in a transformation to a different tumour type[2]. Transformations are generally thought of as any slow-growing (low-grade) disease that changes into a faster-growing (high-grade) disease.

In the past, NDRS have captured transformation events as a separate primary disease registration when a new diagnostic group has emerged. However, following consultation with Laboratory Information Management System Suppliers and the Chair of the Royal College of Pathologists (Working Group on Cancer Services), alterations were made to the structure and contents of the Cancer Outcomes and Services Dataset (COSD) dataset. Such changes included the recording of transformation events, to conform to the recommendations provided by the European Network of Cancer Registration, published in February 2014[3]. These changes were reflected in COSD v9.0, released in April 2020; where the option was created to record a transformation event, affecting cancer registry data from 2018. This change in rules meant that a transformation is to be recorded if the first haematological malignancy transformed into a new morphological entity after a three-month window of the first registration. As such, only the first tumour's morphology and date of diagnosis are to be considered as incident for analysis and reporting.

To allow for greater consistency of reporting, the NDRS decided to create a lookup table of HM capable of transforming using guidelines developed by Gavin *et al* which offer additional coding parameters to the rules defined in the Haemacare manual[4]. Here, transformations events were defined using the International Classification of Disease Oncology (ICD-O) 3rd edition, first revision[5] and mapped back to ICD-O-2 descriptions of disease for patients diagnosed between 1995 and 2012, so that lower-grade / indolent diseases (slow growing) where the time to transformation can be measured in decades can included in our analysis.

To account for variation in the recording of diagnosis dates, which can be the date the diagnosis was confirmed at multi-disciplinary team meetings or signed off by the senior pathologist, a transformation event can be recorded up to 31 days before the precursor condition, or any time afterwards.

The two most common types of transformation are those to acute myeloid leukaemia and diffuse large B-cell lymphoma.

Transformations to acute myeloid leukaemia

AML emerges because of a complex series of genetic changes in a haematopoietic precursor cell. These changes typically alter the haematopoietic growth and differentiation (the process by which cells, tissue, and organs acquire specialised features) of cells, resulting in an accumulation of large numbers of abnormal, immature myeloid cells in the bone marrow and peripheral blood.

The Get Data Out project has defined transformations from both MDS and MPN, with a separate grouping for other myeloid neoplasms capable of transforming to AML. This group was separated to protect patient anonymity for rarer cases.

Table 1: Possible transforms to AML

Lineage	Precursor broad subtyping	Precursor subtyping
Myeloid	Chronic myelomonocytic leukaemia (CMML)	
	Mastocytosis	
	Myelodysplastic syndromes (MDS)	Myelodysplastic syndromes (MDS) unclassifiable and NOS
	Myelodysplastic syndromes (MDS)	Myelodysplastic syndromes (MDS) with excess blasts
	Myelodysplastic syndromes (MDS)	Myelodysplastic syndromes (MDS) with isolated del(5q)
	Myelodysplastic syndromes (MDS)	Myelodysplastic syndromes (MDS) with multilineage dysplasia
	Myelodysplastic syndromes (MDS)	Myelodysplastic syndromes (MDS) with ringed sideroblasts
	Myelodysplastic syndromes (MDS)	Myelodysplastic syndromes (MDS) with single lineage dysplasia
	Myeloproliferative neoplasms (MPN)	Chronic myeloid leukaemia (CML)
	Myeloproliferative neoplasms (MPN)	Essential thrombocythaemia (ET)
	Myeloproliferative neoplasms (MPN)	Myelofibrosis
	Myeloproliferative neoplasms (MPN)	Other myeloproliferative neoplasms (MPN)
	Myeloproliferative neoplasms (MPN)	Polycythaemia vera (PCV)
	Other myeloid neoplasms	
Other haematological malignancies	Neoplasms and leukaemias of ambiguous lineage	

MDS or MPN:

Our current understanding for the mechanisms which drive transformation from MDS or MPN to more aggressive AML are still poorly understood, in part due to the genetic heterogeneity of disease. AML is characterised by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. Transformations to AML from MDS are defined as a patient appearing with ≥20% myeloblasts in the bone marrow or peripheral blood.

Transformations to diffuse large B-cell lymphoma

Cell lineage	Transformation subtype	Precursor
Lymphoid	Richters transformation (Diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma)	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Diffuse large B-cell lymphoma (DLBCL), Hodgkin, and other high grade	Follicular lymphoma
		Marginal lymphoma
		Hodgkin lymphoma from other precursors

Richter's transformations:

Special consideration was given to patients who developed a DLBCL or less commonly HL in the context of background Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Leukaemia (SLL). Transformation is thought to occur because of dysregulation of signalling pathways. Please note that transformations to DLBCL or HL from other precursor conditions have been grouped together to protect patient anonymity.

Follicular lymphoma:

Transformation of follicular lymphoma is pathologically defined as the clonal progression of FL grade 1, 2 or 3a to DLBCL. Recent studies have indicated that low-grade follicular lymphomas typically express driver mutations not identified in the transformed disease, which would imply that follicular lymphomas are subject to several transformative processes during a patient's lifetime[7].

Transformation to diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma from other precursors

Any indolent lymphomas is capable of transforming to aggressive lymphomas, but are less common than FL.

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