National Cancer Registry Ireland **Cancer Trends**

Myeloproliferative Neoplasms and *Myelodysplastic Syndromes*

Case numbers and histological types

The World Health Organisation (WHO) 2008 classification of tumours of haematopoietic and lymphoid tissue[1] forms the basis of the HAEMACARE classification.[2] This subdivides these neoplasms into 25 main groups. Two of the groups involved – myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) – largely comprise conditions that (pre-2000) were not considered fully malignant neoplasms but are now recognised as such. Until recently, separate incidence and survival statistics have not been widely reported for MPN (except chronic myeloid leukaemias specifically) and MDS. This report presents the first comprehensive national statistics for these groups in Ireland.

The myeloproliferative neoplasms (MPN) are characterized by proliferation of one or more myeloid cell lineages, predominantly in the bone marrow. This results in increased numbers of normal granulocytes (granular white blood cells), erythrocytes (red blood cells) or platelets in peripheral blood.

Myelodysplastic syndromes (MDS) are another group of haematopoietic stem cell diseases. MDS are characterised by cytopenia (deficiency of one or more blood cell types), and dysplasia (abnormal development) in one or more of the major myeloid cell lines (blood cells derived from bone marrow). MDS are the most common precursors of leukaemia.

Table 1. Annual case numbers of myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) in Ireland

	Annual average cases			
Group	1994-99	2000-05	2006-12	Total
All haematological malignancies (HAEMACARE)	1,228	1,543	1,869	1,564
	100.0%	100.0%	100.0%	100.0%
MPN (total)	121	158	176	153
	9.9%	10.3%	9.4%	9.8%
MPN (excluding chronic myeloid leukaemia)	95	129	145	124
	7.7%	8.4%	7.7%	7.9%
MDS	78	106	147	112
	6.3%	6.9%	7.8%	7.2%

On average, 153 cases of MPN (124 excluding chronic myeloid leukaemias [CML]) and 112 cases of MDS were registered per year during the period 1994-2012 (*Table 1*). MPNs made up 9.8% of all haematological malignancies (or 7.9% for MPNs excluding CML), MDS 7.2%. The proportion of MDS rose over time, but the proportion of MPNs was more stable (or variable).

A detailed breakdown of specific morphologies within the MPN and MDS groups is given in *Appendices 1 & 2*, respectively. The most frequent morphological subtypes in the MPN group were chronic myeloproliferative disease, not otherwise specified [NOS] (average 49 cases per year 1994-2012), polycythaemia vera (37), essential thrombocythaemia (31) and chronic myeloid leukaemia, NOS (29 per year). Among MDS, myelodysplastic syndrome, NOS (83 cases per year) was the most common diagnosis.

See *Appendix 3* (p. 5) for technical details of the coding rules applied in categorising cases for analyses presented in this report.

Incidence rates and trends over time

Rates standardised to the European population standard are summarized in *Table 2*, by diagnostic group and diagnosis period.

Table 2. Age-standardised rates (per 100,000) of myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) in Ireland

	European age-standardised rates (95% CI)			
Group	1994-99	2000-05	2006-12	Total
(a) All haematological malignancies (HAEMACARE inclusions)				
Male rate	42.3	49.2	50.9	48.1
(95% confidence interval)	(41.0-43.6)	(47.9-50.6)	(49.8-52.1)	(47.3-48.8)
Female rate	28.8	32.0	33.8	31.8
(95% CI)	(27.8-29.8)	(31.0-33.1)	(32.9-34.7)	(31.3-32.4)
(b) MPN (total)				
Male rate	4.0	5.1	4.5	4.5
(95% CI)	(3.6-4.4)	(4.6-5.5)	(4.2-4.8)	(4.3-4.8)
Female rate	2.9	3.2	3.5	3.3
(95% CI)	(2.6-3.2)	(2.9-3.6)	(3.2-3.8	(3.1-3.4)
(c) MPN (excluding chronic myeloid leukaemia)				
Male rate	3.0	4.0	3.7	3.6
(95% CI)	(2.6-3.3)	(3.6-4.4)	(3.3-4.0)	(3.4-3.8)
Female rate	2.3	2.8	2.9	2.7
(95% CI)	(2.1-2.6)	(2.5-3.1)	(2.6-3.1)	(2.5-2.9)
(d) MDS				
Male rate	2.7	3.6	4.3	3.6
(95% CI)	(2.3-3.0)	(3.3-4.0)	(3.9-4.6)	(3.4-3.8)
Female rate	1.7	1.8	2.2	1.9
(95% CI)	(1.4-1.9)	(1.6-2.0)	(2.0-2.4)	(1.8-2.0)

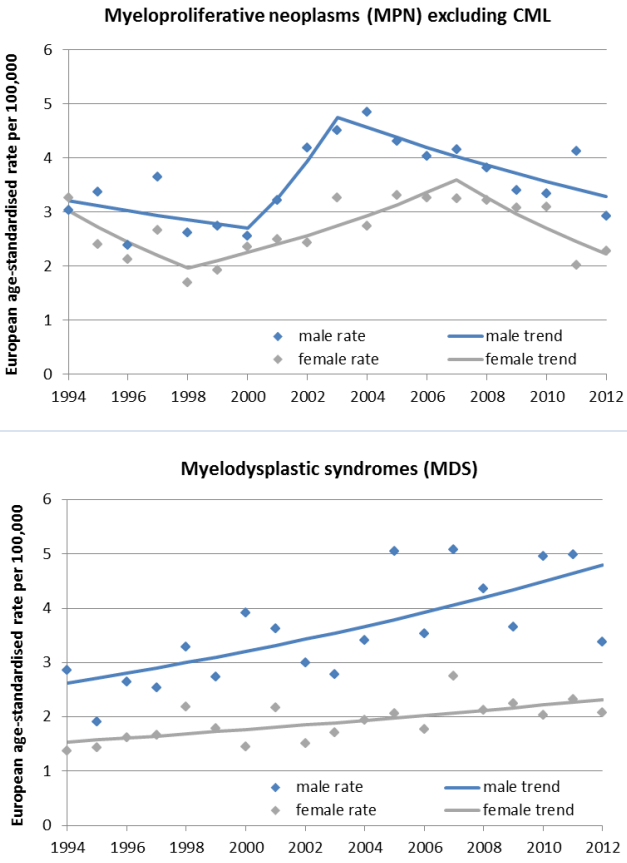
European age-standardised rates (EASRs) of MPN averaged 4.5 cases per 100,000 males and 3.3 cases per 100,000 females per year during 1994-2012 as a whole (*Table 2b*). MPN excluding chronic myeloid leukaemia averaged 3.6 and 2.7 cases per 100,000, respectively (*Table 2c*). Rates of MPN in the most recent diagnosis period (2006-2012) suggested no clear trend over time among males but some increase among females (*Table 2b-c*).

EASRs of MDS averaged 3.6 cases per 100,000 males and 1.9 cases per 100,000 females per year during 1994-2012. Both sexes showed evidence of an increase in MDS rates between successive diagnosis periods (*Table 2d*).

A more detailed analysis of trends (annual rates of change assessed by Joinpoint analysis)[3] is presented in *Figure 1*. This suggests a complex trend for MPN (excluding CML), with an initial decrease in rates during the 1990s followed by an increase then a subsequent decrease. Overall, for 1994-2012 as whole, there was no single significant trend for this group: an annual rate of change averaging +1.2% (95% CI -0.5% to +3.0%) in males, +0.9% (95% CI -0.9% to +2.7%) in females. In contrast, MDS showed more straightforward trends, with significant average annual increases in both males (+3.4%, 95% CI +1.6% to +5.2%) and females (+2.3%, 95% CI +1.0% to +3.6%).

These trends should be interpreted cautiously, however, as they may in part reflect under-diagnosis, under-reporting or under-registration of some conditions in earlier years.

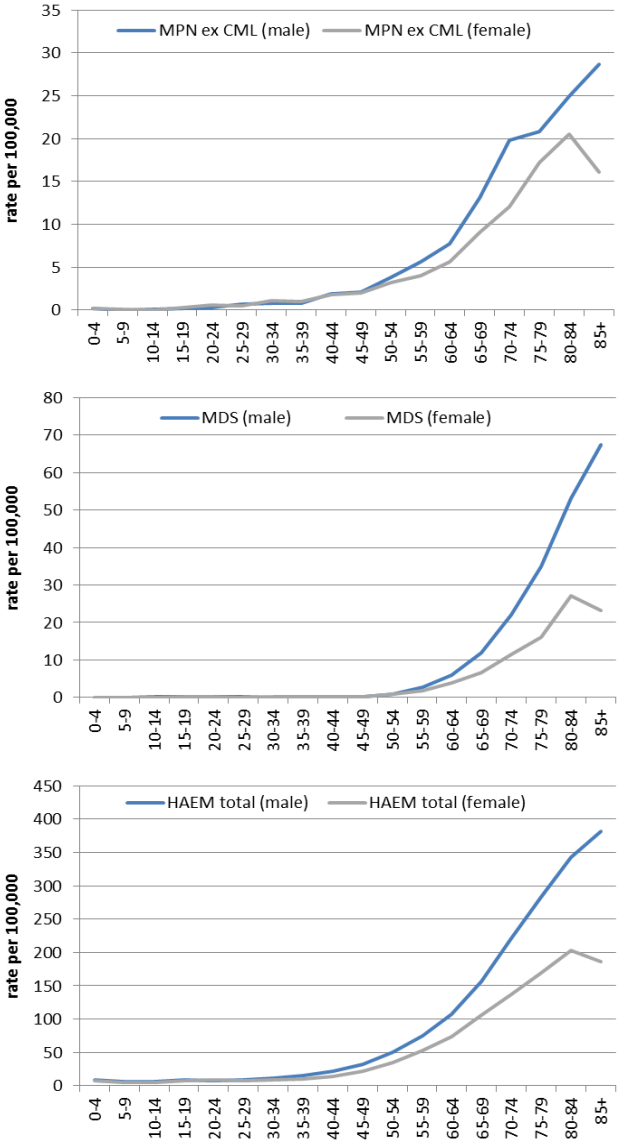
Figure 1. Trends in rates of myeloproliferative neoplasms and myelodysplastic syndromes in Ireland, 1994-2012



Age at diagnosis

Figure 2 summarises the age-profile of MPN and MDS cases. Rates were highest in the oldest populations, especially for MDS. The median age at diagnosis for MPN as a whole (67 years) and MPN excluding CML (68 years) was similar to that for haematological malignancies overall (67 years), but median age for MDS was higher (76 years).

Figure 2. Age-specific rates of myeloproliferative neoplasms and myelodysplastic syndromes in Ireland, 2006-2012



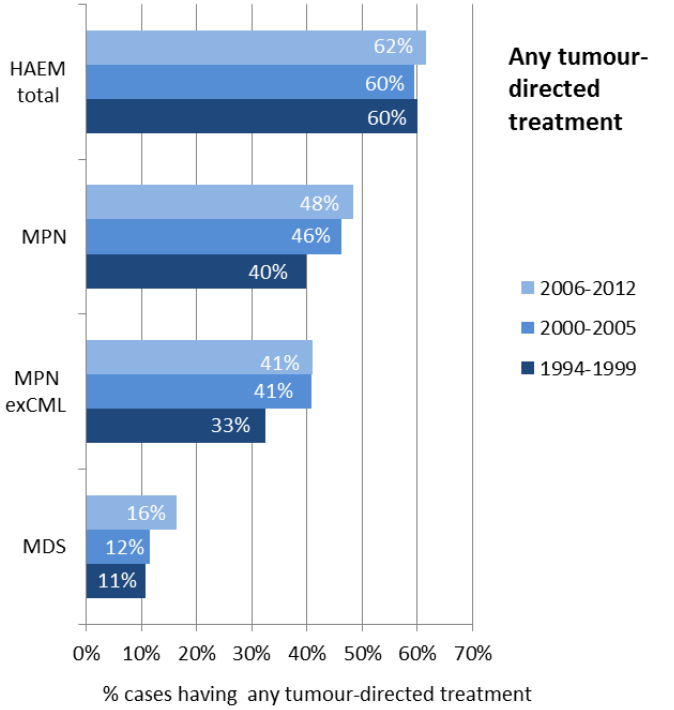
International variation in incidence

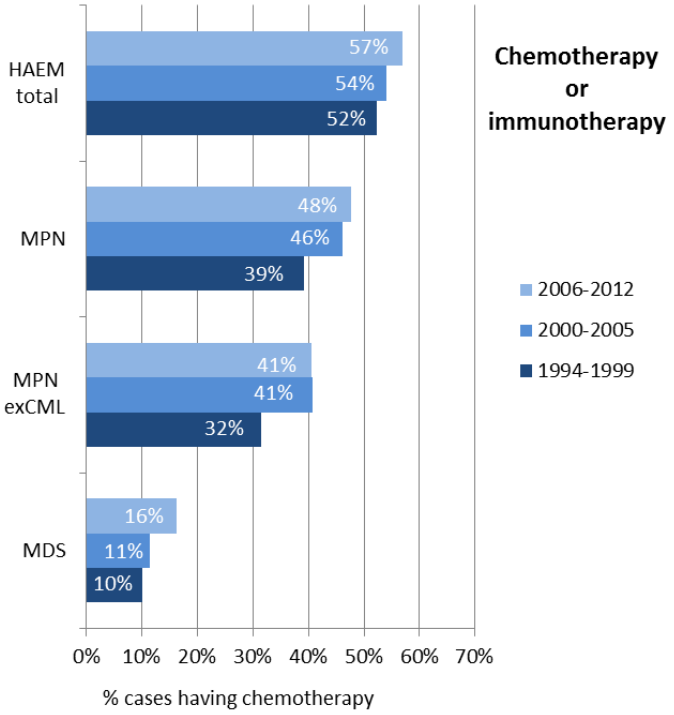
International comparisons of MPN and MDS incidence are not straightforward, because of geographic differences in quality of morphology coding or completeness of registration. Reported rates in the UK and Ireland for 2000-2002 averaged 2.08 cases per 100,000 (EASR) for MDS in 2000-2002 and 2.35 for MPN excluding CML, higher than for Europe as a whole (1.24 and 1.76 respectively).[4] However, MPN and MDS comprised only 4.2% and 0.8% of haematological cases for Europe (2000-2002)[4] compared with 9.8% and 7.2% for Ireland (1994-2012) in this report, suggesting under-registration of MDS at least.

Tumour-directed treatment

Treatments received within a year following diagnosis are summarised in *Figure 3*.

Figure 3. Tumour-directed treatment of patients with myeloproliferative neoplasms and myelodysplastic syndromes in Ireland, within a year of diagnosis, by diagnosis period. Treatment of all patients with haematological malignancies is included for comparison





For patients with MPN, 48% received tumour-directed treatment in the most recent diagnosis period (2006-2012), or 41% of patients with MPN other than chronic myeloid leukaemia. Treatment mainly involved chemotherapy or immunotherapy (<1% of patients had radiotherapy or non-diagnostic surgery). The proportion of patients treated showed little change between the two most recent diagnosis periods. A smaller proportion of patients appeared to be treated in the earliest period (1994-1999), but treatment data may have been less complete in earlier years.

A much smaller proportion of patients with MDS had tumour-directed treatment – only 16% during 2006-2012 (compared with 11-12% in earlier periods). Again, this was almost all chemotherapy or immunotherapy (<1% of MDS patients had radiotherapy and none had non-diagnostic surgery).

It is important to note, however, that these figures exclude any treatments given later during disease progression, thus some patients who did not receive tumour-directed treatment initially may have been treated a year or more after diagnosis. Some patients undergo 'watchful waiting' initially, i.e. monitoring of the patient's condition without giving any treatment until signs or symptoms appear or change. Likewise, these treatment figures do not include treatments that are purely aimed at alleviating symptoms, e.g. phlebotomy to remove excess blood cells or platelet apheresis to remove excess platelets from the blood in MPN patients.

For further details of treatment options for MPN and MDS, see:

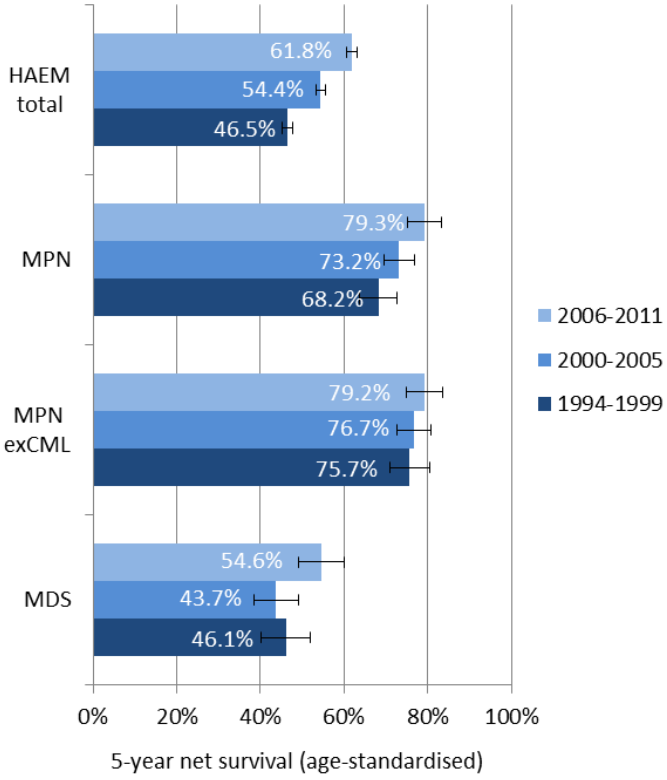
http://www.cancer.gov/types/myeloproliferative/patient/chronic-treatment-pdq#section/_28

http://www.cancer.gov/types/myeloproliferative/patient/myelodysplastic-treatment-pdq#section/_92

Survival

Net survival is the survival of patients having corrected for other causes of death (by comparison with the general population of the same age and sex).[5] Survival of patients diagnosed with MPN or MDS is summarised in *Figure 4* for three diagnosis periods. These figures are based on the first malignancy in each patient (i.e. exclude patients for which MPN or MDS followed an earlier diagnosis of a different or similar malignancy).

Figure 4. Five-year net survival of patients with myeloproliferative neoplasms and myelodysplastic syndromes in Ireland, by diagnosis period. Survival of all patients with haematological malignancies is included for comparison



For MPN, 5-year net survival averaged 79% in the most recent period, both overall and if chronic myeloid leukaemia is excluded. Survival for MPN as a whole, and haematological malignancies as a whole, improved significantly between all successive diagnosis periods (based on statistical models adjusted for age and length of follow-up). Survival for MPN excluding CML showed no significant change between 1994-1999 and 2000-2005, but improved significantly in 2006-2011. Survival from MPN was higher than the average for all haematological malignancies (5-year net survival 62% 2006-2011).

For MDS, 5-year net survival averaged 55% in the most recent period (2006-2011), lower than for haematological malignancies as a whole. There was no significant improvement in survival between 1994-1999 and 2000-2005, but survival of 2006-2011 cases was significantly improved.

International variation in survival

Survival of patients with for haematological malignancies in Europe has recently been summarised as part of the EUROCARE-5 study.[6] These figures excluded Ireland and some other countries because available data did not cover a sufficiently long diagnosis period.

For Europe as a whole, age-standardised 5-year relative survival for MPN patients excluding chronic myeloid leukaemia increased from 70.3% for 1997-1999 to 74.9% for 2006-2008, with a statistically significant trend overall. Chronic myeloid leukaemia also showed a significant upward trend in 5-year survival, from 32.3% for 1997-1999 to 54.4% for 2006-2008. Combined figures for the full MPN grouping were not presented.

Equivalent trends for MDS survival could not be assessed by EUROCARE-5, because of geographic variation in coding or completeness, but 3-year relative survival estimates showed no change between 2003-2005 (48.9%) and 2003-2005 (48.8%).

Mortality trends

Because the coding and classification of these tumours have changed over time, and because death may result from progression to other malignant conditions including acute leukaemias, trends in deaths and mortality rates from MPN and MDS cannot reliably be assessed and are not presented here.

References

[1] Swerdlow SH, Campo E, Harris NL *et al*. 2008. *WHO classification of tumours of haematopoietic and lymphoid tissues*. Lyon, International Agency for Research on Cancer.

[2] HAEMACARE Working Group. 2010. Manual for coding and reporting haematological malignancies. *Tumori* 2010; 96: i-A32.

[3] Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000; 19: 335-351.

[4] Sant M, Allemani C, Tereanu C *et al*. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood* 2010; 116: 3724-3734.

[5] Pohar Perme M, Stare J, Estève J. On estimation in relative survival. *Biometrics*. 2012; 68: 113-120.

[6] Sant M, Minicozzi P, Mounier M *et al*. 2014. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. *Lancet Oncology* 2014; 15: 931-942.

Appendix Table 1. Morphology breakdown of cases of myeloproliferative neoplasm (MPN) in Ireland

		Annual average cases			
Morphology		1994-1999	2000-2005	2006-2012	Total
	Including CML:				
M-9863/3	Chronic myeloid leukaemia, NOS	26	29	30	29
M-9875/3	Chronic myelogenous leukaemia, BCR/ABL +ve	0	0	1	1
subtotal		26	29	31	29
	Excluding CML:				
M-9740/1	Mastocytoma, NOS	0	1	1	<1
M-9740/3	Mast cell sarcoma	0	0	<1	<1
M-9741/3	Malignant mastocytosis	<1	<1	1	<1
M-9742/3	Mast cell leukaemia	<1	<1	<1	<1
M-9950/3	Polycythaemia vera	38	36	36	37
M-9960/3*	Chronic myeloproliferative disease, NOS	26	58	60	49
M-9961/3	Myelosclerosis with myeloid metaplasia	3	4	11	6
M-9962/3	Essential thrombocythaemia	28	30	35	31
M-9963/3	Chronic neutropholic leukaemia	0	0	0	0
M-9964/3	Hypereosinophilic syndrome	0	0	1	<1
subtotal		95	129	145	124
total		121	158	176	153

*M-9960/3 includes cases originally coded as M-9975/1 (myeloproliferative disease, NOS) – these are now codable as M-9960/3 according to the January 2010 World Health Organization update of the ICD-O-3 coding scheme.

Appendix Table 2. Morphology breakdown of cases of myelodysplastic syndrome (MDS) in Ireland

		Annual average cases			
Morphology		1994-1999	2000-2005	2006-2012	Total
M-9980/3	Refractory anaemia	7	9	7	8
M-9982/3	Refractory anaemia with sideroblasts	6	5	5	6
M-9983/3	Refractory anaemia with excess blasts	3	8	12	8
M-9984/3	Refractory anaemia with excess blasts in transformation	1	1	<1	1
M-9985/3	Refractory cytopenia with multilineage dysplasia	0	1	18	7
M-9986/3	Myelodysplastic syndrome with 5q deletion	0	<1	1	1
M-9987/3	Therapy related myelodysplastic syndrome	0	0	<1	<1
M-9989/3	Myelodysplastic syndrome, NOS	61	82	103	83
Total		78	106	147	112

Appendix 3 Technical note on coding

Morphologies and behaviour used to classify cases in *Tables 1-2* , *Figures 1-4* and *Appendices 1-2* follow the January 2010 update of ICD-O-3, including recodes where appropriate. MPNs include cases originally coded to 9975/1 (lymphoproliferative disorder, NOS), now recoded to 9960/3 (chronic myeloproliferative disease, NOS). Incldence and survival figures presented for haematological malignancies as a whole ("HAEM total" group) exclude morphologies 9765/1 (monoclonal gammopathy of undetermined significance), 9766/1 (angiocentric immunoproliferative lesion), 9768/1 (T-gamma lymphoproliferative disease) and 9769/1 (immunoglobulin deposition disease), which are not included in the HAEMACARE classification. Morphology 9767/1 (angioblastic immunopathy) is recoded to 9705/3 (angioblastic T-cell lymphoma) and morphologies 9751-9753/1 (Langerhans cell histiocytosis) are recoded to 9753/3, and included in the "HAEM total" group.