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Treatment and survival for non-Hodgkin's lymphoma: Influence of histological subtype, age, and other factors in a population-based study (1999–2001)

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ABSTRACT

Aims: This population-based study investigates the use of chemotherapy and radiotherapy for non-Hodgkin's lymphoma (NHL) treatment in clinical practise generally, and for specific histologies, and identifies factors associated with treatment and survival.

Methods: Data for NHL patients, diagnosed during 1999–2001, were obtained from the National Cancer Registry (Ireland). Multivariate models were analysed on survival and treatment.

Results: 45–77% of patients received chemotherapy, 22–34% of patients received the radiotherapy, depending on the histology. Patients aged <65, married, with early stage B-cell aggressive disease were more likely to receive chemotherapy($P < 0.05$). Patients >65 or with advanced stage were less likely to receive radiation ($P < 0.05$). Survival was poorer in older($P < 0.001$) and unmarried patients ($P < 0.05$), and those with B-cell aggressive lymphoma($P < 0.001$). Patients who received chemotherapy and radiation had lower hazard ratios.

Conclusions: Overall, the use of chemotherapy and radiation in this European population was similar to the findings in the US where older patients received treatment less often. However, the age disparity here was greater than that in the US.

1. Introduction

Incidence rates of non-Hodgkin's lymphoma (NHL) in developed countries have increased since the 1960s.[1] While mortality rates initially rose, mirroring the trends in incidence, in recent years they have begun to stabilise. These patterns suggest that the outlook for NHL patients has improved over time, which is reflected in the increased survival rates reported in many countries.[2]

NHL encompasses a heterogeneous array of haematological malignancies. Indolent lymphomas can have a prolonged disease course.[3] In contrast, aggressive lymphomas proliferate quickly and, if untreated, can be rapidly fatal.[4] Other than histological subtype and stage, factors associated with survival are not firmly established. Studies suggest poorer survival among elderly patients,[5] those with a high international prognostic index (IPI) score,[6] and those with co-morbidities, due to poor performance status.[7] However, a few studies have been population-based; most are clinical series, which may suffer from selection biases and lack generalisability.

The stabilisation in mortality is likely attributable to treatment improvements (combination chemotherapy, *etc.*), coupled with advances in diagnostic tools (*e.g.* PET scans).[4,8–10]

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The optimal treatment of NHL is complex.[9] Radiotherapy can be curative in early stage indolent lymphoma.[10] Chemotherapy (with/without radiotherapy) can be effective against rapidly proliferating aggressive lymphomas.[4]

The extent to which therapeutic advances have disseminated into clinical practise is unclear. A recent population-based study of patients diagnosed in 1999 in the USA, based on Surveillance Epidemiology and End Results (SEER) data, found that the immunotherapy, rituximab, was administered to approximately 15% of the patients.[11] Together with the rates of chemotherapy (>70% of those with aggressive subtypes) and radiotherapy (23% of those with indolent subtypes), this suggests a relatively widespread adoption of newer therapies in the US. Similar data for European populations at the subtype level are lacking.

A range of clinical and non-clinical characteristics can influence how likely a patient is to receive cancer therapy.[11,12] As regards NHL, population-based data on patterns of care are limited to the aforementioned SEER-based study,[11] and a Dutch study of co-morbidity.[7] In the US study, stage and systemic symptoms at diagnosis were strongly associated with treatment receipt. After adjustment for these factors, the elderly patients were significantly less likely to receive treatment.[11]

We describe a population-based analysis of patterns of care and survival in a large European series of NHL patients. We investigate the use of chemotherapy and radiotherapy in clinical practise overall, and according to histology, and explore factors associated with both treatment receipt and survival.

2. Patients and methods

The information on NHL patients was abstracted from the National Cancer Registry, Ireland (NCRI), which records data on all cancer patients diagnosed within the Republic of Ireland (www.ncri.ie). Cancer registration in Ireland is voluntary. The majority (97.5%) of registrations are made by tumour registration officers (TRO), the remainder from death certificates (2%), and general practitioners (<0.5%) (NCRI, unpublished data). The TROs, qualified nurses, are based nationwide, each responsible for gathering data from one or more hospitals and other sources (hospices, nursing homes, *etc.*). They collate and abstract data from sources including pathology and haematology laboratories, radiotherapy clinics, hospital in-patients systems and medical records departments. Monitoring and quality control of the registration process is carried out centrally. For each registration, clinical (*e.g.* tumour site (ICD10), morphology (ICD-O), *etc.*), non-clinical (*e.g.* date of birth, sex, *etc.*), and treatment (*e.g.* ICD9-CM, date, *etc.*) details are recorded. When available, clinical and/or pathological TNM stage data are recorded. Registration completeness is estimated to be 98% (NCRI unpublished data).

All men and women aged at least 20 years, diagnosed with histologically confirmed NHL between 1999 and 2001, were included (ICD-O2 codes M9590-M9595 and M9670-M9714).[13] Patients were excluded either when diagnosis was made by death certificate only or at autopsy. NHL occurring as a second malignant cancer (other than when non-melanoma skin was the first primary), or simultaneously with another cancer, was also excluded.

Cases were classified by receipt of: (1) any chemotherapy, (2) any radiotherapy, and (3) surgery approximately within one year of diagnosis. Since we aimed to investigate treatment and survival accounting for the heterogeneity in management by histological subtype, we included all subtypes, grouped into treatment-based categories: B-cell aggressive (large cleaved cell, diffuse large B-cell, Burkitt's and lymphoblastic lymphoma), B-cell indolent (marginal zone, follicular, small lymphocytic and MALT lymphomas), other (angiocentric T-cell, peripheral T-cell, pleomorphic small cell, angioimmunoblastic T-cell, pleomorphic medium and large cell (Ki1+), hepatosplenic gamma delta T-cell, cutaneous T-cell, mycosis fungoides and mantle B-cell) and a group comprising unspecified lymphomas, non-Hodgkin's Lymphoma-not otherwise specified (NHL-NOS). This classification was consistent with that used in the previous analyses.[11] We formed anatomic site categories based on the ICD-02 codes. The staging categories were based on the 4th edition of the TNM system.[14]

The patients were followed-up till death or the end of December 2002, whichever was sooner giving a maximum follow-up of four-years. The date and cause of death were ascertained by linkage to the Central Statistics Office national mortality statistics. Statistical analyses were carried out using Stata version 8.0. Logistic regression models assessed factors associated with the receipt of: (1) chemotherapy and (2) radiation. The factors considered for inclusion in the models included: age, sex, marital status, stage, health board and year of diagnosis. An interaction between the stage and histology was observed, which was fitted by an 8-level variable with two stage levels for each category of histology (stages I–III; stage IV/unknown). Observed and adjusted percentages of patients receiving each treatment are presented in addition to the odds ratios obtained from the regression analyses, adjusted for gender and factors significantly related to receipt of therapy, according to the likelihood ratio tests. Survival analyses for all-cause, cause-specific (NHL) and (any) cancer mortality were undertaken using the Cox regression models. Models were similar so only all-cause mortality is presented. Wald-type F statistics was used to assess statistical significance of each factor to the multivariate models. Two-sided P-values <0.05 were considered statistically significant.

3. Results

3.1. *Characteristics of cases*

This analysis included 1257 cases, among which 53% were males and 47% were females. 32% of patients had B-cell aggressive tumours, 15% B-cell indolent tumours, 8% other histological sub-types, and 46% NHL-NOS. Table 1 shows, by histology, the distribution of cases for a range of clinical and non-clinical characteristics. The median age at diagnosis was higher for women than men (64 *versus* 62 years) and lower among patients with 'other' and B-cell indolent lymphomas (56 and 60 years, respectively) than those with other histologies. The proportion of patients with stage I disease was similar across the histological groups (24–28%), while stage IV disease was most common among those with B-cell aggressive or unspecified lymphomas. The proportion of pa-

Table 1 – Clinical and non-clinical factors by histological group (%[a]) (N = 1257)

Characteristic	B-cell aggressive (N = 396)	B-cell indolent (N = 184)	Other (N = 97)	NHL, NOS (N = 580)
Age				
<50	23	29	38	20
50–64	28	32	25	30
65–74	24	27	16	25
⩾75	25	13	22	25
Gender				
Female	45	47	43	49
Male	55	53	57	51
Marital status				
Other	40	40	39	42
Married	60	60	61	58
Dead at December 2002	54	25	32	48
Stage[b]				
I	24	27	24	28
II	23	15	9	14
III	17	28	13	15
IV	22	16	10	29
Unknown	14	14	43	21
Site at presentation (ICD-O2 codes)				
Lymph nodes (C77.0–C77.9)	56	82	30	56
Gastrointestinal Tract (C15.4–C26.9)	15	3	3	17
Oro/nasopharynx (C00.0–C14.0)	11	8	1	7
Skin (C44.1–C44.9)	1	3	64	3
Other	17	5	2	16
Health board				
Eastern	37	42	34	35
Midlands	5	3	3	6
Mid-Western	8	5	7	12
North-Eastern	8	7	11	7
North-Western	6	4	5	6
Southern	15	14	19	11
South-Eastern	11	11	12	12
Western	10	13	8	12
Treatments received[c]				
Chemotherapy	72	63	40	65
Radiotherapy	33	27	19	28
Chemo- and radiotherapy	24	13	11	20
Surgery	21	21	25	20
Palliative treatment	16	20	18	22
No treatment	15	13	31	18
Year of diagnosis				
1999	28	30	30	30
2000	38	35	35	36
2001	34	34	35	34

a Percentages are rounded to the nearest whole number.
b Where available, pathological stage was recorded. If pathological stage was available, the clinical stage was used.
c Treatments are not mutually exclusive. Figures do not sum to 100%.

tients with unknown stage varied by histology: 14% B-cell lymphomas, 21% NHL-NOS and 43% other defined sub-types. The lymph nodes were the most frequent site of presentation, except among patients with 'other' lymphomas where the skin was most frequent, due to the inclusion of the T-cell cutaneous lymphomas. Fifteen precent of B-cell aggressive patients presented with lymphoma in the gastrointestinal tract, more often males (17%) than females (11%). A similar pattern was evident for B-cell aggressive tumours presenting in the oro- or nasopharynx (13% males, 8% females).

4. Treatment

The proportions of patients receiving surgery and palliative treatment were similar across the histological groups: 20–25% for surgery and 16–22% for palliative care (Table 1). The highest proportion of patients receiving no treatment was those with 'other' lymphomas (31%); the percentages for the other histologies were 13–18%. Among those with stages I–III disease, patients with B-cell aggressive lymphoma were more likely to have received radiotherapy than those with

other histologies (adjusted percentages; Table 2 – 79% of B-cell aggressive, 66% of B-cell indolent, 71% of NHL-NOS and 49% of other). For each histology, patients with more advanced stage (IV and unknown) were less likely to receive chemotherapy (Table 2), although this difference was less pronounced for NHL-NOS than for patients with specific histologies. The proportions of patients with B-cell aggressive or indolent tumours who received radiotherapy did not differ notably by stage (adjusted percentages: Table 2; B-cell aggressive – stages I–III: 33%; stage IV/unknown: 32%; B-cell indolent – stages I–III: 27%; stage IV/unknown: 23%). For other and unspecified lymphomas, receipt of radiotherapy was lowest among those with stage IV/unknown disease ('other' lymphomas (10%) and NHL-NOS (20%).

Multivariate logistic regression (Table 2, Model 1) indicated that patients aged 65+ were less likely to receive chemotherapy than those under 50; the odds ratio (OR) was reduced by almost 50% in patients aged 65–74 (OR = 0.57, 95% confidence interval (CI) = 0.40–0.84) and by 75% in those aged 75+ (OR = 0.24, 95%CI = 0.16–0.35). Patients with stages I–III B-cell aggressive disease were significantly more likely to receive chemotherapy than any of the other histology-stage combinations ($P < 0.001$). Married patients received chemotherapy more often than those who were unmarried (OR = 1.35, 95%CI = 1.04–1.76).

Age, histology-stage, and area of residence were significant predictors of radiotherapy receipt in the multivariate model (Table 2, Model 2). Patients aged <50 years at diagnosis ($P = 0.007$) were most likely to receive radiotherapy. Patients with stage IV and unknown NHL-NOS or 'other' lymphomas were significantly less likely to receive radiotherapy (OR = 0.24, 95%CI = 0.10–0.58, and OR = 0.49, 95%CI = 0.33–0.74). Those resident in the South-Eastern Health Board were twice as likely as those in the Eastern Health Board to receive radiotherapy (OR = 2.04, 95% CI = 1.37–3.04) (see Table 3).

4.1. *Survival analysis*

Due to significant interactions between stage, histological subtype and treatment, all-cause mortality for stages I–III and for stage IV/unstaged lymphomas was analysed separately. For both stage strata, the hazard increased with increasing age at diagnosis ($P < 0.005$). Compared with the youngest patients, those aged 65–74 and 75+ had approximately 2-fold and 3-fold increased risk of death, respectively. Among patients with stages I–III, men were more likely to die

Table 2 – Multivariate logistic regression analysis illustrating the factors that influenced the receipt of chemotherapy (model 1) and the receipt of radiotherapy (model 2)

Characteristic[a]	Model 1: receipt of chemotherapy					Model 2: receipt of radiotherapy				
	Obs. %	Adj. %[b]	P-value[c]	OR	95% CI	Obs. %	Adj. %[b]	P-value[c]	OR	95% CI
Age			<0.001					0.007		
<50	74	76		1.0		36	35		1.00	
50–64	76	76		1.00	0.69–1.45	28	27		**0.68**	**0.49–0.96**
65–74	65	65		**0.57**	**0.40–0.84**	24	22		**0.54**	**0.38–0.78**
⩾75	42	43		**0.24**	**0.16–0.35**	25	25		**0.61**	**0.42–0.89**
Histological group			<0.001					0.001		
B-cell aggressive, stages I–III	76	79		1.00		33	33		1.00	
B-cell aggressive, stage IV and unknown	64	66		**0.53**	**0.33–0.85**	32	32		0.95	0.61–1.50
B-cell indolent, stages I–III	68	66		**0.51**	**0.31–0.84**	28	27		0.73	0.45–1.18
B-cell indolent, stage IV and unknown	51	48		**0.25**	**0.13–0.47**	24	23		0.59	0.30–1.18
Other, stages I–III	53	49		**0.26**	**0.13–0.52**	27	24		0.66	0.32–1.36
Other, stage IV and unknown	29	27		**0.10**	**0.05–0.19**	12	10		**0.24**	**0.10–0.58**
NHL-NOS, stages I–III	69	71		**0.65**	**0.44–0.96**	32	32		0.94	0.66–1.34
NHL-NOS, stage IV and unknown	60	62		**0.44**	**0.29–0.66**	20	20		**0.49**	**0.33–0.74**
Marital status			0.02					0.90		
Other	58	63		1.00		27	27		1.00	
Married	70	69		**1.35**	**1.04–1.76**	29	27		1.02	0.78–1.33
Health Board			0.18					0.009		
Eastern	65	67		1.00		25	25		1.00	
Midlands	66	67		1.01	0.60–1.84	32	31		1.38	0.78–2.45
Mid-Western	63	63		0.84	0.53–1.32	27	26		1.06	0.66–1.70
North-Eastern	67	70		1.18	0.71–1.97	22	21		0.84	0.49–1.44
North-Western	51	56		0.9	0.38–1.12	17	17		0.63	0.32–1.23
Southern	61	63		0.86	0.58–1.27	28	27		1.10	0.74–1.66
South-Eastern	76	76		**1.61**	**1.02–2.54**	42	40		**2.04**	**1.37–3.04**
Western	65	66		0.97	0.63–1.48	31	30		1.31	0.86–2.0

Bold text indicates statistically significant observations.

a Models also adjusted for gender.

b Adjusted for all other variables in the model.

c *P*-values were obtained using Wald tests for the association of each investigated covariate with the receipt of treatment in each model.

Table 3 – Cox proportional hazards regression for all-cause mortality stratified by stage

Characteristic	Model 3: stages I–III			Model 4: stage IV and unknown stage		
	P-value[a]	Hazard ratio	95% CI	P-value[a]	Hazard ratio	95% CI
Age	<0.005			<0.005		
<50		1.00			1.00	
50–64		1.16	0.78–1.74		1.20	0.79–1.81
65–74		**2.08**	**1.43–3.02**		**1.85**	**1.23–2.79**
⩾75		**3.23**	**2.23–4.69**		**2.81**	**1.89–4.17**
Gender	0.05			0.83		
Female		1.00			1.00	
Male		**1.27**	**1.00–1.62**		1.03	0.80–1.33
Histological group	<0.005			<0.005		
B-cell aggressive		1.00			**1.00**	
B-cell indolent		**0.27**	**0.17–0.43**		**0.39**	**0.23–0.68**
Other		**0.48**	**0.27–0.86**		**0.32**	**0.18–0.57**
NHL, NOS		0.79	0.62–1.02		0.97	0.74–1.29
Marital status	0.03			0.01		
Other		1.00			1.00	
Married		**0.76**	**0.59–0.97**		**0.71**	**0.55–0.93**
Health board	0.22			0.25		
Eastern		1.00			1.00	
Midlands		0.99	0.58–1.69		1.53	0.90–2.61
Mid-Western		0.73	0.46–1.15		1.08	0.69–1.70
North-Eastern		1.24	0.81–1.90		1.08	0.64–1.82
North-Western		0.99	0.57–1.71		0.64	0.37–1.12
Southern		**1.46**	**1.03–2.07**		1.36	0.93–1.98
South-Eastern		1.02	0.66–1.55		1.23	0.82–1.85
Western		1.19	0.81–1.74		1.02	0.63–1.66
Receipt of chemotherapy	0.01			0.001		
No/unknown		1.00			1.00	
Yes		**0.71**	**0.55–0.93**		**0.64**	**0.49–0.83**
Receipt of radiotherapy	0.001			0.28		
No/unknown		1.00			1.00	
Yes		**0.64**	**0.49–0.84**		0.85	0.63–1.14
Year of diagnosis	0.008			0.14		
1999		1.00			1.00	
2000		1.02	0.78–1.34		0.92	0.68–1.23
2001		**0.67**	**0.50–0.90**		0.73	0.53–1.01

Model 3: stages I–III, Model 4: stage IV and unknown stage. Bold text indicates statistically significant observations.
a *P*-values were obtained using Wald tests for the association of each investigated covariate with the receipt of treatment in each model.

than women (Hazard Ratio (HR) = 1.27, 95%CI = 1.00–1.62). The hazard was higher among patients with B-cell aggressive lymphoma than for other histologies ($P < 0.005$ in both strata). Married patients had significantly better survival than unmarried patients ($P < 0.05$). Chemotherapy receipt was associated with a decreased hazard (HR = 0.71, 95%CI = 0.55–0.93 and HR = 0.64, 95%CI = 0.49–0.83 for stages I–III and stage IV/unknown stage, respectively). Radiation receipt was significantly related to the risk of death for stages I–III NHL ($P = 0.001$). For stage IV/unknown stage, the hazard ratio associated with radiotherapy receipt was reduced, but not significant.

5. Discussion

In this population-based analysis, age, histology and stage predicted treatment receipt; marital status was associated with chemotherapy and area of residence with radiotherapy. Age, histology, stage, gender, marital status and treatment predicted survival.

We included patients diagnosed during 1999–2001, the most recent years of diagnosis with complete follow-up, permitting investigation of recent treatment and survival patterns. Moreover, three years gave sufficient numbers in the less common histological groups to enable multivariate analyses. Cases aged 20 and older were included to ensure the exclusion of children with non-specific lymphomas (*e.g.* childhood NHL, M9590/3, can be categorised as 'lymphoma, NOS'[15]).

A few population-based studies have investigated treatment, survival, and associated factors for all lymphoma subtypes.[7,11] Most previous studies reported efficacy of particular treatments (*e.g.* CHOP, rituximab, *etc.*), described treatment or survival by subtype,[16–19] or were selected clinical series, potentially lacking generalisability. This study is the largest of treatment and survival in all incident NHLs, with bias minimised by inclusion of cases from a population-based registry.

We observed fewer B-cell aggressive and indolent patients than the recent SEER-US population-based study (32% and

15% *versus* 65% and 23%, respectively).[11] 46% of our cases were NHL-NOS compared to approximately 20% in SEER registries in the 1990s.[20] Our percentage of unspecified cases is not unique among cancer registries (*e.g.* 56% NHL-NOS in Northern Ireland 1999–2001 (Northern Ireland Cancer Registry, personal communication, 2006)). The complexity of diagnosing NHL and accurately assigning histology[21] undoubtedly contributes to the high proportion with unspecified histologies.[8,20] This is probably further exacerbated by the lack of centralisation and specialisation of oncology services in Ireland, at least in 1999–2001. In the SEER study,[21] the proportion with specified histologies was maximised through reabstraction from patient records and verification with treating clinicians. We did not have resources to conduct a similar exercise. However, the experience of tumour registration officers, and thorough registration procedures, including medical record review for registrations, suggest that such an exercise in Ireland would not substantially reduce the proportion of NHL-NOS; we believe the most of these cases were not histologically subtyped.

Population-based studies indicate B-cell aggressive lymphoma is the most common subtype, comprising at least 60% of cases.[7,11] In our study, it is likely that most NHL-NOS cases were B-cell aggressive lymphomas. The NHL-NOS and the B-cell aggressive cases were similar in terms of patient and tumour characteristics, likelihood of radiotherapy receipt, hazards ratios, and overall survival (not shown). Repeating the analysis combining NHL-NOS with B-cell aggressive cases did not appreciably alter the odds and hazards ratios (and confidence intervals) reported for B-cell aggressive lymphoma.

Overall, 65% of patients received chemotherapy and 28% radiotherapy, comparable to the US figures (69% and 26%, respectively).[11] Consistent with another previous report,[7] we observed significant stage-histology interactions in relation to treatment receipt. For example, for B-cell aggressive disease, there was a little difference in the odds of receiving radiotherapy by stage (0.95 for stage IV/unknown *versus* 1.0 for stages I–III), while for the 'other' histologies group, stages I–III were more than 2.5 times as likely to have radiotherapy (OR = 0.66) than stage IV/unknown (OR = 0.24). Early stage B-cell aggressive disease was most likely to be treated with chemotherapy or radiotherapy, an expected finding as, untreated, this subtype can rapidly advance into incurable disease.[4] Approximately 40% of our B-cell indolent patients with early stage (I or II) disease received radiotherapy, compared to 25% of early stage (locoregional) US patients.[11] As radiotherapy can be curative in early stage indolent disease,[9,10] further dissemination of radiotherapy into clinical practice is warranted in both countries.

We found that 13% of the B-cell indolent patients appeared to receive no treatment. Since indolent lymphomas with a low tumour burden are often followed through 'watchful waiting' and treated only when symptoms appear,[10] this percentage may be an overestimate.

Age was inversely associated with treatment receipt, a previously documented finding.[11,22] There may be a perception of decreased treatment tolerance, or a preference for avoiding treatment toxicity, in elderly patients.[23,24] Elderly patients may be equally reluctant to trade the quality of life for a prolonged survival[25] or more likely to reject the treatment.[26] We observed a stronger relationship with age for chemotherapy (OR 75+ *versus* <50 = 0.3) than radiotherapy (OR = 0.6), suggesting that there may be concerns about heightened chemotherapy-induced toxicity in elderly patients.

Treatment-related age disparities were slightly more pronounced in this European population than in the US.[11] Among patients aged 75+, chemotherapy was received by 43% in Ireland *versus* 60% in the US; for radiotherapy, the figures were 25% and 29%. These differences are partly because the US study included treatments received up to three years post-diagnosis, compared to one-year for the present study; in the US ~85% of chemotherapy and ~75% of radiotherapy were administered within one year post-diagnosis.

We found married patients received chemotherapy more often and had higher survival than unmarried patients, consistent with reports on other cancers.[27] We also found a non-significant increase in radiotherapy among married patients. The reasons underlying treatment (and survival) differences by marital status are unclear, but might include intervention or support from patients' families in treatment planning, or perception of a higher 'value' of life in patients with dependents.

The influence of co-morbidities on NHL treatment is unclear.[25] In the Netherlands, elderly patients with co-morbidities were less likely to receive chemotherapy.[7] In contrast, co-morbidities had no significant impact on treatment (or survival) in the US.[11] We had no information on co-morbid conditions. Since their prevalence usually increases with age,[7,25] the effect attributed to age in our analysis may reflect a combination of the effects of age and co-morbidities.

Cancer survival and treatment can vary according to the patients proximity to treatment centres, and local clinical practise.[28] We found that the Health Board of Residence predicted radio- but not chemotherapy receipt. This most likely reflects the geographical organisation of cancer services in Ireland in 1999–2001; radiation-oncology services were located in the south and the east (the areas with highest population density) while chemotherapy was more widely available.

Five-year relative survival for all NHLs in Ireland increased from 53.6% (95%CI = 48.7–58.5) for women and 43.7% (95%CI = 38.4–49.0) for men diagnosed during 1995–1997, to 54.7% (95%CI = 48.6–60.8) and 54.3% (95%CI = 46.9–61.7), respectively, for diagnoses during 1997–1999,[29] similar to what has been reported elsewhere.[2] The inverse relationships between age and stage and survival observed in the current study, and the magnitude of the hazard ratios for age (>75% higher among patients aged 75+ *versus* <50), are consistent with other population-based studies.[5,11,30] Histology strongly predicted survival, with hazards highest for B-cell aggressive lymphomas. This was consistent with the US-SEER study.[11] We observed lower hazards for 'other' and indolent lymphomas, despite the fact that 'other' included T-cell lymphomas for which five-year survival may be only 30%.[31] In the maximum four-year follow-up period, patients with indolent and some 'other' lymphomas may have remained asymptomatic – a potential explanation for the apparently lower mortality in these groups than for B-cell aggressive disease. Longer-term follow-up of the present (and the US) series will clarify this.

Chemotherapy receipt significantly increased survival and the effect was similar irrespective of the stage. Radiotherapy

receipt reduced the hazard, more so (and significantly) for stages I–III than stage IV/'unknown'. In the US-SEER, neither treatment significantly impacted on the hazard ratio.[11] The Dutch study found that chemotherapy reduced the hazard for B-cell aggressive disease and increased it for B-cell indolent disease, although these results were not statistically significant.[7] In our study, the treatment effects were less pronounced than those of stage and age.

Chemoradiotherapy can improve NHL survival.[9] In further analyses, we found a lower hazard among patients receiving both chemo- and radiotherapy (crude HR = 0.53) than for either treatment alone.

One aim of our study was to compare treatment and mortality between histological groups. To deal with the stage-histology interactions in the treatment analysis, we created stage groupings suitable for all histologies (*i.e.* stages I–III and IV/unknown). Since stage I B-cell aggressive lymphoma can be managed differently from stages II–IV and unknown stage disease,[4] and treatment of patients with other histologies may differ for stages I/II than the other (and unknown) stages,[9] we repeated our analyses stratifying by histology and using these stage categorisations within the strata. The findings were similar to those presented. We observed less treatment in advanced stage disease, higher chemotherapy among married patients, and less treatment in the elderly, excepting radiotherapy for other histologies, which was unrelated to age. Older patients and those with more advanced stage had significantly higher hazards. Chemotherapy receipt reduced the hazards.

In conclusion, almost half of this population-based series were not assigned a distinct morphology, suggesting that from diagnosis many patients receive suboptimal medical care, particularly as treatment depends so strongly on histology. Consistent with the US study, in this European population, histology, stage and age determined the likelihood of treatment. The impact of age on chemotherapy receipt, however, was slightly more pronounced in this than the US, series. The explanations for these age-related treatment patterns require further investigation. Since the population is ageing, if such age-based treatment disparities continue then NHL mortality rates are unlikely to improve. In contrast with the US study, marital status was associated with treatment – another socio-demographic disparity warranting further investigation. Mortality was lower among patients receiving cancer-directed therapy. Overall, these findings suggest that wider availability of specialist diagnostic procedures needed to ensure accurately assigned histology, and improved dissemination of treatment to all segments of the clinical and patient communities, and has the potential to improve NHL morbidity, survival and mortality.

Conflict of interest statement

None declared.

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