

# Parental Longevity and Prognosis in Elderly Patients with Aggressive Non-Hodgkin's Lymphoma

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In general, elderly patients with aggressive non-Hodgkin's lymphoma (NHL) have a less favourable prognosis than younger patients. Established predictors of prognosis in NHL are less discriminatory in the elderly, which is why there is a need for additional markers giving guidance on treatment decisions and prediction of outcome. The expected length of life of an individual in the general population is intimately associated with that of his/her parents. The aim of this study was to test the hypothesis that parental longevity is associated with improved outcome also among elderly patients with aggressive NHL and thus serves as an easily accessible non-disease associated prognostic factor. A total of 220 patients (> 60 years) with aggressive NHL with a median age of 71 years (range 60–86) were included. Patients were randomized to receive CHOP or CNOP (doxorubicin replaced with mitoxantrone) chemotherapy with or without the addition of granulocyte colony-stimulating factor. The median follow-up time was 56 (19–89) months. Parental data regarding age at death were available through parish offices for 425 (97%) parents. Relative risk (RR) of death (disease-specific and all-cause) associated with parental lifespan was assessed using Cox proportional hazards regression analyses, with adjustment for sex, age, prognostic index, symptoms, and calendar period of diagnosis. Maternal lifespan below (versus above) median was associated with a borderline significant reduced disease-specific (adjusted RR of death from NHL = 1.5; 95% confidence interval 1.0–2.1) and overall survival. The effect of maternal lifespan was somewhat more pronounced in patients receiving CHOP than CNOP treatment. Paternal lifespan below the median was associated with a borderline significant increased disease-specific (adjusted RR of death from NHL = 0.8 [0.5–1.0]) and overall survival. Combined, maternal, and paternal lifespan had little impact on survival. These effects were true also when CHOP and CNOP treated patients were analysed separately. Maternal and paternal lifespan may predict survival in NHL, but with opposing effects. At present parental age appears not to be a clinically useful predictor of prognosis in the elderly with aggressive NHL.

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Elderly patients with aggressive non-Hodgkin's lymphoma (NHL) constitute a heterogeneous patient population with regard to treatment tolerance as well as outcome. In general, the prognosis of elderly patients is considerably worse than that of younger patients (1–6). Factors contributing to a poor prognosis in this patient population include (a) decreased treatment tolerance due to comorbidity, organ dysfunction, altered drug metabolism, and irregular drug clearance rates, (b) biology of the disease, i.e. the accumulation of certain clinical and tumour-related risk factors, and (c) reluctance to diagnostic procedures and treatment. Besides age, the discriminatory power of easily accessible prognostic factors is reported to be less pronounced in elderly NHL patients compared with younger patients (3, 5, 7). Thus, despite numerous attempts to define the contribution of the above-mentioned factors to the age-related worsening of prognosis, there is a need for more

appropriate markers in elderly patients with aggressive NHL to help in predicting prognosis and to choose the treatment strategy.

In the general population, the length of life of an individual is significantly longer in those with long-lived parents (8). Similar findings have been reported in patients with specified diagnoses, e.g. coronary heart disease (9, 10). We have previously studied familial longevity and prognosis in Hodgkin's lymphoma (HL) (11). An increased lifespan of the previous two generations was associated with a significantly superior survival in 30 elderly HL patients. However, no prognostic discriminatory capacity of familial longevity was seen in younger patients (< 50 years). The aim of the present study was to assess the significance of parental longevity as a potential predictor of prognosis in a well-defined cohort of patients above 60 years of age with aggressive NHL.

## MATERIAL AND METHODS

### Patient characteristics and procedures

Between May 1992 and January 1997, 254 previously untreated Swedish patients > 60 years with newly diagnosed high-grade NHL were included in a Nordic multi-centre study comprising a total of 458 patients (6). After exclusion of patients born abroad (n = 20) and patients whose census records did not permit complete tracing of parents (n = 14), 220 patients were included in the final analysis. There were 119 males and 101 females with a median age of 71 years (range 60–86 years). Eligibility criteria were: age > 60 years of age, histologically diagnosed high-grade NHL according to the updated Kiel classification (12), clinical stage II–IV and WHO performance status ≤ 3. Exclusion criteria included HIV infection, history of low-grade lymphoma, overt central nervous system disease, congestive heart failure (New York classification III–IV), history of neoplasm, abnormal liver enzymes (aminotransferases and alkaline phosphatase > 2.5 times the upper limit, bilirubin > 50 µmol/l), renal insufficiency (serum creatinine > 300 µmol/l) and patients with any serious medical or psychiatric illness that would prevent informed consent and/or completion of protocol-prescribed treatment and follow-up.

Cases were entered on the basis of the local pathologist's diagnosis. However, a central panel reviewed all histology. Staging evaluation included initial haematological and chemical surveys, in addition to chest X-rays, computerized tomography of the abdomen, and bone marrow biopsy. Bulky disease was defined as a tumour mass > 5 cm. Patient characteristics are presented in Table 1. For further details see Ösby et al. (6).

### Treatment and response criteria

Patients were randomized in a bifactorial design to receive either cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)+G-CSF, CNOP+G-CSF, CHOP, or CNOP. The CHOP regimen was administered as follows: cyclophosphamide 750 mg/m<sup>2</sup> given intravenously on day 1, vincristine 1.4 mg/m<sup>2</sup> (maximum 2.0 mg) given intravenously on day 1, doxorubicin 50 mg/m<sup>2</sup> given intravenously on day 1 and prednisone 50 mg/m<sup>2</sup> given orally on days 1–5. The CNOP regimen was administered in an identical manner, with the exception that doxorubicin was replaced with mitoxantrone 10 mg/m<sup>2</sup> given intravenously on day 1. Both regimens were administered in 21-day cycles. Recombinant methHu G-CSF (filgrastim, 5 µg/kg, subcutaneously) was started on day 2 and continued for a maximum of 14 days. If the absolute granulocyte count exceeded 10 × 10<sup>9</sup>/l on day 11 or later, G-CSF was discontinued.

The WHO criteria were used (13) and all responses were evaluated by a national review committee (14). For further

**Table 1**  
Patients and parent characteristics

	n (%)
All patients	220 (100)
Sex:	
Female	101 (46)
Male	119 (54)
Age:	
60–69 years	74 (34)
70–79 years	122 (55)
80–	24 (11)
Clinical stage:	
II	86 (39)
III	63 (29)
IV	71 (32)
Increased LDH:	
Yes	139 (63)
No	81 (37)
Performance status (WHO):	
0–1	151 (69)
2–3	69 (31)
Extranodal disease > 1:	
Yes	27 (12)
No	193 (88)
B symptoms:	
Yes	101 (46)
No	119 (54)
Parental information available	425 (97)
Parental lifespan	median (range)
Fathers	75 (32–99)
Mothers	79 (23–98)

details see Ösby et al. (6). The median follow-up time for surviving patients was 56 months (range 19–89 months).

### Parental data

Through the Swedish civil registration system, the parents of each individual were identified and information regarding age at death was manually retrieved at parish offices. Complete data on parental lifespan were obtained for 425 (97%) of the 440 parents of the 220 patients. Eight parents were alive at the end of the observation period.

### Statistical analyses

Disease-specific mortality was defined as death from NHL or death related to treatment of the disease. All-cause mortality was defined as crude death, irrespective of cause. Disease-specific survival was defined as the time from date of randomization to death from NHL or death related to treatment of the disease. Overall survival was measured from the date of randomization to death from any cause. Survival curves were calculated according to the life table method (15). All tests for significance were two-sided (16).

We assessed the significance of maternal, paternal, and combined parental lifespan on the risk of dying using Cox's

proportional hazards regression analysis (17). Lifespan was analysed both as quartiles and as below or above the median in each group. The significance of parental longevity on the risk of dying following diagnosis of NHL was assessed in crude analyses as well as after adjustment for sex, age, age-adjusted international index (including clinical stage, lactate dehydrogenase and performance status), the presence or not of B symptoms, and calendar period of diagnosis. Models restricted to death from NHL as well as models of deaths from all causes were used. The study was approved by the Ethics Committee at Karolinska Institutet.

## RESULTS

Fifty-two percent of the patients reached complete remission. At follow-up 75/220 patients were alive. A total of 132 patients died from lymphoma or treatment-related complications. Thirteen patients died from other causes. As previously reported, mortality rate was the same irrespective of treatment with G-CSF, but patients treated with CHOP (adjusted RR of death from all causes = 1.8

[1.0–3.2]) had a better survival than those treated with CNOP (adjusted RR of death from all causes = 1.2 [0.7–1.8]; 6). Overall, male sex, high age, age-adjusted international index, and the presence of B symptoms were all associated with a marked or suggested increased risk of dying (Table 2).

Low (below the median) maternal lifespan was associated with an increased risk of dying, with regard to both deaths due to NHL and deaths from all causes, and in both adjusted and unadjusted analyses (adjusted RR of death from all causes = 1.4 [95% CI 1.0–2.0], Table 2, Fig. 1a). The effect of maternal lifespan on survival was similar for male and female patients, but somewhat more pronounced for patients treated with CHOP than with CNOP, although the interaction with treatment did not attain formal significance on a multiplicative scale ( $p=0.24$ ). Low (below the median) paternal lifespan was associated with a slight and borderline significant decreased risk of dying from NHL and from any cause, respectively, in both unadjusted and adjusted analyses (adjusted RR of death

**Table 2**

Relative risk (RR) of death with 95% confidence interval (95% CI) following diagnosis of non-Hodgkin's lymphoma ( $> 60$  years;  $n = 220$ ), according to cause of death and parental lifespan. Adjusted models include adjustment for all parameters in the table with (ref.) denoting reference categories

Parameter	RR (95% CI)			
	Disease-specific mortality		All-cause mortality	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Maternal lifespan:				
79 (median) or above	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Below 79 years	1.5 (1.1–2.1)	1.5 (1.0–2.1)	1.5 (1.1–2.0)	1.4 (1.0–2.0)
Paternal lifespan:				
75 (median) or above	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Below 75 years	0.7 (0.5–1.0)	0.8 (0.5–1.0)	0.7 (0.5–1.0)	0.8 (0.5–1.1)
Sex:				
Female		1.0 (ref.)		1.0 (ref.)
Male		1.6 (1.1–2.3)		1.7 (1.2–2.4)
Age at diagnosis (quartiles):				
60–67		1.0 (ref.)		1.0 (ref.)
68–71		2.2 (1.2–4.0)		2.1 (1.2–3.8)
72–76		2.5 (1.4–4.5)		2.5 (1.5–4.3)
77–86		2.3 (1.3–4.1)		2.6 (1.5–4.3)
Year of diagnosis (quartiles):				
1992–1993		1.0 (ref.)		1.0 (ref.)
1994		1.3 (0.8–2.0)		1.2 (0.8–1.9)
1995		1.4 (0.8–2.5)		1.4 (0.9–2.3)
1996		1.4 (0.8–2.5)		1.4 (0.8–2.4)
Age-adjusted international index:				
0–1		1.0 (ref.)		1.0 (ref.)
2–3		2.6 (1.8–4.0)		2.4 (1.7–3.6)
Presence of B symptoms:				
No		1.0 (ref.)		1.0 (ref.)
Yes		1.3 (0.9–1.9)		1.3 (0.9–1.9)

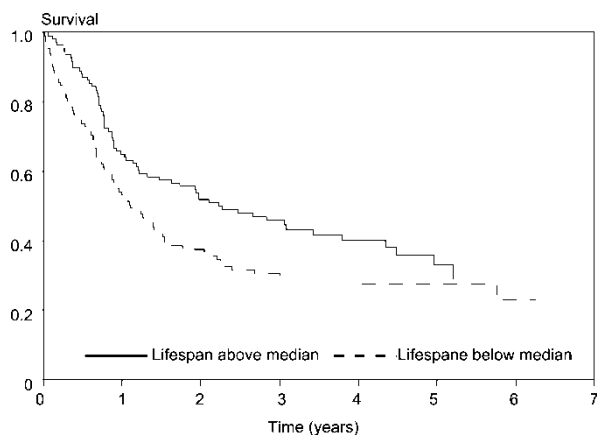


Fig. 1a. Survival following diagnosis of non-Hodgkin's lymphoma according to maternal lifespan.

from all causes = 0.8 [95% CI 0.5–1.1], Table 2, Fig. 1b). Gender or treatment regimen did not materially influence these results. When the combined effect of low maternal and low paternal lifespan was assessed, the overall risk of dying from NHL or from any cause, respectively, was relatively unaffected in patients with both parents' lifespan below the median (adjusted RR of death from all causes = 1.1 [95% CI 0.8–1.6]). There was no evidence that the effect of parental lifespan depended on the gender of the patient. The risk of developing granulocytopenia during the first treatment cycle, when all patients had received standard dosages of each treatment regimen, was also evaluated in relation to parental longevity. A low maternal lifespan was associated, if anything, with a slightly, non-significantly increased risk and a low paternal lifespan, on the other hand, with a slightly, non-significantly reduced risk of developing a granulocyte nadir count of less than  $0.5 \times 10^9/l$ .

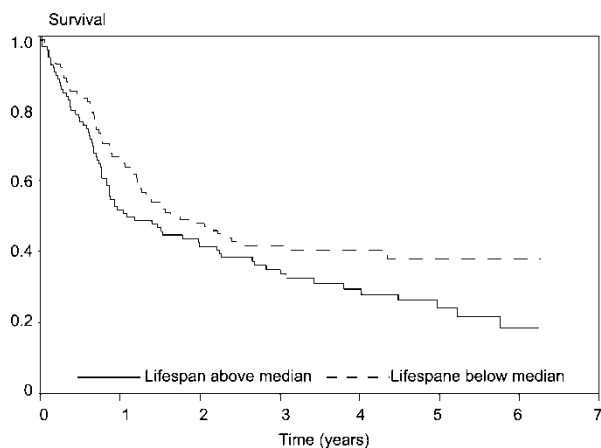


Fig. 1b. Survival following diagnosis of non-Hodgkin's lymphoma according to paternal lifespan.

## DISCUSSION

Elderly patients with aggressive NHL constitute a heterogeneous population as reflected by the great variability regarding tolerance of treatment and outcome (for references see 5, 7). This remains true despite a number of studies focused on the identification of patient- and disease-related factors of potential help in predicting prognosis and to choose the treatment strategy. As an attempt to relate outcome to a factor not directly associated with the patient or his/her disease, we previously assessed the prognostic discriminatory capacity of familial longevity in patients with HL. We observed a close relationship between longevity in the previous two generations and outcome in elderly HL patients, with an absence of association in the younger patients (11). The contribution of the second (oldest) generation was strong in that study, but in an enlarged cohort of elderly patients, parental longevity alone did not predict prognosis (18). The latter study was hampered by the fact that patients were diagnosed over more than two decades with the unavoidable heterogeneity in diagnostics and treatment and also included patients with limited disease (18). This could be circumvented in the present study of parental longevity in NHL focusing on elderly patients with advanced aggressive NHL included in a randomized multicentre study evaluating CHOP and CNOP chemotherapy, and the addition of G-CSF (6). The distribution of clinical characteristics, complete remission rates, disease-specific and overall survivals, and clinical predictors of prognosis are well comparable to those of previously published series of elderly NHL patients (3, 5). Thus, we believe the present series to be representative of aggressive NHL in the elderly. However, in interpreting the results from a parental longevity perspective it should be borne in mind that patients with any serious medical illness that would prevent completion of protocol-prescribed treatment and follow-up were excluded.

In this study, maternal longevity predicted an improved both disease-specific and overall survival. The tendency for this effect to be more pronounced among patients receiving CHOP (rather than CNOP) may be related to the superiority of the CHOP regimen with regard to both disease-free and overall survival (6). However, we also found that paternal lifespan influenced patient outcome, and that this effect, albeit of somewhat lower magnitude, counteracted that of maternal lifespan. Taken together, patients whose parents both had a lifespan below the median in each group had a risk of dying that was similar to patients whose parents had a longer lifespan. The relatively weak associations observed may also reflect the fact that patients had to survive to at least 60 to be included in the cohort and thereby may have overcome the adverse risk attributable to short parental lifespans. The association between parental longevity and treatment toxicity was of similar magnitude and direction as the association between parental longevity

and risk of death. Decreased treatment tolerance may therefore be one explanation for the underlying nature of the diverging effects on survival conferred by parental longevity.

In various studies a familial contribution to human longevity has been recognized, the nature of which is largely unknown (19–21). Similar findings have also been observed in patients with coronary heart disease (9, 10). This contribution does, however, not seem to be gender-specific and we have no explanation other than a potential random variation for the diverging effects of maternal and paternal lifespan in our cohort. This may be explored in prospective studies. However, at present parental age appears not to be a clinically useful predictor of prognosis in the elderly with aggressive NHL.

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