Acta Oncologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

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To cite this article: Siri A. Eikeland, Knut B. Smeland, Floortje Mols, Unn-Merete Fagerli, Hanne S. Bersvendsen, Cecilie E. Kiserud & Alexander Fosså (2021) Chemotherapy-induced peripheral neuropathy after modern treatment of Hodgkin's lymphoma; symptom burden and quality of life, Acta Oncologica, 60:7, 911-920, DOI: 10.1080/0284186X.2021.1917776

To link to this article: https://doi.org/10.1080/0284186X.2021.1917776

Published online: 27 Apr 2021.

ACTA ONCOLOGICA
2021, VOL. 60, NO. 7, 911–920
https://doi.org/10.1080/0284186X.2021.1917776

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ORIGINAL ARTICLE

Chemotherapy-induced peripheral neuropathy after modern treatment of Hodgkin's lymphoma; symptom burden and quality of life

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side effect of Hodgkin's lymphoma (HL) treatment. We aimed to describe the prevalence of CIPN associated symptoms in long-term HL survivors compared to controls, and determine associated factors, including impact on health-related quality of life (HRQoL).

Material and methods: A questionnaire, including EORTC QLQ-CIPN-20 for CIPN related symptoms and SF-36 for HRQoL, was completed by 303 HL survivors at a median of 16 years after diagnosis. CIPN results were compared to a normative population ($n = 606$). CIPN associated factors were identified by linear regression analysis.

Results: Total CIPN score and subscores were significantly higher in HL survivors compared to controls. In multivariate analysis of HL survivors, a number of comorbidities ($p < 0.001$) and female gender ($p = 0.05$) were significantly associated with more CIPN. No association with disease or treatment factors was found. In a multivariate analysis including survivors and controls, the number of comorbidities ($p < 0.001$) and caseness ($p < 0.001$) were significantly associated with more CIPN. In HL survivors higher CIPN score was associated with reduced HRQoL ($p < 0.001$).

Conclusion: HL survivors more than a decade after treatment report higher neuropathy-related symptom burden than controls, with a negative impact on HRQoL. Symptoms may be related to factors other than neurotoxic chemotherapy.

ARTICLE HISTORY
Received 17 January 2021
Accepted 12 April 2021

KEYWORDS
Adverse effects; chemotherapy-induced peripheral neuropathy; Hodgkin's lymphoma survivor; cancer survivorship

Introduction

Modern therapy of Hodgkin's lymphoma (HL) aims to balance cure rates and the risk of short and long-term adverse effects of treatment [1]. Late effects caused by chemotherapy and/or radiotherapy might persist months, years, and even decades after treatment, may be classified into physical [2,3], psychological [4], or social [5], and can affect the quality of life (QoL) [6,7] and life expectancy [8,9]. With a young age at diagnosis, the life-long risk of late effects in HL survivors may add to the risk of similar organ damage arising from aging, lifestyle factors, and other diseases developing during life.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common late effect after cancer treatment. Approximately one-third of all patients who receive neurotoxic chemotherapy report CIPN symptoms shortly after treatment, with prevalence falling over time [10]. Vinca alkaloids, including vincristine and vinblastine, are neurotoxic agents widely used in the treatment of lymphoma, but platinum-based regimens commonly used for relapse may also contribute to the risk of CIPN. In lymphoma treatment, vincristine is the most studied [11]. The severity of CIPN during and shortly after treatment with vincristine is dose-related [12,13], sometimes necessitating dose reduction or cessation of treatment. In general, CIPN is a predominantly sensory neuropathy [14,15], often in a 'glove and stocking' pattern with altered sensations in hands and feet such as tingling or numbness [16]. Motor neuropathy can manifest as muscle weakening or cramps and loss of fine motoric skills. Autonomic dysfunctions such as erectile dysfunction, constipation, and orthostatic hypotension are less frequently reported. With a lack of adequate preventive strategies and treatment [17,18], CIPN is a major cancer survivorship issue and leads to a significant increase in annual healthcare utilization and costs [19,20]. Most studies have evaluated CIPN in lymphoma patients during and shortly after treatment [12,13]. Only a few studies have assessed the prevalence of symptoms in long-term lymphoma survivors, and mainly after vincristine-based regimens used for non-Hodgkin's lymphoma. With follow up ranging

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from 3 to 9 years after treatment, these studies have reported high symptom burden and complications from CIPN [21,22]. These results may however not be transferable to long-term survivors of HL. First, HL patients are younger. Second, for decades, the ABVD regimen, containing doxorubicin, bleomycin, and dacarbazine together with vinblastine has been preferred for primary treatment of HL. Third, contemporary treatment strategies are risk-adapted, with patients in early stages receiving a limited number of cycles followed by consolidative radiotherapy [23,24]. Given these differences, separate studies in HL survivors are needed.

Our primary objective was to report CIPN related symptom burden in HL survivors more than 10 years after treatment, compared to an age- and gender-matched normative population, and to determine associations with the patient and treatment factors. Our secondary objective was to study how symptom burden affects health-related QoL (HRQoL).

Material and methods

Study population

In this national Norwegian multicenter study on late effects, HL survivors were identified by the Norwegian Cancer registry and invited to participate in a survey consisting of a comprehensive questionnaire, blood tests, clinical examination, and echocardiography. Patients treated for HL from 1997 to 2006, 8–49 years of age at diagnosis and alive by 31 December 2016 were eligible. The respondents gave written informed consent and non-respondents received a written reminder once. For the present substudy of CIPN, only survivors from the Health region South-East, Mid and North Norway were included. The study was approved by the Regional committees for medical and health research ethics South East (2016/2311).

Patients were treated by contemporary stage and risk-adapted strategies. From 1997 adult patients with classical HL stage I-IIA were treated with 2–4 courses of ABVD followed by modified involved-field radiotherapy 30–35 Gray (Gy) [25]. Treatment of nodular lymphocyte-predominant HL in stage I-IIA consisted of 30 Gy involved-field radiotherapy, or in isolated cases of stage IA disease, surgical removal only. For stage IIB-IV, most adults received 6–8 courses of ABVD, but from 1999 patients with an International Prognostic Score of 4–7 were treated with 6–8 courses of BEACOPP (bleomcyin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine) [26,27]. Radiotherapy could be given to sites of initial bulky mass or tumor residuals in doses of 30–40 Gy. From 1998 children $<$18 years at diagnosis were treated with OEPA (vincristine, etoposide, prednisone, and doxorubicin) and COPP (cyclophosphamide, vincristine, prednisone, and procarbazine) followed by involved-field radiotherapy 20–30 Gy [23,24]. Salvage chemotherapy usually included ifosfamide, gemcitabine, and vinorelbine (IGEV) [28], less often DHAP (dexamethasone, cytarabine, and cisplatin) or brentuximab vedotin, often followed by high dose therapy with autologous stem cell transplant (HDT-ASCT) and radiotherapy [29].

Diagnostic and treatment data

Data on histology, stage, and treatment were extracted from medical files. For each patient, the number of courses consisting of a planned dose of vincristine 1.4–1.5 mg/m^2, vinblastine 12 mg/m^2, brentuximab vedotin 1.8 mg/m^2, vinorelbine 20 mg/m^2, carboplatin AUC = 5 (max. 800 mg) or cisplatin 75–100 mg/m^2 was recorded; separately for each agent; combined for vincristine and vinblastine; for the total number of courses containing any of the mentioned neurotoxic compounds. For analyses of the cumulative burden of neurotoxic chemotherapy, the total sum of courses with neurotoxic drugs, calculated for each patient, was used either as a continuous variable or dichotomized at different levels ($>$2, $>$4, or $>$6) into low or high exposure to neurotoxic agents. Sensitivity analyses included patients receiving courses containing only vinblastine or vincristine. Exposure was assessed from the number of administered courses, and dose reductions or omissions of the neurotoxic component were not considered. No exact cumulative doses were calculated.

Patient-reported outcome measures

The mailed questionnaire encompassed socio-demographic, clinical, and lifestyle characteristics (weight, height, alcohol consumption, and smoking) along with published instruments addressing patient-reported outcomes. For the present study, these were SF-36 [30], an adapted version of the Self-administered Comorbidity Questionnaire [31], and EORTC QLQ-CIPN20 [32].

EORTC QLQ-CIPN20 is a 20-item questionnaire assessing our primary objective, sensory-, motor- and autonomic-(including erection in men) symptoms experienced in the last week, with severity measured on a Likert scale (1= not at all to 4 = very much). The neuropathy sum score (NSS) was based on 18 items. Question 19, problems with pedal use, was frequently not answered and question 20 on erectile dysfunction was only relevant to males, therefore these two items were excluded from the NSS [33]. Questions 1–6, 9, 10, and 18 address sensory symptoms and were summarized into a sensory subscore. Similarly questions 7, 8, 11–15 address motor symptoms, and questions 16 and 17 address autonomic symptoms, these were summarized into the motor and autonomic subscores, respectively. Erectile dysfunction, captured by question 20, was recorded separately in men. All scores were linearly transformed into 0–100 scales, with a higher score indicating more symptom burden [32]. Internal consistency assessed by Cronbach's α showed for the 18-item NSS $\alpha = 0.9$, sensory scale $\alpha = 0.8$, motor scale $\alpha = 0.8$, and autonomic scale $\alpha = 0.5$. Responses to questions 1–18 were also dichotomized into not having symptoms if scored 1 and 2 ('not at all'/'little') and having symptoms if scored 3 and 4 ('quite a bit'/'very much'), to report the percentage of patients with moderate to severe symptoms for each item.

For HRQoL, the secondary objective, scores from SF-36 were generated by summarizing the questions into four

physical and four mental basic health dimensions. The scores were transformed to a 0–100 score, with lower scores representing more disability and lower QoL. To correlate mental and physical health we used oblique rotations, with a mean score of 50 and standard deviation (SD) of 10, calculating physical composite score (PCS) and mental composite score (MCS) [34].

Reference data on peripheral neuropathy was available from the PROFILES registry on a general Dutch population ($n = 2702$) that used the EORTC QLQ CIPN20 questionnaire [33]. After exclusion of non-respondents we randomly drew age- and gender-matched controls ($n = 606$) in a 1:2 ratio.

Survivors and controls reported the presence of pre-specified comorbid conditions. HL survivors reported ever having been diagnosed with a disease, including secondary malignancies other than relapse of lymphoma, while the controls were asked if the diagnosis was present at the moment or during the last 12 months. The number of self-reported comorbidities for each individual was summarized into a total comorbidity score. Alcohol consumption was reported as glasses of alcohol (beer, wine, or liquor) per week. Smoking history was dichotomized into never/prior and current/occasionally.

Statistical analysis

Categorical data are presented as absolute numbers and percentages, continuous data represented by mean and SD when normally distributed, otherwise as median and range. Groups were compared using *t*-tests for normally distributed data, Mann–Whitney *U* tests for skewed distributions, and Chi-square for categorical variables. Effect size is expressed as Hedges' *g*, where values of 0.2, 0.5, and 0.8 are interpreted as small, medium, and large effects, respectively [35]. Internal consistencies of the instruments were examined with Cronbach's alpha coefficient.

To evaluate factors associated with CIPN, simple and multiple linear regression analyses were performed with NSS as a dependent variable. To adjust for differences between survivors and controls, we performed a multivariate regression analysis in survivors and controls combined. With NSS as the dependent variable, the independent variables included caseness (survivor or control), age group, gender, body mass index (BMI), the total number of comorbidities, and smoking. Alcohol consumption was excluded due to a negative association with increasing NSS, a result that would contradict the accepted role of ethanol in the development of neuropathy [36]. For analysis of factors associated with NSS in survivors alone, the multivariate regression analysis included, in addition to the total number of cycles with any neurotoxic agent, all variables with a significant univariate association, that is, age, gender, time since diagnosis, number of comorbidities, BMI and smoking. Alcohol consumption was excluded as above.

With a minimum of 108 or 755 respondents, a regression model of 8 independent variables would have a power of 0,8 to exclude a moderate or small effect (Cohen's f of 0.15 or 0.02), respectively.

The association of NSS with PCS and MCS was assessed by simple regression analysis. The strength of associations was expressed as regression coefficient B with 95% confidence intervals (CI) and adjusted r^2 values.

All tests were two-sided and *p*-values below 0.05 were considered significant. Matching of survivors and control subjects was done with Stata SE version 15, otherwise, International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 25 for PC (IBM Corporation, Armonk, USA) was used.

Results

Demographics of survivors

According to the Norwegian Cancer Registry a total of 726 patients aged 8–49 were diagnosed with HL in Norway from 1997 to 2006. Of these, 61 were reported dead, 1 patient was excluded due to nonmalignant histology and 14 patients no longer lived in Norway, leaving 650 eligible HL survivors in all four health regions. For the three health regions contributing data for the present study, 518 survivors were invited and 303 survivors completed the EORTC QLQ-CIPN 20 questionnaire. 215 survivors were not included (209 did not respond, 5 did not consent and 1 did not complete the EORTC QLQ-CIPN 20 questionnaire). Compared to respondents, survivors that were not included were more likely to be men ($p < 0.001$) and were younger at diagnosis ($p = 0.01$).

Details concerning participating survivors and controls are shown in Table 1. For survivors, the median age at diagnosis was 29 years (range 8–50 years), the median age at survey was 45 years (range 21–70 years) and 52% were men. Median observation time since diagnosis was 16 years (range 10–22 years). The prevalence of any self-reported comorbidity was 75% and 35% in the group of survivors and controls, respectively ($p < 0.001$). The most common comorbidities reported by the survivors were thyroid disease (29%), depression (23%), rheumatism (17%), arthritis (16%), and hypertension (16%).

Ninety percent of survivors had classical HL, 62% had stage I-IIA and 94% received chemotherapy as part of their treatment. Seventeen patients did not receive any chemotherapy, and 12 of these had nodular lymphocyte-predominant HL. 216 survivors received vinblastine (2–8 doses) as the only neurotoxic drug, 43 were given only vincristine (3–18 doses), whereas 26 had received a combination of different neurotoxic drugs (4–23 doses). A total of 46 (15%) patients had primary progression or relapse, and 38 (13%) received HDT-ASCT.

Chemotherapy-induced peripheral neuropathy

Forty-nine percent of survivors scored 3 (quite a bit) or 4 (very much) for at least one of the 18 items of the NSS, compared to 8% in the control group ($p < 0.001$). The items most frequently scored as 3 or 4 by survivors were tingling and

Table 1. Characteristics of HL survivors and controls.

Variable	Survivors included ($n = 303$)	Controls ($n = 606$)	p-Value
Sociodemographic factors			
Gender, *n* (%), Females/Males	146/157 (48/52)	292/314 (48/52)	1
Lymphoma and treatment			
Median age at diagnosis/years (range)	29 (8–50)		1
Median age at survey invitation/years (range)	45 (21–70)	43 (20–70)[a]	
Median time from diagnosis to survey invite/years (range)	16 (10–22)		
Primary diagnosis, *n* (%)			
Classical Hodgkin's lymphoma	273 (90)		
Nodular lymphocyte predominant Hodgkin's lymphoma	29 (10)		
Unclassified	1 (0.3)		
Stage, *n* (%)			
I-IIA	188 (62)		
IIB-IV	115 (38)		
Radiotherapy given, *n* (%)	235 (78)		
Chemotherapy given, *n* (%)	286 (94)		
Chemotherapy regimens, *n* (%)			
ABVD	240 (84)		
Number of cycles 1-2/3-4/5-6/≥7	47/84/24/85		
BEACOPP	22 (8)		
Number of cycles 1-2/3-4/5-6/≥7	3/3/2/14		
CHOP/CHOEP	7 (2)		
Number of cycles 1-2/3-4/5-6/≥7	1/1/2/3		
OEPA/OPPA/COPP	26 (9)		
Number of cycles 1-2/3-4/5-6	12/4/10		
High dose therapy with autologous stem cell transplant	38 (13)		
Other neurotoxic regimens	12 (4)		
IGEV/Platinum regimens/Other	6/2/4		
Progression/relapse, *n* (%)	46 (15)		
Self-reported comorbidity, *n* (%)[b]			
Reported one or more comorbidities	224 (75)	210 (35)	<0.001
Diabetes	15 (5)	28 (5)	0.8
Myocardial infarction	11 (4)	6 (1)	0.05
Heart failure	10 (4)	7 (1)	0.02
Stroke	8 (3)	7 (1)	0.1
Hypertension	49 (16)	81 (13)	0.2
Peptic ulcer	12 (4)	3 (1)	<0.001
Lung disease	44 (15)	51 (8)	0.004
Thyroid disease	86 (29)	20 (3)	<0.001
Depression	70 (23)	31 (5)	<0.001
Arthritis	47 (16)	40 (7)	<0.001
Rheumatism	52 (17)	13 (2)	<0.001
Other cancer	29 (10)	31 (5)	0.02
Lifestyle factors			
Smoking, *n* (%)			
Never or prior	257 (85)	495 (82)	0.2
Current or occasionally	46 (15)	111 (18)	
Alcohol, median number of glasses weekly (range)	1.5 (0–28)	4 (0–56)	<0.001
Body mass index, kg/m^2, median (range)	25.7 (17.3–5.9)	25 (17.0–0.2)	<0.05

[a]Age of controls reported in 5 year categories; [b]Missing 3 survivors.
ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etopocide, doxorubicin, cyclophosphamide, vincristine, prednisolone, and procarbazine; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; OPPA = vincristine, doxorubicin, procarbazine, and prednisone; CHOEP = cyclophosphamide, doxorubicin, vincristine, etopocide, and prednisone; OEPA = vincristine, etoposide, prednisone, and doxorubicin; COPP = cyclophosphamide, vincristine, prednisone, and procarbazine; IGEV = ifosfamide, gemcitabine, vinorelbine, and prednisone. Platinum regimens: DHAP = cisplatin, cytarabine and dexamethasone; GDP = gemcitabine, cisplatin, dexamethasone; ICE = ifosfamide, carboplatin and etoposide. Other: BOP = bleomycin, vincristine, and prednisone. Brentuximab vedotin.

numbness in upper and lower limb and dizziness and blurred vision.

For all symptom scores, that is, the NSS covering the 18 items, the sensory-, motor- and autonomic subscores as well as erectile dysfunction in men, survivors reported significantly higher symptom burden than controls (Figure 1). Specifically, for NSS, the mean value was 12.8 in survivors and 2.3 in controls ($p < 0.001$), with a large effect size of 1.2 (Table 2). Similar differences were seen for the sensory ($p < 0.001$, Hedges' $g = 1.1$), motor ($p < 0.001$, Hedges' $g = 0.8$), and autonomic subscores ($p < 0.001$, Hedges' $g = 1.2$). The mean score on erectile dysfunction was also higher in surviving males than controls ($p < 0.001$, Hedges' $g = 0.5$).

In the multivariate analysis comparing survivors and controls, being a survivor retained a significant association with NSS ($p < 0.001$), but a higher number of comorbidities ($p < 0.001$), female gender ($p = 0.05$), and smoking ($p = 0.02$) were also independently associated with higher NSS (Table 3). We explored factors associated with neuropathy symptom burden expressed as NSS in survivors (Table 3). Significant univariate associations were seen for female gender ($p = 0.04$), increasing age at the survey ($p = 0.01$), increasing BMI ($p = 0.03$), a higher number of comorbidities ($p < 0.001$), decreasing alcohol consumption ($p = 0.01$) and smoking ($p = 0.01$). The only disease or treatment-related factor associated with NSS was having received HDT-ASCT ($p = 0.04$). No significant association was found for other treatment-related

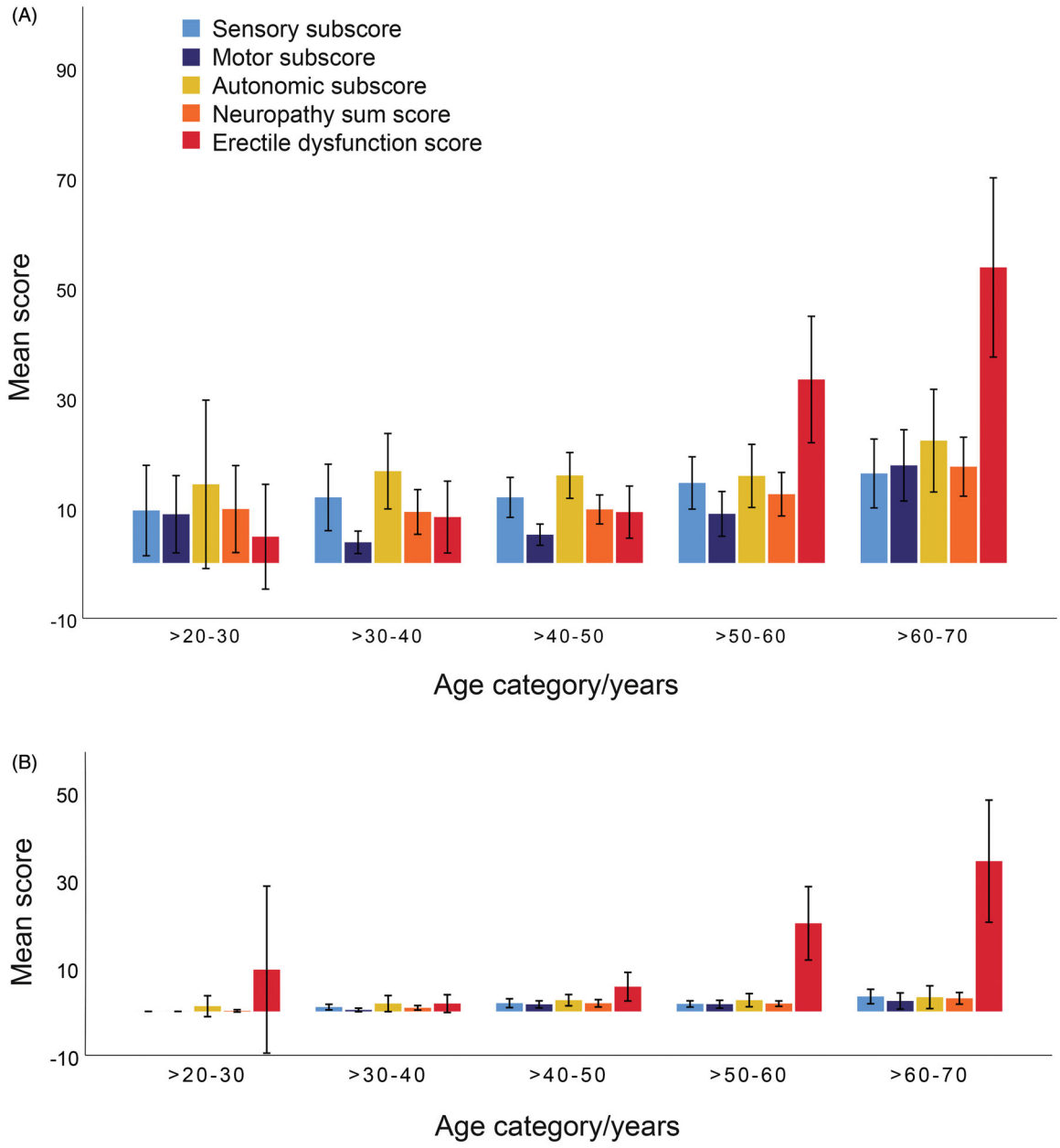

Figure 1. Neuropathy sum score by age in Hodgkin's lymphoma survivors (A) and controls (B). Colored bars represent mean scores, thin lines represent two standard errors of the mean. All scores are linearly transformed into a 0–100 scale with higher scores representing higher symptom burden.

factors, such as having received any chemotherapy at all, number of courses containing vinblastine or vincristine, number of courses containing any vinca alkaloid, the total number of courses with any neurotoxic drug (tested as a continuous variable or dichotomized at various levels) or having received radiotherapy. Female gender ($p = 0.05$) and the number of comorbidities ($p < 0.001$) were significantly associated with increasing NSS in multivariate analysis. This final regression model gained an adjusted r^2 of 0.1.

Health related quality of life

The survivors reported a mean PCS of 46.4 (SD 11.0) and mean MCS of 48.8 (SD 10.2). In univariate regression analyses, NSS was inversely and significantly associated with both PCS and MCS ($p < 0.001$; Figure 2).

Discussion

Compared to an age- and gender-matched normative population, HL survivors with a median follow-up of 16 years reported significantly higher neuropathy symptom burden. Being female and having a higher number of comorbidities were significantly associated with reported symptoms in survivors. No independent association of symptoms with disease or treatment-related variables was found, neither type nor number of chemotherapy courses given, or the use of radiotherapy.

Table 2. Neuropathy score in HL survivors and controls.

	Males			Females			Total			
	Survivors $n = 157$	Controls $n = 314$	p-Value	Survivors $n = 146$	Controls $n = 292$	p-Value	Survivors $n = 303$	Controls $n = 606$	p-Value	Hedges' g
Neuropathy sum score Mean (95% CI)	11.2 (9.4–13.0)	1.7 (1.3–2.1)	<0.001	14.4 (11.9–17.0)	2.9 (2.3–3.6)	<0.001	12.8 (11.2–14.3)	2.3 (1.9–2.7)	<0.001	1.2
Sensory score Mean (95% CI)	13.0 (10.7–15.3)	1.8 (1.3–2.3)	<0.001	14.6 (11.7–17.5)	2.3 (1.7–3.0)	<0.001	13.7 (11.9–15.6)	2.0 (1.6–2.5)	<0.001	1.1
Motor score Mean (95% CI)	7.4 (5.8–9.1)	1.4 (1.0–1.9)	<0.001	11.5 (8.8–14.2)	3.2 (2.4–4.0)	<0.001	9.4 (7.8–11.0)	2.3 (1.8–2.7)	<0.001	0.8
Autonomic score Mean (95% CI)	16.7 (13.9–19.5)	2.4 (1.7–3.2)	<0.001	24.1 (20.4–27.8)	4.9 (3.6–6.1)	<0.001	20.2 (17.9–22.6)	3.6 (2.9–4.3)	<0.001	1.2
Erectile dysfunction score Mean (95% CI)	20.0 (15.2–24.7)	8.4 (6.1–10.7)	<0.001							0.5

CI: confidence interval.

With small differences in the way demographic-, lifestyle- and comorbidity-related factors were captured, the difference in neuropathy symptom burden in survivors and healthy controls appeared also to be independently associated with other factors, that is, the number of comorbidities, female sex, and smoking habits. These are factors found to correlate with neuropathy symptoms also in the general population, in the absence of any cancer treatment. For instance, neuropathy is a well-characterized complication of diabetes, pulmonary disease, and rheumatoid arthritis [33]. Smoking has also been suggested to contribute to the development of peripheral neuropathy in conjunction with pulmonary disease and diabetes [37,38]. Still, a large part of the difference between the survivors and controls may still be attributed to caseness, that is, having had HL/or having received treatment for the disease, is a risk factor alone.

Surprisingly, the degree of neuropathy symptoms in survivors was not correlated with treatment. Other studies on short-term symptom burden in HL survivors have shown a clear association with commonly used neurotoxic compounds such as vincristine [12,13]. We are not aware of studies in this patient group that have assessed neuropathy symptoms with validated questionnaires more than a decade after treatment. The discrepancies to published short-term results may have different explanations. First, we did not collect individual cumulative chemotherapeutic doses but assessed only the number of courses containing a potentially neurotoxic drug. However, in this patient group, all under the age of 50 at diagnosis, dose reductions or omissions, especially relating to vinblastine or vincristine, were uncommon. Second, in risk and response-adapted algorithm, most patients had received ABVD, containing vinblastine, commonly viewed as less neurotoxic than vincristine [39]. Third, the lack of a relationship with the number of doses of vincristine may be due to the fact that OEPA/COPP and BEACOPP regimens were preferentially given to the youngest patients, with increasing age being a risk factor for CIPN [40]. To corroborate these unexpected findings, different sensitivity analyses with the number of doses of any potentially neurotoxic drug or subgroups treated only with vinblastine or vincristine, did not reveal any effect on symptom burden. The only hint to an effect of treatment was seen in univariate analysis, where undergoing salvage treatment, often involving additional neurotoxic drugs and HDT-ASCT was significantly associated with higher neuropathy symptom load. Of note, all but 17 survivors in our study population had received at least some potentially neurotoxic treatment, leaving us with the possibility that even small doses, independent of cumulative exposure, are enough to cause long-term CIPN symptoms.

Consistent with other studies, HL survivors reported more comorbidities compared to the normative population [41]. Differences in how questions concerning comorbidities were posed may to some degree explain the lower prevalence in the control group. However comorbidities such as diabetes, coronary heart disease, thyroid disorders, and hypertension, are chronic conditions, and if present at some point after treatment, they most likely will be present in the last 12 months prior to the assessment, rendering numbers comparable. For some comorbidities, the higher prevalence may be a direct result of treatment for HL, such as hypothyroidism, cardiovascular disease, or secondary malignancies after chemotherapy and/or radiotherapy. Survivors may also have more frequent contacts with the health care system [19] and be more aware of an increased risk of common chronic diseases after treatment. As outlined above, certain comorbidities are by themselves associated with symptom severity captured by the EORTC QLQ-CIPN 20 questionnaire [33] and may indirectly contribute to long-term symptoms from neuropathy in survivors of HL.

The survivors were assessed at a median of 16 years after diagnosis. For cancer patients in general, CIPN symptoms seem to peak the first months after treatment, and then to fall gradually over time [10]. Our survivors may have had more symptoms earlier after treatment, but even in the second-decade post-treatment, at a median age of only 45 years, the survivors report a higher symptom burden than healthy individuals. Since neuropathy is a phenomenon of aging, symptoms that result from HL and treatment thereof may add to the underlying life-long risk of neuropathy. Further follow-up into the third and fourth-decade post-treatment may therefore be warranted. The persistence of neuropathy may also need attention in ongoing studies with brentuximab vedotin in first-line treatment, where considerably more patients are at risk of neurotoxicity in the short term [42].

Long-lasting CIPN symptoms appear common also in other groups of long-term cancer survivors, such as survivors of childhood leukemia and testicular cancer [43,44]. With increasing CIPN symptom burden we found both significantly

Table 3. Factors associated with neuropathy sum score (dependent variable) in HL survivors and controls.

	Survivors only						Survivors and controls combined					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Variable	*B*	95% CI	*p*-Value	*B*	95% CI	*p*-Value	*B*	95% CI	*p*-Value	*B*	95% CI	*p*-Value
Gender (female vs. male)	3.2	0.1 – 6.3	**0.04**	3.1	0.1 – 6.1	**0.05**	1.9	0.6 – 3.2	**0.005**	1.5	0.5 – 2.7	**0.05**
Age at survey (years)	0.2	0.1 – 0.4	**0.01**	0.1	−0.1 to 0.3	0.2						
Age category (5 year groups)							0.8	0.1 – 1.5	**0.002**	0.1	−0.2 to 0.4	0.4
Time from diagnosis to survey (years)	0.4	−0.1 to 1.0	0.1	0.2	−0.4 to 0.7	0.6						
Stage (I-IIA vs. IIB-IV)	−0.8	−4.0 to 2.5	0.6									
Received chemotherapy (yes vs. no)	0.2	−6.6 to 7.0	1.0									
Received radiotherapy (yes vs. no)	2.0	−1.7 to 5.8	0.3									
Number of neurotoxic doses	−0.01	−0.5 to 0.4	1.0	0.003	−0.4 to 0.5	1						
Number of vinblastine doses only	−0.01	−0.7 to 0.6	1.0									
Number of vincristine doses only	−0.2	−0.1 to 0.6	0.6									
Relapse (yes vs. no)	4.2	−0.2 to 8.5	0.1									
High dose therapy with autologous stem cells transplant (yes vs. no)	5.0	0.3 – 9.6	**0.04**	3.2	−1.4 to 7.8	0.2						
Number of comorbidities	3.6	2.6 – 4.6	**<0.001**	2.5	1.2 – 3.5	**<0.001**	3.7	3.3 – 4.2	**<0.001**	2.2	1.7 – 2.7	**<0.001**
Diabetes (yes vs. no)	2.3	−5.0 to 9.7	0.5									
Lung disease (yes vs. no)	10.7	6.3 – 15.1	**<0.001**									
Rheumatism (yes vs. no)	10.4	6.1 – 14.6	**<0.001**									
Peptic ulcer (yes vs. no)	10.6	2.8 – 18.5	**0.01**									
Thyroid disease (yes vs. no)	1.3	−2.3 to 4.8	0.5									
Myocardial infarction (yes vs. no)	1.0	−7.3 to 9.3	0.8									
Heart failure (yes vs. no)	8.7	0.6 – 16.9	**0.04**									
Stroke (yes vs. no)	3.4	−7.1 to 13.8	0.5									
Hypertension (yes vs. no)	1.1	−3.1 to 5.3	0.6									
Depression (yes vs. no)	7.5	3.8 – 11.3	**<0.001**									
Arthritis (yes vs. no)	13.7	9.7 – 17.7	**<0.001**									
Other cancer (yes vs. no)	0.1	−5.2 to 5.4	1.0									
Smoking (Current/occasional vs. never/past)	5.4	1.1 – 9.7	**0.01**	2.6	−1.6 to 6.8	0.2	1.7	−0.7 to 3.4	**0.004**	1.6	0.2 – 3.1	**0.02**
Number of glasses of alcohol per week	−0.7	−1.2 to −0.2	**0.01**				−0.3	−0.4 to −0.2	**<0.001**			
Body mass index (kg/m^2)	0.4	0.03 – 0.7	**0.03**	0.3	−0.1 to 0.6	0.1	0.2	0.1 – 0.4	**0.01**	0.1	−0.03 to 0.2	0.2
Caseness (survivor vs. control)							10.5	9.2 – 11.7	**<0.001**	8.2	7.0 – 9.5	**<0.001**

CI: Confidence interval.
p-values below 0.05 are indicated in bold.

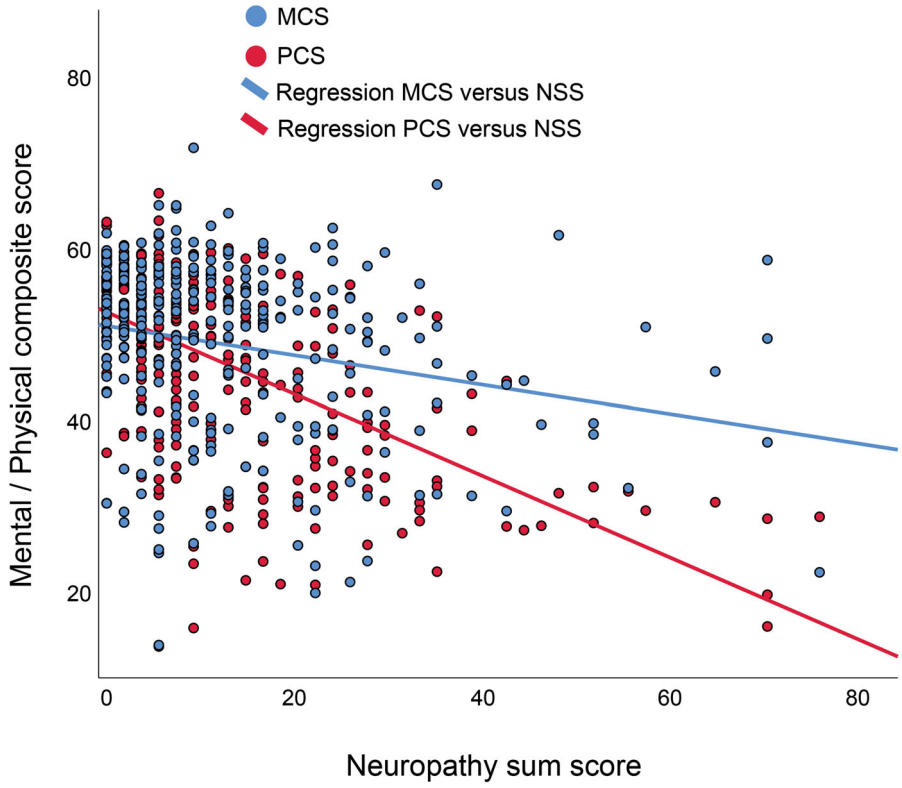

Figure 2. Physical and mental quality of life versus neuropathy sum score. Survivors' responses on the physical composite score (PCS, red circles) and mental composite score (MCS, blue circles) versus neuropathy sum score (NSS). Linear regression lines for PCS (red line) and MCS (blue line) versus NSS are shown. For the association NSS versus PCS, the unstandardized coefficient B was −0.7 (95% CI −0.9 to −0.6; $p < 0.001$) and r^2 was 0.4, and for the association of NSS with MCS the unstandardized coefficient B was −0.3 (95% CI −0.5 to −0.2; $p < 0.001$) and r^2 was 0.05.

reduced physical and mental QoL, confirming studies from other cohorts of cancer survivors [43,45]. Neuropathy symptoms seem to impact the physical aspects of QoL more than they affect mental well-being, as previously also shown for short-term complaints after treatment in non-Hodgkin's lymphoma [46].

The present study is a cross-sectional assessment based on participants' self-reported peripheral neuropathy symptom burden. Although we used a validated tool, without clinician-based neurological and neurophysiologic examination might prove inadequate [47]. A neurologic examination, including thermal sensory testing, neurography, and electromyography would have been beneficial. Since survivors were asked to assess symptoms experienced during the last week only, any short-term symptom with similarity to neuropathic complaints may have influenced their responses. On the other hand, electrophysiological examinations often do not reflect symptom burden, the impact of which must not be underestimated or trivialized on the basis of objective tests [48].

Considering the long follow-up time since treatment, our study had a reasonable response rate of 58%. Still, this might be too low and thus hamper the generalizability of the results.

In conclusion, HL survivors more than a decade after treatment reported more neuropathy-related symptoms than controls, with a negative impact on physical and mental HRQoL. No association with the disease- or treatment-related factors was found, but female gender and comorbidities appeared related to symptom burden. As CIPN is a major survivorship issue with implications for QoL and healthcare costs, further studies on CIPN in long-term HL survivors and associated factors are needed, preferably in longitudinal studies, with a combination of subjective and objective CIPN assessment.

Acknowledgments

The authors acknowledge Dr. Victoria C. Simensen and Prof. Stein Kvaløy for the clinical evaluation of survivors and for registration of comorbidities. Professor Alv A. Dahl for help with oblique rotation of SF-36 results. PhD and statistician Ragnhild Falk for guidance on statistics. Photographer Ine Eriksen for help with figures.

Author contributions

Study concept and design: K.S., C.K., and A.F.; acquisition of data: S.E., K.S., U.F., H.B., and F.M.; statistical analysis: S.E., A.F., and K.S.; interpretation of data: S.E., A.F., K.S., and C.K.; drafting of the paper: S.E. and A.F.; critical revision of the paper for important intellectual content: S.E, A.F, K.S., C.K., F.M, U.F., and H.B.

Ethical approval

Ethics approval was granted by Regional committees for medical and health research ethics South East (2016/2311). The study was performed in accordance with the declaration of Helsinki.

Informed consent

Informed written consent from all participants in the study was obtained.

Disclosure statement

The authors declare no conflict of interest. The study funders had no role in the study design, collection, analysis and interpretation of the data, writing of the paper or the decision to submit the paper for publication.

Funding

This work was supported by the Norwegian Cancer Society and the DAM foundation, project number 2019/FO247426.

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Data availability statement

All data supporting the results reported in this article is stored at Oslo University Hospital and can be provided upon request.

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