Total late effect burden in long-term lymphoma survivors after high-dose therapy with autologous stem-cell transplant and its effect on health-related quality of life

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Supplementary methods

Treatment

Lymphoma- and treatment-related data were obtained from patients' charts. Treatment of lymphomas in Norway, including HDT-ASCT, has followed international and national guidelines, and has evolved over time.[1] In the period 1987-1995 the high-dose regimen consisted of total body irradiation (TBI) and high-dose cyclophosphamide, and from 1996 chemotherapy only (BEAM: carmustine, etoposide, cytarabine and melphalan). The participating survivors received their first line treatment between 1979 and 2008. In this period, patients with limited stage Hodgkin lymphoma (HL) were treated with extended field radiotherapy of 40 Gy (i.e. mantle field and inverted-Y field), either alone or after chemotherapy, [2] until 1997 after which treatment has consisted of 2–4 courses of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) followed by modified involved-field radiotherapy 30–35 Gy.[3] Patients with advanced stage HL have been treated with chemotherapy supplemented with radiotherapy of 30-40 Gy to bulky tumors or residual disease, intially 6-8 courses of MOPP-like chemotherapy (chlorambucil, vinblastine, procarbazine and prednisolone),[4] gradually replaced with ABVD from 1985.[5] From 1999 high risk patients identified by the International Prognostic Score were treated with 6–8 courses of BEACOPP (bleomcyin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone).[6, 7]

Follicular lymphoma patients in need of therapy were traditionally treated with Chlorambucil alone in first line. More intensive regimens with combination chemotherapy with cyclophosphamide, vincristine and prednisolone with or without doxorubicin (CHOP and CVP, respectively), were commonly used at relapse.[8] Rituximab was introduced from

2000 and became standard first line treatment for follicular lymphoma, either in combination with CHOP or in monotherapy. Radiotherapy has been used throughout the period, and considered potentially curative for localized follicular lymphoma (2 Gy x 15).[9] For advanced stages, it has mainly been used as palliation for local symptomatic disease.

CHOP has been the backbone of treatment of aggressive non-Hodgkin lymphoma (NHL) throughout the period, [10] 8 courses for diffuse large B-cell lymphoma (DLBCL) initially, and 6 courses with addition of rituximab since 2002/2003,[11, 12] High risk DLBCL patients have later received intensified regimens such as addition of etoposide (R-CHOEP).[13] Mantle cell lymphoma were mainly treated with Chlorambucil until 1995, and later CHOP with addition of rituximab[14] and cytarabine[15] and dose intensification (maxi-CHOP). High dose therapy with autologous stem cell transplantation (HDT-ASCT) has been given to consolidate first remissions in mantle cell lymphoma since 1997[16, 17] and peripheral T-cell lymphomas since 2000.[18]

Burkitt and lymphoblastic lymphoma were treated with CHOP combined with high dose intravenous and intrathecal methotrexate (MmCHOP), which from 1987 was consolidated with HDT-ASCT in patients achieving complete remission.[19] Since 1995, intensive combination chemotherapy regimens adapted from acute leukemia protocols (German Berlin-Frankfurt-Munster (BFM) regimen and later German Multicenter Study Group for Adult ALL (GMALL) regimen) have been used without HDT-ASCT in first remission for Burkitt lymphoma.[19] For lymphoblastic lymphoma, the induction treatment has been given according to standard ALL-protocols (Hammersmith 82) consolidated with HDT-ASCT since 1992.[20, 21] Mediastinal radiotherapy has been given to patients with mediastinal mass (2 Gy x 12-16).[21]

The number of treatment lines prior to HDT-ASCT (1 vs ≥2) and use of radiotherapy (any site, mediastinal and infradiaphragmatic), anthracyclines (ie, doxorubicin and daunorubicin), cyclophosphamide, cisplatin, bleomycin and rituximab was registered, and the total cumulative dose was calculated for doxorubicin and cyclophosphamide. Daunorubicin doses were converted to doxorubicin isotoxic doses using a conversion factor of 0.83.[22] The survivors were also grouped based on primary diagnosis (HL, aggressive NHL (DLBCL, T-cell lymphomas, mantle cell lymphoma, Burkitt's lymphoma and lymphoblastic lymphoma) and indolent NHL (mostly follicular lymphomas)).

Clinical assessments and patient-reported outcome measures

The clinical examination was performed over two days and included separate standardized medical consultations by an oncologist, including documentation of comorbidities and medications and physical examination, and a cardiologist, who performed echocardiography, symptom-limited cardiopulmonary exercise test and pulmonary function tests.[23-25] Participants also underwent dual energy X-ray absorptiometry (DXA) measurements, [26] and blood samples were drawn at 8 am after an overnight fast.

All participants also completed a 125-item multi-instrument questionnaire, including socio-demography, comorbidities, medications, life-style, Fatigue Questionnaire (FQ),[27] Hospital Anxiety and Depression Score (HADS),[28, 29] Impact of event scale (IES),[30] Brief Sexual Function Inventory (BSFI),[31] Sexual Activity Questionnaire (SAQ).[32] Details on the questionnaire and operationalization of these scales have been described previously.[33-37]

HRQoL was rated by the SF-36 instrument, which assesses dimensions (four physical and four mental) of generic HRQoL.[38] Based on converting algorithms, poorest HRQoL is 0 and best is 100. The physical (PCS) and mental (MCS) composite scales are T-transformed and

have a mean of 50 and standard deviation (SD) of 10 in the Norwegian population. Poor physical and mental HRQoL was defined as PCS and MCS score <40, respectively (1 SD below the norm).

Ethics

The study was approved by the South East Regional Committee for Medical and Health Research Ethics (no:2011/1353). All participants gave written informed consent.

Supplementary table S1: Late effect severity grading and grouping:

Organ/System	Grading Source	Grading Rubric
Cardiovascular		
Coronary artery disease	**Modified** SJLIFE: Coronary artery disease CTCAE v4.03: Myocardial infarction Acute coronary syndrome	1: **-** 2: Cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes / **Angina pectoris, medical treatment only** (n=6) 3: **Confirmed acute myocardial infarction; Angina treated with CABG or angioplasty** (n=14) 4: Life-threatening consequences; hemodynamically unstable (n=0)
Dysrhythmia	SJLIFE: Dysrhythmia CTCAE v4.03: Atrial fibrillation	1: Asymptomatic, intervention not indicated (n=3) 2: Non-urgent medical intervention indicated (n=11) 3: Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation (n=1) 4: Life-threatening consequences; urgent intervention indicated (n=0)
Heart failure	**Modified** SJLIFE: Congestive heart failure **(Laboratory abnormalities not included, imaging abnormalities specified)**	1: Asymptomatic with cardiac imaging abnormalities (**Left ventricular global peak longitudinal strain >-17% or ejection fraction (EF) <50%)** (NYHA I) (n=52) 2: Symptoms with mild to moderate activity or exertion (NYHA II) (n=24) 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated (NYHA III) (n=5) 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support (NYHA IV) (n=0)
Heart valve disorder	SJLIFE: Heart valve disorder	1: Asymptomatic valvular thickening**/**calcifications with or without mild valvular regurgitation or stenosis by imaging (n=20) 2: Asymptomatic; moderate regurgitation or stenosis by imaging (n=61) 3: Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention (n=0) 4: Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty) (n=0)
High cholesterol	**Modified** SJLIFE: High total cholesterol CTCAE v4.03: Cholesterol high, Hypertriglyceridemia	1: Cholesterol >ULN - 7.75 mmol/L; triglyceride 1.71 mmol/L - 3.42 mmol/L (n=37) 2: Cholesterol >7.75 -10.34 mmol/L; triglyceride >3.42 mmol/L - 5.7 mmol/L; treatment with lipid lowering agent**(s)** (n=47) 3: Cholesterol >10.34 - 12.92 mmol/L**;** triglyceride >5.7 mmol/L - 11.4 mmol/L (n=0) 4: Cholesterol >12.92 mmol/L; triglyceride >11.4 mmol/L (n=0)
Hypertension (from resting blood pressure – mean of three most consistent measures)	SJLIFE: Hypertension	1: Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg) (n=90) 2: Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); treatment with antihypertensive medication (n=73)

		3: Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); with or without medication (n=29) 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated (n=0)
Left ventricular systolic dysfunction	CTCAE v4.03: Ejection fraction decreased	1: - 2: Resting ejection fraction (EF) 50-40%; (n=30) 3: Resting EF 39-20% (n=10) 4: Resting EF <20 (n=0)
Right ventricular systolic dysfunction	**Modified** SJLIFE: Right ventricular dysfunction **Cardiac imaging abnormalities specified**[39] (Grade 2-4 covered by heart failure, and classified as such)	1: Asymptomatic cardiac imaging abnormalities (**at least 2 of following paramters: TAPSE < 17 mm, RV FAC < 35%, RV S0 < 9.5 cm/sec, RIMP > 0.54, and absolute RV free wall strain < 20%**) (n=17) 2: Symptoms with mild to moderate activity or exertion (n=0) 3: Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated (n=0) 4: Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated
Thromboembolic event	**Modified** SJLIFE: Thrombus CTCAE v4.03: Thromboembolic event, Transient ischemic attack	1: Venous thrombosis (e.g., superficial thrombosis) 2: Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated; Transient ischemic attack (n=8) 3: Thrombosis (e.g., non-embolic cardiac mural [aterial] thrombus); medical intervention indicated; arterial insufficiency, invasive intervention indicated (n=4) 4: Life-threatening (e.g., cerebrovascular event); hemodynamic or neurologic instability; urgent intervention indicated (n=14)
Organ/System	**Grading Source**	**Grading Rubric**
Endocrine		
Abnormal glucose metabolism	**Modified** SJLIFE: Abnormal glucose metabolism CTCAE v4.03: Glucose intolerance, Hyperglycemia	1: Fasting glucose value >ULN - 8.9 mmol/L (n=48) 2: Fasting glucose value >8.9 - 13.9 mmol/L; oral agent indicated or initiated (n=9) 3: Fasting glucose value >13.9 - 27.8 mmol/L; insulin indicated or initiated (n=8) 4: Fasting glucose value >27.8 mmol/L (n=0)
Adrenal insufficiency	CTCAE v4.03: Adrenal insufficiency	1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (n=15) 2: Moderate symptoms; medical intervention indicated (n=0) 3: Severe symptoms; hospitalization indicated (n=0) 4: Life-threatening consequences; urgent intervention indicated (n=0)

Hypogonadism (males)	**Modified**: SJLIFE: Hypogonadism	1: Asymptomatic; clinical or diagnostic observations only **(ie FSH, LH or testosterone beyond the age-related norm. range)**; intervention not indicated (n=121) 2: Symptomatic; medical intervention indicated or initiated **(i.e. testosterone substitution)** (n=8) 3. Severe symptoms; medical intervention indicated or initiated (n=0) 4. -
Primary ovarian failure (females)	SJLIFE: Primary ovarian failure	1: - 2: - 3: Present **(menopause before age of 42 y)** (n= 37) 4: -
Hypothyroidism	**Modified** SJLIFE: hypothyroidism	1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (compensated hypothyroidism, **defined as TSH ≥3.6 mU/l and fT4 >9.0 pmol/l**) (n=78) 2: Symptomatic; thyroid replacement indicated or initiated (n=51) 3: Severe symptoms; limiting self- care ADL; hospitalization indicated (n=0) 4: Life-threatening consequences; urgent intervention indicated (n=0)
Obesity	SJLIFE: Obesity	1: - 2: BMI 25 - 29.9 kg/m2 (n=115) 3: BMI 30 - 39.9 kg/m2 (n=37) 4: BMI ≥40 kg/m2 (n=3)
Underweight	SJLIFE: Underweight	1: - 2: BMI < 18.5 kg/m2 (n=4) 3: - 4: -
Organ/System	**Grading Source**	**Grading Rubric**
Genital/sexual		
Anorgasmia (females)	CTCAE v4.03: Anorgasmia (Information about effect on relationship not available, graded as 1 only)	1: Inability to achieve orgasm not adversely affecting relationship (n=9) (2: Inability to achieve orgasm adversely affecting relationship) 3: - 4: -
Dyspareunia (females)	SJLIFE: Dyspareunia	1: Mild discomfort or pain associated with vaginal penetration (n=13) 2: Moderate discomfort or pain associated with vaginal penetration (n=7) 3: Severe discomfort or pain associated with vaginal penetration (n=9) 4: -
Ejaculation disorder (males)	CTCAE v4.03: Ejaculation disorder	1: Diminished ejaculation (n=22) 2: Anejaculation or retrograde ejaculation (n=11) 3: -

		4: -
Erectile dysfunction (males)	SJLIFE: Erectile dysfunction	1: Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump) (n=19) 2: Decrease in erectile function (frequency/ rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump) (n=73) 3: Decrease in erectile function (frequency/ rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present) 4: -
Libido decreased	CTCAE v4.03: Libido decreased (Information about effect on relationship not available, graded as 1 only)	1: Decrease in sexual interest not adversely affecting relationship (n=79) 2: Decrease in sexual interest adversely affecting relationship 3: - 4: -
Vaginal dryness	CTCAE v4.03: Vaginal dryness	1: Mild vaginal dryness not interfering with sexual function (n=19) 2: Moderate vaginal dryness interfering with sexual function or causing frequent discomfort (n=6) 3: Severe vaginal dryness resulting in dyspareunia or severe discomfort (n=13) 4: -
Organ/System	**Grading Source**	**Grading Rubric**
Hearing		
Hearing loss	CTCAEv4.03: Hearing impaired (Information about hearing aid not available)	1: Subjective change in hearing in the absence of documented hearing loss. 2: Hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. (n=41) 3: Hearing loss with hearing aid or intervention indicated; limiting self-care ADL. 4: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); nonservicable hearing.
Organ/System	**Grading Source**	**Grading Rubric**
Hematologic		
Anemia	CTCAEv4.03: Anemia	1: Hemoglobin (Hgb) <LLN - 10.0 g/dL (n=27) 2: Hgb <10.0 - 8.0 g/dL (n=1) 3: Hgb <8.0 g/dL; transfusion indicated (n=0) 4: Life-threatening consequences; urgent intervention indicated (n=0)
Leukocytopenia	CTCAEv4.03: White blood cells decreased	1: <LLN – 3.0 x 10e9 /L (n=14) 2: <3.0 – 2.0 x 10e9 /L (n=4) 3: <2.0 – 1.0 x 10e9 /L (n=0)

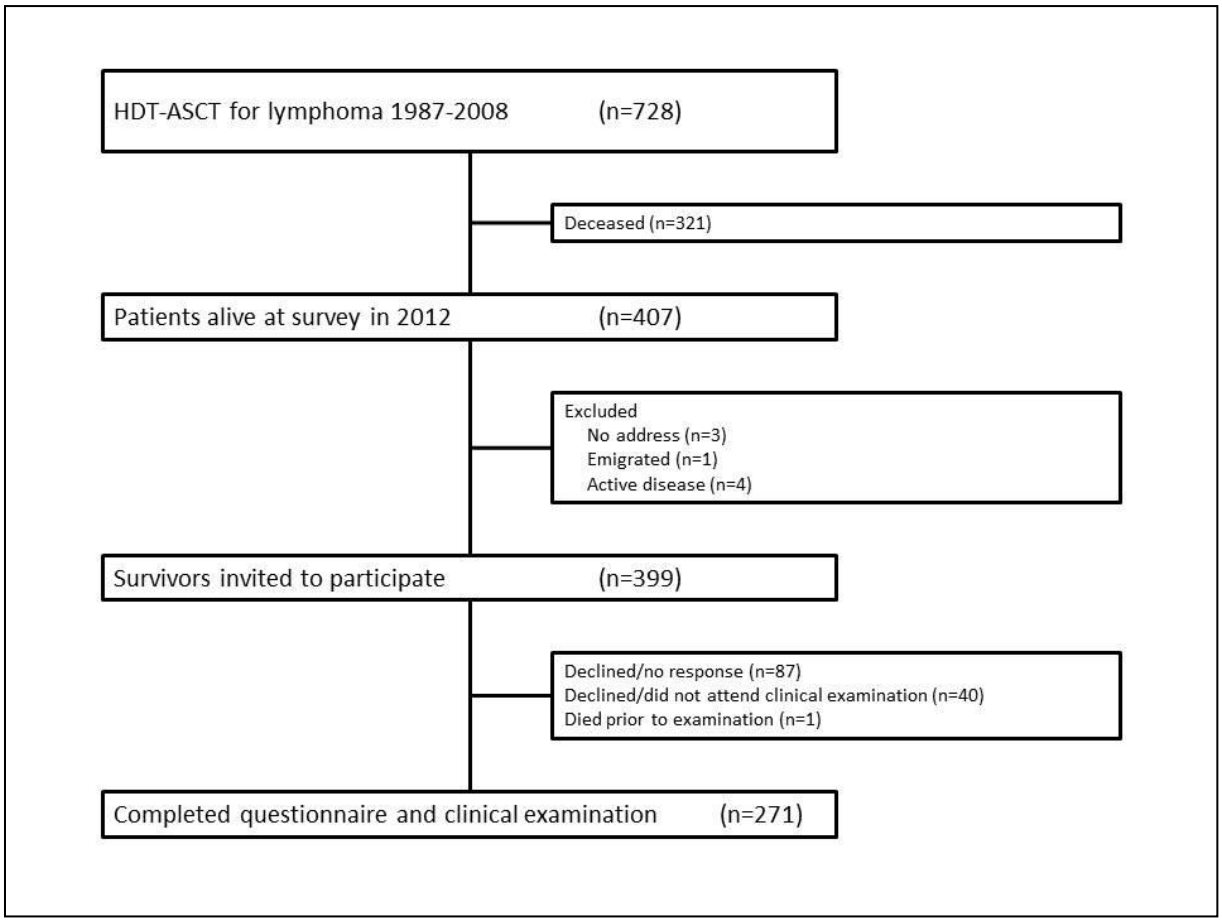
		4: <1.0 x 10e9 /L (n=0)
Neutropenia	CTCAEv4.03: Neutrophil count decreased	1: >LLN - 1.5 x 10e9 /L (n=0) 2: <1.5 - 1.0 x 10e9 /L (n=0) 3: <1.0 - 0.5 x 10e9 /L (n=1) 4: <0.5 x 10e9 /L (n=0)
Thrombocytopenia	CTCAEv4.03: Platelet count decreased	1: <LLN - 75 x 10e9/L (n=27) 2: <75 - 50 x 10e9/L (n=2) 3: <50 - 25 x 10e9/L (n=0) 4: <25 x 10e9/L (n=1)
Hepatobiliary		
Hepatopathy	SJLIFE: Hepatopathy	1: Alanine (ALT) or aspartate aminotransferase (AST) >ULN - 3.0 x ULN (n=10) 2: ALT or AST >3.0 - 5.0 x ULN (n=0) 3: ALT or AST >5.0 - 20.0 x ULN (n=0) 4: ALT or AST >20.0 x ULN (n=0)
Organ/System	**Grading Source**	**Grading Rubric**
Neuro-/musculoskeletal		
Arthritis	SJLIFE: Arthritis	1: Mild pain with inflammation, erythema, or joint swelling (n=33) 2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL (n=17) 3: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL 4: -
Bone mineral density deficit	SJLIFE: Bone mineral density deficit	1: Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no intervention indicated (n=98) 2: BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated or initiated; therapy to improve BMD indicated or initiated; limiting instrumental ADL (n=31) 3: Loss of height >=2 cm; hospitalization indicated; limiting self-care ADL 4: -
Osteonecrosis	SJLIFE: Osteonecrosis	1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated (n=0) 2: Symptomatic; medical intervention indicated (e.g., analgesics, anti-inflammatory); limiting instrumental ADL (n=2) 3: Severe symptoms; limiting self-care ADL; elective operative intervention indicated (n=4) 4: Life-threatening consequences; urgent intervention indicated
Peripheral neuropathy	SJLIFE: Peripheral neuropathy	1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated 2: Moderate symptoms; limiting instrumental ADL (n=100)

	(Information on severity of symptoms not sufficient to distinguish between grade 2 and 3)	3: Severe symptoms; limiting self- care ADL; assistive device indicated (n=0) 4: Life-threatening consequences; urgent intervention indicated (n=0)
Organ/System	**Grading Source**	**Grading Rubric**
Pulmonary		
Asthma	SJLIFE: Asthma	1: Mild symptoms; intervention not Indicated (n=6) 2: Symptomatic; medical intervention indicated; limiting instrumental ADL; intermittent asthma requiring short-acting beta agonists as needed (n=5) 3: Limiting self-care ADL; oxygen saturation decreased; persistent asthma requiring daily controller medication (oral or inhaled) (n=7) 4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated (n=0)
Chronic obstructive pulmonary disease (COPD)	SJLIFE: Chronic obstructive pulmonary disease (COPD)	1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated (n=5) 2: Moderate; minimal, local or noninvasive intervention indicated or initiated (inhaled medications); limiting age-appropriate instrumental ADL (n=2) 3: Severe or medically significant but not immediately life-threatening (e.g., requiring supplementation of oxygen, systemic corticosteroids, BIPAP, or CPAP); hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL (n=0) 4: Life-threatening consequences; urgent intervention indicated (n=0)
Gas diffusing capacity impairment	**CTCAEv3:** Carbon monoxide diffusing capacity decreased	1: DLCO or DLCO/VA ≤90-75%predicted (n=78) 2: DLCO or DLCO/VA <75-50%-predicted (n=29) 3: DLCO or DLCO/VA <50-25%-predicted (n=2) 4: DLCO or DLCO/VA 25%-predicted (n=0)
Obstructive pulmonary impairment	**New grading source** GOLD criteria[40]	**1: FEV1/FVC <0.70 and FEV1 ≥ 80%-predicted** (n=24) **2: FEV1/FVC <0.70 and FEV1 <80-50%-predicted** (n=26) **3: FEV1/FVC <0.70 and FEV1 <50-30%-predicted** (n=0) **4: FEV1/FVC <0.70 and FEV1 <30%-predicted** (n=0)
Obstructive sleep apnea	SJLIFE: Obstructive sleep apnea	1: Documentation of apnea; no need for medication 2: Documentation of mild apnea; behavioral intervention initiated or indicated 3: Documentation of moderate apnea; CPAP initiated or indicated (n=3) 4: Documentation of severe apnea with secondary complications (CHF, HTN, headache)
Restrictive ventilatory defect	SJLIFE: Restrictive ventilatory defect	1: TLC ≤ 90–75%-predicted (n=36) 2: TLC <75–50%-predicted (n=13) 3: TLC <50%-predicted (n=1) 4: -

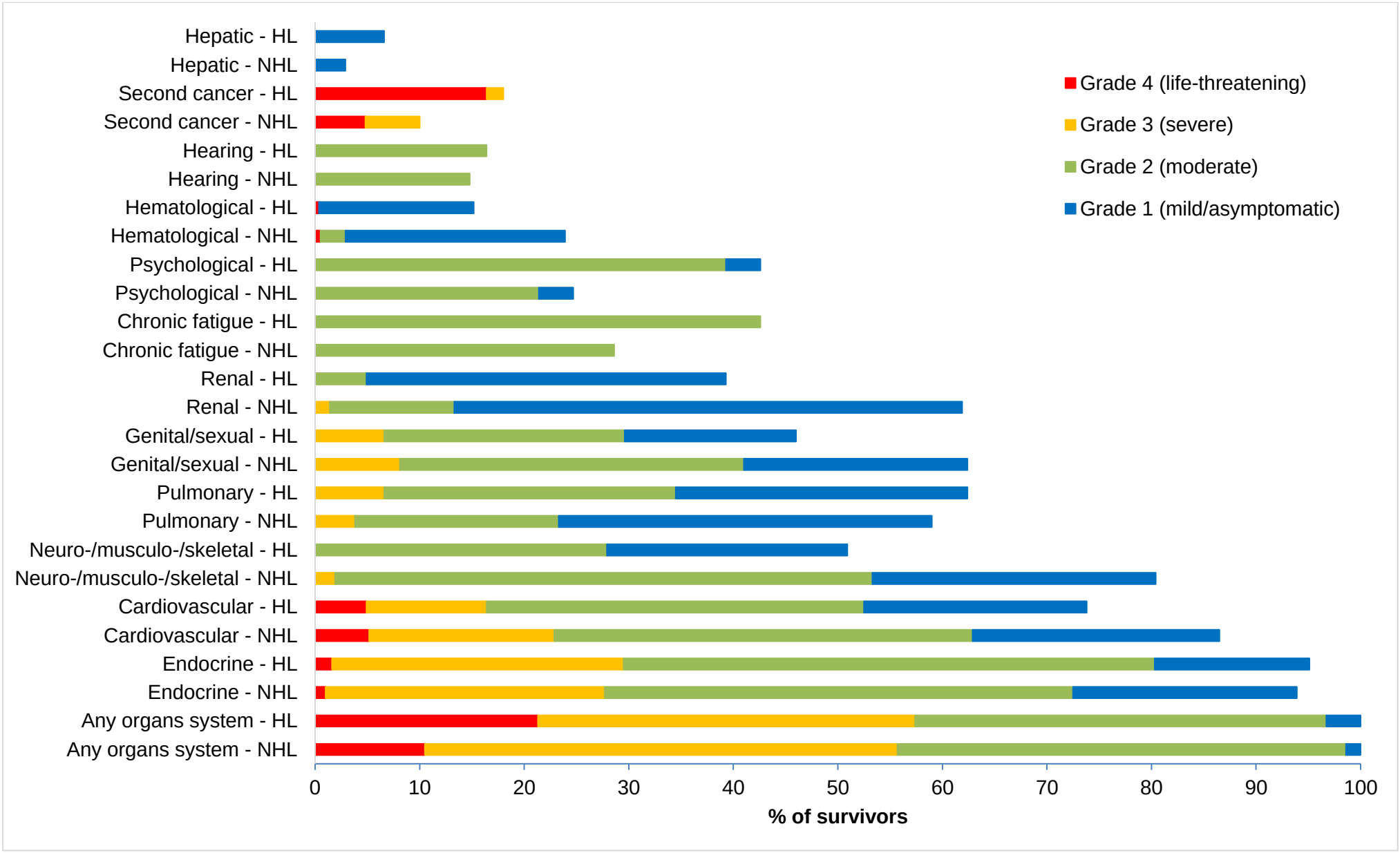
Organ/System	Grading Source	Grading Rubric
Renal		
Chronic kidney disease	SJLIFE: Chronic kidney disease	1: eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN – 60 ml/min/1.73 m^2 (n=123) 2: eGFR or CrCl 59-30 ml/min/1.73 m^2 (n=28) 3: eGFR or CrCl 29-15 ml/min/1.73 m^2 (n=3) 4: eGFR or CrCl <15 ml/min/1.73 m^2; (dialysis or renal transplant indicated) (n=0)
Organ/System	**Grading Source**	**Grading Rubric**
Second cancer		
Second malignant neoplasm	**Modified**: CTCAEv4.03: Leukemia secondary to oncology chemotherapy, Myelodysplastic syndrome Treatment related secondary malignancy Neoplasm, benign, malignant and unspecified	1: - 2: - 3: Non-life threatening **(non-melanoma skin ca)** (n=12) 4: Life threatening consequences **(other sec cancer)** (n=20)
Organ/System	**Grading Source**	**Grading Rubric**
Chronic fatigue		
Chronic fatigue	**New grading source** Chalder fatigue questionnaire[27, 33]	1: - **2: Chronic fatigue present (>6 months)** (n=86) 3: - 4: -
Organ/System	**Grading Source**	**Grading Rubric**
Psychological		
Anxiety	**New grading source** Hospital Anxiety and Depression Scale (HADS)[29]	1: - **2: HADS anxiety subscale score ≥8** (n=47) 3: - 4: -
Depression	**New grading source** Hospital Anxiety and Depression Scale (HADS)[29]	1: - **2: HADS depression subscale score ≥8** (n=37) 3: - 4: -
Post-traumatic stress (PTSD)	**New grading source** Impact of event scale (IES)[30, 33]	**1: Total IES score 26-34 (partial PTSD)** (n=25) **2: Total IES score ≥35 (full PTSD)** (n=20) 3: - 4: -

Supplementary table S1: Late effect severity grading and grouping primarily adopted from the St. Jude Lifetime Cohort Study (SJLIFE) modification of the common terminology for adverse events (CTCAE) v4.03[41] and the original CTCAE v4.03 as applicable. Bolded fonts represent modified or new grading categories.

Supplementary figures:



Supplementary figure 1: Flowchart of recruitment of eligible lymphoma survivors after high dose therapy with autologous stem-cell transplantation (HDT-ASCT) in Norway.



Supplementary figure 2: Maximum grade late effect per survivor for each organ-system category and for any organ system, for Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

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