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CT-Diagnosed Mesenteric Alterations in Patients with Non-Hodgkin's Lymphoma: A Population-Based Study

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Key Words
Non-Hodkgin's Lymphoma · Mesenteric alterations · Misty mesentery

Summary
Background: Mesenteric alterations are associated with non-Hodgkin's lymphoma (NHL), but the frequency and prognostic value of mesenteric alterations are unknown in patients with NHL. **Patients and Methods:** We retrospectively screened 120 patients that were treated for NHL between January 1996 and December 2001 for the presence of mesenteric alterations, defined on computed tomography (CT) scans as nodular or diffuse infiltration of the abdominal mesentery with increased density of mesenteric fat. **Results:** 21 patients (17.5%) had radiological findings of mesenteric alterations at the time of the initial NHL diagnosis. Mesenteric alterations were significantly associated with mesenteric lymphadenopathy (p = 0.01). In about 50% of the patients, mesenteric alterations could not be explained by direct mesenteric tumour invasion or overt lymphatic obstruction. Patients with initial findings of mesenteric alterations tended to have a better 4-year survival as compared to patients without such findings (79 vs. 43%, p = 0.11). The International Prognostic Index (IPI) score was the only independent predictor of survival in the multivariate analysis. **Conclusion:** This retrospective screening study found a moderate prevalence of mesenteric alterations in patients with various subtypes of NHL. The diagnostic and prognostic value of mesenteric alterations should be further assessed in prospective studies.

Schlüsselwörter
Non-Hodgkin-Lymphom · Mesenteriale Veränderungen · Misty Mesenterium

Zusammenfassung
Hintergrund: Obwohl mesenteriale Veränderungen bekanntermaßen mit Non-Hodgkin-Lymphomen (NHL) assoziiert sind, ist die Häufigkeit und prognostische Bedeutung dieser mesenterialen Veränderungen unbekannt. **Patienten und Methoden:** 120 zwischen Januar 1996 und Dezember 2001 in Behandlung stehende NHL-Patienten wurden retrospektiv auf das Vorliegen mesenterialer Veränderungen untersucht. Computertomographie (CT)-Kriterien umfassten noduläre oder diffuse, mesenteriale Infiltrate, mit konsekutiven Signalalterationen des mesenterialen Fettgewebes. **Ergebnisse:** Bei 21 Patienten (17,5%) fanden sich radiologisch mesenteriale Veränderungen zum Zeitpunkt der NHL-Diagnose. Mesenteriale Veränderungen waren signifikant assoziiert mit mesenterialer Lymphadenopathie (p = 0,01). Bei rund 50% der Patienten konnten die mesenterialen Veränderungen nicht durch direkten mesenterialen Tumorbefall oder lymphatische Obstruktion erklärt werden. Patienten mit Nachweis mesenterialer Veränderungen bei Diagnosestellung der Grundkrankheit (NHL) hatten ein nichtsignifikant höheres 4-Jahresüberleben verglichen mit Patienten ohne solche Veränderungen (79 vs. 43%, p = 0,11). Der International Prognostic Index (IPI)-Quotient war der einzige unabhängige prognostische Faktor bezüglich Gesamtüberleben in der multivariaten Analyse. **Schlussfolgerung:** Diese retrospektive Studie fand eine hohe Prävalenz mesenterialer Veränderungen in Patienten mit verschiedenen NHL-Entitäten. Der diagnostische und prognostische Wert mesenterialer Veränderungen sollte in prospektiven Studien untersucht werden.

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Introduction

The annual incidence rate of non-Hodgkin's lymphoma (NHL) from 1995 to 1999 was 19.1 cases per 100,000 persons, as estimated from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute [1]. The overall incidence rate is 23.6 per 100,000 for males and 15.4 per 100,000 for females, and increases with age [1]. While the majority of NHL cases arise in lymph nodes, primary extranodal disease is found in 20–30% [2, 3]. The current World Health Organisation (WHO) classification recognises 2 categories of NHL – B-cell neoplasms and T-/natural killer (NK) cell neoplasms – both being stratified into immature precursor lymphoblastic lymphomas/leukaemias and mature peripheral neoplasms [4]. The International Prognostic Index (IPI) separates 4 risk groups of patients with diffuse large B-cell lymphoma (DLBCL) [5] or low-grade lymphoma [6], and is widely used for therapeutic stratification of individual patients and the design of clinical trials. C-reactive protein (CRP) serum level was reported to have some prognostic value in a small group of patients with various entities of NHL [7], but the IPI stratification reveals the most useful prognosticator in patients with NHL so far.

Alterations of the abdominal mesenteries have recently been found to be associated with NHL in a substantial part of these patients [8–10]. Daskalogiannaki et al. [9] found mesenteric alterations in 0.6% of a general population with abdominal symptoms, where it was associated with malignancy in 69% of cases, mostly extraabdominal NHL (in 12% of patients), breast cancer (10%), and colorectal cancer (10%). The abdominal mesenteries are primarily composed of fat, through which run the major arteries, veins, and lymphatic vessels of the bowel. An alteration in the density of the mesenteric fat is often the principal evidence of underlying mesenteric and bowel disease. Mindelzun et al. [8] have coined the term of 'misty mesentery' to describe the appearance of altered mesenteric fat on computed tomography (CT) [8]. Mesenteric abnormalities as diagnosed by CT scans have further been described as 'primary (idiopathic) mesenteritis' [11], 'mesenteric lipodystrophy' [12, 13], 'retractile mesenteritis' [14–17], 'intraabdominal panniculitis' [18], 'mesenteric panniculitis' [9, 19, 20], or 'sclerosing mesenteritis' [21] among others. With infiltration of the mesentery by fluid or cells, the mean density of mesenteric fat increases to –28 to –85 Hounsfield Units, and the mesenteric arteries and veins often lose their sharp interfaces [9]. Depending on the nature and extent of the infiltration, mesenteric vessels may be either completely or partially effaced. Etiologically, mesenteric alterations may be caused by mesenteric oedema (due to hypoalbuminaemia, cirrhosis, nephrosis, heart failure, mesenteric artery and vein thrombosis, vasculitis, and trauma), lymphoedema (due to congenital abnormalities, inflammation, neoplasms, surgery, and radiotherapy), inflammation (primarily pancreatitis), haemorrhage and trauma, or neoplasms. The most common tumour involving the mesentery is NHL that typically presents with bulky adenopathy [8]. However, NHL-associated mesenteric alterations may more readily be recognized after therapy-induced tumour size reduction [8]. In a series of 53 patients with mesenteric lipodystrophy by Kipfer et al. [12], 8 patients were found to have NHL. The diagnosis of mesenteric alterations may precede NHL, as was the case in 2 of 27 patients with 'mesenteric panniculitis' [20]. In the present study, the authors retrospectively assessed the frequency and prognostic value of mesenteric alterations in NHL patients by using abdominal CT scans.

Patients and Methods

Patients

All consecutive patients treated for NHL at the Department of Oncology of the Kantonsspital St. Gallen, Switzerland, between January 1996 and December 2001 were included in a retrospective analysis. The study population included patients with prevalent NHL (diagnosis before 1996) and incident NHL (diagnosis between January 1996 and December 2001). Clinical data were extracted from patient and electronic files, and abdominal CT scans were reviewed for the presence of mesenteric alterations. Histological diagnoses were retrospectively adapted to the current WHO classification [4]. Patients with secondary malignancies were excluded. Clinical and laboratory parameters such as stage, histology, and disease location, B-symptoms, ECOG performance status, weight, abdominal surgery, comorbidity, haematology, and blood chemistry were assessed at the time of initial NHL diagnosis. Stage of disease according to the Ann Arbor classification [22] and IPI score [5] were assessed from individual patient data. Time and modality of treatment (chemotherapy, radiotherapy, surgery), treatment response, and clinical outcome (i.e. overall survival) were assessed in all patients.

International Prognostic Index

As detailed by the International Non-Hodgkin's Lymphoma Prognostic Factors Project [5], variables used in the IPI are age (< 60 vs. > 60 years), performance status (ECOG 0 or 1 vs. 2–4), Ann Arbor stage (I or II vs. III or IV), serum lactate dehydrogenase (LDH) level (normal vs. elevated), and number of extranodal sites. Patients with no or 1 unfavourable variable were considered to be at low risk, those with 2 to be at low-intermediate risk, those with 3 to be at high-intermediate risk, and those with 4 or 5 unfavourable variables to be at high risk.

CT Scans

Hardcopies of 825 CT scans were reviewed retrospectively, including 736 abdominopelvic and 89 abdominal CT scans in a total of 120 patients. Radiological examinations had been performed with different types of whole-body CT scans. One radiologist reviewed all scans with special emphasis towards the diagnosis of infradiaphragmatic lymph node involvement, involvement of the liver or the spleen, and the presence of mesenteric alterations. Mesenteric alteration was defined as a mass-like focal area of increased nodular, linear, or irregular attenuation within the mesenteric fat, surrounded by a hyperattenuating pseudocapsule. The so-called fat ring or fatty halo sign, which means preservation of the fat nearest to the mesenteric vessels within the observed mass, was not mandatory for the diagnosis of mesenteric alterations. Accordingly, CT scans were classified as either presenting or not presenting mesenteric alterations.

Data Analysis

Statistical analysis was performed using the statistical package SAS for windows, version 8.2 (SAS Institute, Cary, NC, USA). Categorical vari-

Table 1. Patient characteristics

Parameter	All patients median (range)	Patients with MA median (range)	Patients without MA median (range)	p value
Age, years	58 (15.5–87.8)	54.4 (20.2–70.9)	58.6 (15.5–87.8)	> 0.05
Male sex, %	60	61.9	59.6	> 0.05
Mesenteric lymphopathy, %	25	47.6	20.2	0.013
Abdominal lymphopathy, %	47.5	61.9	44.4	> 0.05
IPI[a]	2 (0–4)	1.5 (0–3)	2 (0–4)	> 0.05
Performance status	0 (0–3)	0 (0–3)	0 (0–2)	> 0.05
BMI, kg/m^2	24.1 (16.4–37.3)	23.2 (17.7–29.6)	24.3 (16.4–37.3)	> 0.05
Hemoglobin, g/l	130 (44–167)	139 (69–167)	130 (44–165)	> 0.05
Leukocytes, 10^9/l	6.8 (2.0–52.9)	6.7 (2.0–14.4)	6.8 (2.0–52.9)	> 0.05
Thrombocytes, 10^9/l	237 (5–664)	242 (7–422)	236 (5–664)	> 0.05
LDH, U/l	455 (132–11,710)	438 (231–859)	462 (132–11,710)	> 0.05
Albumin, g/l	43 (30–54)	45 (30–51)	43 (30–54)	> 0.05
Creatinine clearance[b], ml/min	62 (21–114)	63 (40–104)	61 (21–114)	> 0.05
ASAT, U/l	24 (10–263)	28 (15–61)	23 (10–263)	> 0.05
ALAT, U/l	18 (7–342)	24 (13–67)	18 (7–342)	> 0.05
CRP, mg/l	9 (0–269)	9 (0–113)	9 (0–269)	> 0.05
β2 microglobulin, mg/l	4.6 (2.4–7.9)	4.5 (2.5–7.4)	4.6 (2.4–7.9)	> 0.05

[a]IPI 0 and 1 = low risk, 2 = low-intermediate risk, 3 = high-intermediate, 4 and 5 = high risk.
[b]Creatinine clearance according to the Cockcroft-Gault formula: (140-age) × weight/serum creatinine, with a 15% correction for females.
MA = Mesenteric alterations (as defined in the Methods section); IPI = International Prognostic Index; BMI = body mass index; LDH = lactate dehydrogenase; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; CRP = C-reactive protein.

Table 2. NHL subtypes and prevalence of mesenteric abnormalities (MA); MA with capsule-like structure in brackets

Subtypes of NHL (WHO classification 2001)	All patients[a]	MA at initial diagnosis (Capsule-like structure)	MA during follow-up (Capsule-like structure)
B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma	8	1 (1)	2 (1)
Hairy cell leukaemia	1	1 (1)	1 (1)
Plasma cell neoplasm	1	0	0
Extranodal marginal zone B-cell lymphoma (MALT lymphoma)	3	0	0
Follicular lymphoma, grade I/II	28	7 (4)	16 (12)
Follicular lymphoma, grade III	8	0	3 (1)
Follicular lymphoma, undefined grading	2	0	0
Mantle cell lymphoma	9	1 (1)	1 (1)
Diffuse large B-cell lymphoma	26	3 (2)	7 (4)
Burkitt's lymphoma/leukaemia	4	1 (0)	1 (0)
B-cell lymphoma, unclassifiable	4	1 (1)	2 (2)
Precursor T-lymphoblastic leukaemia/lymphoma	1	0	0
Peripheral T-cell lymphoma, unspecified	6	3 (0)	4 (2)
Anaplastic large cell lymphoma	3	1 (0)	1 (1)
Lymphoid neoplasm/lymphoma, unclassifiable	1	0	0
B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma and diffuse large B-cell lymphoma	2	0	0
Extranodal marginal zone B-cell lymphoma and diffuse large B-cell lymphoma	2	0	1 (0)
Follicular lymphoma grade I/II and diffuse large B-cell lymphoma	2	1 (1)	2 (2)
Follicular lymphoma grade III and diffuse large B-cell lymphoma	5	1 (0)	3 (1)
Follicular lymphoma and diffuse large B-cell lymphoma	1	0	1 (0)
Angioimmunoblastic T-cell lymphoma	0	0	0

[a]Histology was not evaluable in 2 patients.
NHL = Non-Hodgkin's lymphoma.

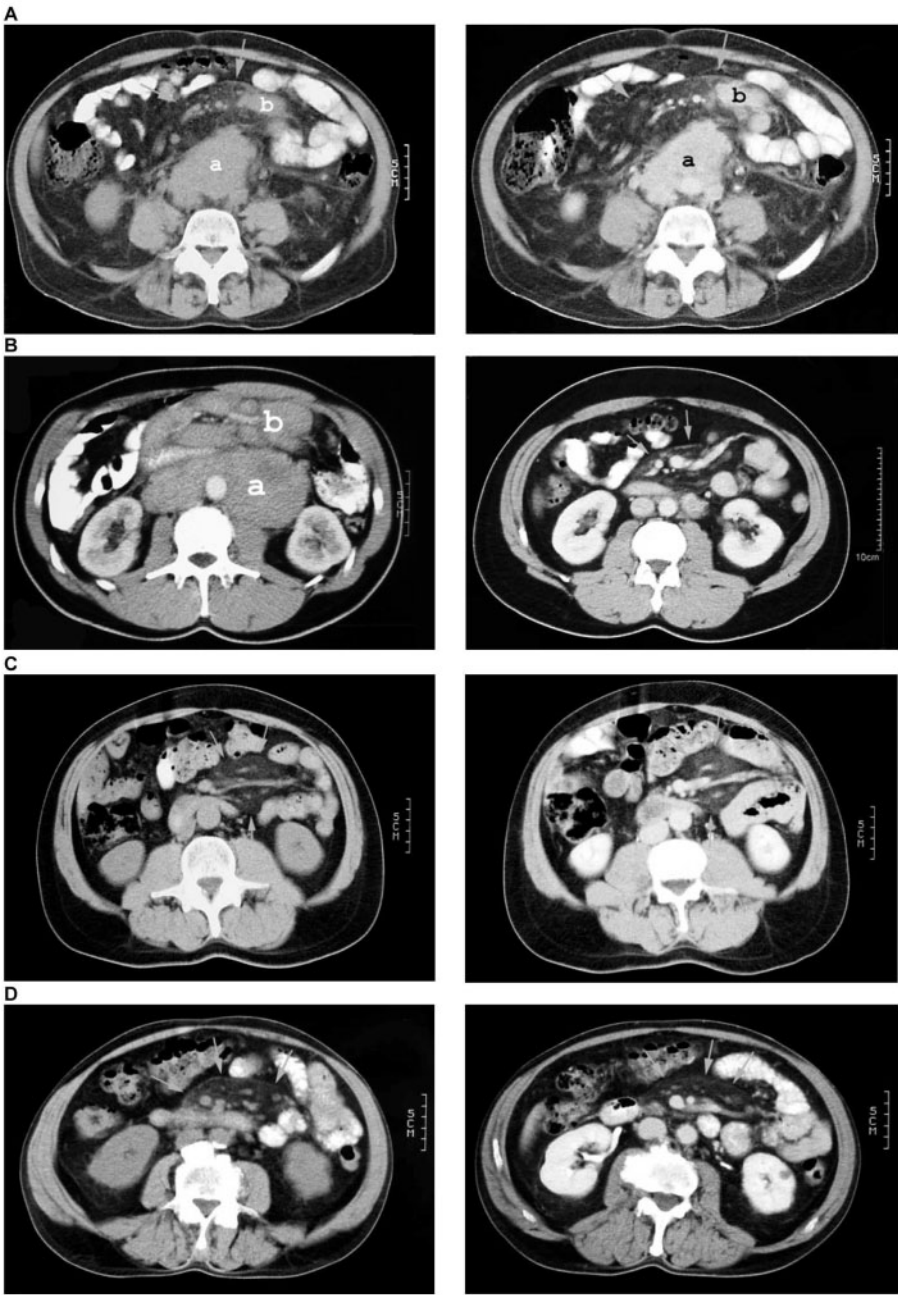

Fig 1. **A** Extensive retroperitoneal (**a**) and mesenterial (**b**) lymphoma with additional mesenteric alterations (higher density compared to surrounding fat tissue, arrows) (native CT scan left, intravenous (iv) contrast right). **B** Extensive retroperitoneal (**a**) and mesenterial (**b**) lymphoma (iv contrast left) with near complete remission and remaining mesenteric alterations (arrows) (iv contrast right). **C** Mesenteric alterations in a patient with extraabdominal lymphoma (arrows) (native CT scan left, iv contrast right). **D** Mesenteric alterations in a patient with adenocarcinoma of the colon (native CT scan left, iv contrast right).

ables were compared using Fisher's exact test. Continuous variables were compared using Student's t-test or Wilcoxon rank-sum test according to normality assumptions. Univariate survival analysis was done using the Kaplan-Meier technique and the log rank test on the original data set. In order to account for a possible lead-time bias as to the retrospective inclusion of NHL patients with an initial diagnosis before 1996, the origin of survival calculations was reset to 1996 for this group of patients. For multivariate analysis, the problem of missing covariates was addressed by a conservative imputation technique. If a continuous variable was unavailable in more than one third of cases, it was not further processed; otherwise, the median was substituted for missing values. No other transformations or interaction terms were applied. Subsequently, multivariate stepwise Cox regression was used to develop a parsimonious model. A significance level of 0.1 was requested for model entry, and a level of 0.05 to remain in the model. Covariates that were contained in disease stage (Ann Arbor) or IPI score were not separately modelled in the multivariate analysis to avoid collinearity. The final model was then recalculated using the original data set, and a bootstrap procedure was performed for validation purposes.

Results

120 patients were included in this study. NHL was diagnosed before 1996 in 33 patients and thereafter in 87 patients (time frame: December 1983 to March 2001). Median follow-up was 2.15 years (8 days to 17.8 years). Table 1 summarises the patient characteristics. IPI could be assessed in 92 patients, and was lacking in the remaining patients (including 15 patients with follicular lymphoma and 3 patients with DLBCL). According to the IPI score, 36 patients (39%) were at low risk, 27 (29%) at low-intermediate risk, 24 (26%) at high-intermediate

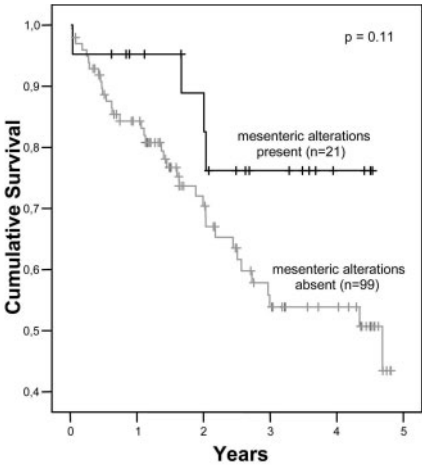

Fig 2. Kaplan-Meier curves of overall survival according to mesenteric alterations at initial diagnosis.

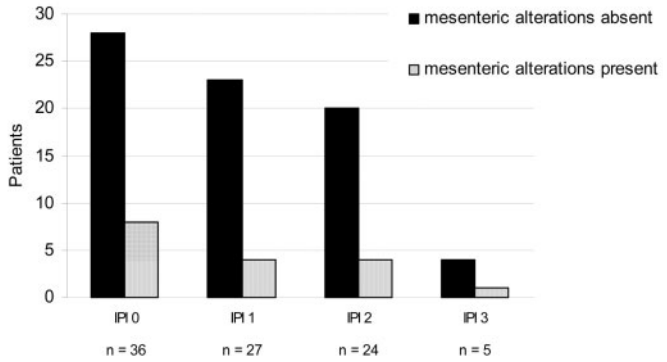

Fig 3. Presence of mesenteric alterations per IPI risk group (p value for trend > 0.05). IPI 0 and 1 = low risk, 2 = low-intermediate risk, 3 = high-intermediate, 4 and 5 = high risk.

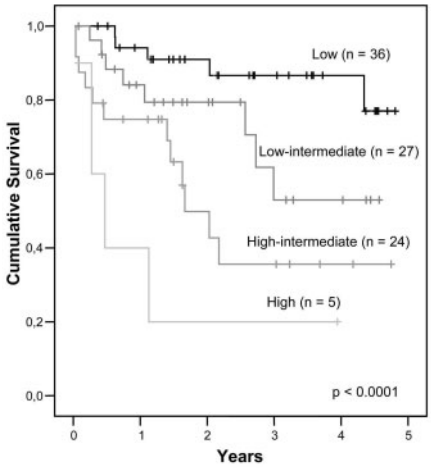

Fig 4. Kaplan-Meier curves of overall survival according to IPI risk groups.

risk, and 5 (5%) at high risk. At the time of first diagnosis, 21 of 120 patients (17.5%) had findings consistent with mesenteric alterations (fig. 1). Another 24 patients (20%) had radiological findings of mesenteric alterations on subsequent CT scans. Ten of these 24 patients (42%) had large mesenterial tumour burden at first diagnosis, which made the diagnosis of mesenteric alterations at first radiological assessment impossible. Mesenteric alterations with capsule-like structures were found in 11 patients (53% of all patients with mesenteric alterations) at the time of first diagnosis, and in 28 patients at follow-up (63% of all patients with mesenteric alterations at follow-up). Ten of the 21 patients (48%) with initial mesenteric alterations had enlarged mesenterial lymph nodes, but only 20 of the 99 patients (20%) without initial mesenteric alterations had enlarged mesenterial lymph nodes (p = 0.013 for the difference).

Patients with an initial diagnosis of mesenteric alterations showed a trend towards increased overall survival as compared to patients without these findings (4-year survival 79 vs. 43%, p = 0.11) (fig. 2). No correlation was found between IPI scores and radiological findings of mesenteric alterations at initial diagnosis (fig. 3). Furthermore, no significant correlation was found between lymphoma subtypes and mesenteric alterations. NHL subtypes according to the current WHO classification are outlined in table 2.

In the univariate analysis, elevated C-reactive protein (CRP), gamma glutamyl transferase (GGT) or LDH, lower creatinine clearance, abnormal leukocyte or thrombocyte counts, and higher IPI scores were significant predictors of worse overall survival (table 3, fig. 4). However, only the IPI score was an independent predictor of overall survival in the multivariate analysis and after adjustment for gender and year of diagnosis, with a hazard ratio of 2.2 by each unit increase of IPI (95% confidence interval (CI) 1.5–3.3).

Discussion

So far, a single systematic screening study assessed 7,620 abdominal CT scans from symptomatic patients [9]. Mesenteric alterations were found in 49 patients (0.6%), and an association with NHL was found in 6 of these 49 patients (12%). As to our knowledge, this is the first systematic study on mesenteric alterations in NHL patients. This retrospective study found mesenteric alterations in a moderate 22 of 120 patients (17.5%) at the time of first diagnosis of lymphoma, and in 45 of 120 patients (37.5%) at any point in time. However, as no histological confirmation of suspected mesenteric lymphoma is available, the association between mesenteric alterations and NHL needs further study. In the presented study, mesenteric alterations were diagnosed in 24 of 120 patients (20%) on follow-up examinations, including 10 patients with initial bulky disease. Gross initial tumour load might have made the initial diagnosis of mesenteric alterations impossible in these patients, while these alterations became radiologically visible after tumour shrinkage. In a general patient population, the differential diagnosis of mesenteric alterations includes a wide range of diseases, such as mesenteric oedema by hypoalbuminaemia, heart failure, lymphoedema, inflammation by pancreatitis, haemorrhage and trauma, or neoplasms [8]. The pathophysiologic mechanism underlying mesenteric abnor-

Table 3. Significant univariate prognostic factors for overall survival

	Patients with available data, n	HR	95% CI	p value
CRP > 8 mg/l	68	4.8	1.6–14.4	0.005
γ-GT > 50 U/l	91	3.2	1.4–7.2	0.004
Lower clearance (by 10 ml/min)	92	1.2	1.0–1.5	0.033
LDH > 450 U/l	93	2.8	1.2–6.1	0.01
Abnormal leukocytes	91	3.3	1.5–7.1	0.002
Abnormal thrombocytes	91	2.7	1.3–5.9	0.01
Higher IPI (by 1 unit)	120	2.3	1.5–3.3	<0.0001

HR = Hazard ratio; CI = confidence interval; CRP = C-reactive protein; GT = glutamyltransferase; LDH = lactate dehydrogenase; IPI = International Prognostic Index.

malities in lymphoma patients has not been studied systematically, but neoplastic infiltration of the mesentery and lymphoedema secondary to obstruction of the lymphatics may be most likely. No correlation with lymphoma subtypes was found in the presented study, but mesenteric alterations were frequently found in the small subgroup of patients with peripheral T-cell lymphoma (3 out of 6 patients). Although patients with mesenteric alterations on initial CT scans had a non-significant increase in mean overall survival (fig. 2), interpretation of this finding remains hypothetical. Mesenteric alterations might be a surrogate for active immune response to underlying lymphoma, which in turn could result in improved clinical outcome.

Increased CRP levels and lower creatinine clearance were significantly associated with increased mortality in the univariate model (table 3), but not in the multivariate model. CRP has previously been described as a prognostic marker in NHL by Legouffe et al. [7]. Physiologically, CRP synthesis is boosted by IL-6 which in turn plays a central role in normal B-cell maturation and proliferation of some B-cell neoplasms [23]. In the latter study, CRP was significantly correlated with IL-6 and LDH levels. This collinearity between CRP and LDH may account for the lack of an independent prognostic value of CRP in addition to the IPI score. Similarly, impaired renal function was no longer significant in a multivariable survival model. However, our study did not have the power to exclude a milder association between decreased renal function and mortality.

In conclusion, this retrospective screening study found a moderate prevalence of mesenteric alterations in patients with various subtypes of NHL. In about 50% of the patients, these findings could not be explained by direct mesenteric tumour invasion or overt lymphatic obstruction. Further studies should clarify the diagnostic value of mesenteric alterations for underlying lymphoma.

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