

# **Clinical aspects of extranodal non-Hodgkin's lymphoma manifestations of the central nervous system and the gastric ventricle**

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## 2. ABBREVIATIONS

ASCT	autologous stem cell transplantation
CI	confidence interval
CNS	central nervous system
CR	complete remission
CSF	cerebrospinal fluid
CT	computer tomography
DLBCL	diffuse large B-cell lymphoma
FL	follicular lymphoma
GIT	the gastrointestinal tract
Gy	Gray
HDT	high dose therapy
HRQOL	health related quality of life
i.t.	intrathecal
IPI	international prognostic index
LDH	serum lactate dehydrogenase
MRI	magnetic resonance imaging
NHL	non-Hodgkin`s lymphoma
NRH	the Norwegian Radium Hospital
OS	overall survival
PGL	primary gastric lymphomas
PR	partial remission
QOL	quality of life
REAL	Revised European-American Classification of Lymphoid Neoplasms
SCNSL	systemic CNS lymphoma
WHO	World Health Organisation

### **3. LIST OF PUBLICATIONS**

#### **Paper I**

A.Hollender, S.Kvaloy, K.Lote, O.Nome, H.Holte.

Prognostic factors in 140 adult patients with non-Hodgkin`s lymphoma with systemic central nervous system (CNS) involvement. A single centre analysis.

European Journal of Cancer. 2000; 36: 1762-1768.

#### **Paper II**

A.Hollender, S.Kvaloy, O.Nome, E.Skovlund, K.Lote, H.Holte.

Central nervous system involvement following diagnosis of non- Hodgkin`s lymphoma: a risk modell.

Annals of Oncology. 2000;13: 1099-1107.

#### **Paper III**

M.J. Hjermsstad, A.Hollender, T.Warloe, K.O.Karlsen, I.Ikonomou, S.Kvaloy, O.Nome, H.Holte.

Quality of life after total or partial gastrectomy for primary gastric lymphoma.

Acta Oncologica. 2006; 45: 202-209.

#### **Paper IV**

A.Hollender, T.Bjørø, K.O.Karlsen, S.Kvaloy, O.Nome, H.Holte.

Vitamin D deficiency in patients operated on for gastric lymphoma.

Scandinavian Journal of Gastroenterology. 2006; 41: 673-81.





## **4. INTRODUCTION**

This thesis deals with clinical aspects of extra nodal manifestations of non-Hodgkin's lymphoma (NHL) of patients treated at the Norwegian Radium Hospital. Paper I and II describes clinical symptoms and outcome in lymphoma patients with manifestations of the central nervous system (CNS) from systemic lymphoma (paper I) and investigates risk factors for developing CNS disease (paper II). In paper III and IV, we have investigated the outcome and long term side effects of the treatment involving primary surgery in patients with primary involvement of the gastric ventricle.

Extranodal non-Hodgkin's lymphomas arise from tissues other than lymph nodes. These lymphomas constitute 25% of all lymphomas in North America compared to 30-48% in Western Europe (Freeman et al. 1997, Glass et al. 1997, Otter et al. 1989, D'Amore et al. 1991).

Primary CNS lymphoma is defined as isolated lymphoma involvement of the CNS and constitutes only 1-2% of all non-Hodgkin's lymphomas (Krogh-Jensen et al. 1994). In most cases, the manifestation presents as parenchymatous intracerebral lesions, but isolated cerebrospinal fluid (CSF) involvement may occur. Primary CNS lymphomas are not discussed further in this thesis.

CNS involvement at the time of diagnosis of systemic lymphoma most often involves the CSF. Progression or relapse in CNS is a feared complication, and occurs both in the brain parenchyma and in the CSF. Its occurrence is described in detail in paper I and II. The gastrointestinal tract (GIT) is the most common primary extranodal localization, accounting for 12-13 % of all NHL and 30-40% of all extranodal sites (Herrmann et al. 1980, d'Amore et al. 1994).

The incidence of NHL has increased during the last decades, with 852 new cases of NHL in Norway in 2006 (Cancer Registry of Norway).

### **4.1 Lymphoma classifications**

Various lymphoma classifications have been used in the Western world during the last decades, but in Norway at the time this thesis was performed, the updated Kiel classification was used (Stansfeld et al. 1988). This classification divides the lymphoma entities based on their presumed cell of origin. In essence the diagnosis is based on

light microscopic histological examinations. Standard formalin-fixed haematoxylin-eosin stained slides are used. In addition, T-and B-cell origin of the lymphomas have been examined on either immunostained formalin fixed slides or mononuclear cell suspensions prepared from the lymphoma biopsies. It also divided the histologies into low- and high grade disease based on their clinical aggressiveness (Brittinger et al. 1984).

In 1999, The *World Health Organisation (WHO) Classification of Hematologic Malignancies* was published (Jaffe et al. 2001). This classification was largely based on *The Revised European-American Classification of Lymphoid Neoplasms (REAL)*, a lymphoma classification suggestion published in 1994 (Harris et al. 1994). Each disease was defined by morphology and more detailed immunophenotype as well as molecular characteristics and clinical features. The WHO classification was very soon adopted throughout the world. Thereby, it is possible to compare lymphoma epidemiology and treatment results worldwide. In paper I and II, the Kiel classification is used while in paper III and IV, the histology is revised according to the WHO classification. The REAL and WHO classification may be divided into three clinically relevant categories, indolent, aggressive and very aggressive disease (Hiddemann et al.1996).

#### **4.2 Staging of lymphomas**

Lymphomas are staged according to the Ann Arbor classification (Carbone et al. 1971) with modifications (Lister et al. 1989) as listed in the following table:

Stage I: Involvement of one lymph node region (spleen, thymus and Waldeyers ring are regarded as nodal).

Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm, or one or more lymph node regions on the same side of the diaphragm with growth into extralymphatic organ / tissue (IIE).

Stage II suffix 1: Involvement of two neighbouring regions which can be included in one radiation field.

Stage III: Involvement of lymph node regions on both side of diaphragm, or one or more lymph node regions on both side of the diaphragm (with growth into extranodal organ / tissue (IIIE)).

Stage IV: Diffuse or disseminated lymphoma in one or more extralymphatic organ / tissue with or without involvement of lymph nodes.

The suffix E for stages I-III denotes extranodal disease.

The stage of the disease is an important risk factor for non-Hodgkin's lymphoma and is used in treatment decisions.

### **4.3 Disease assessment**

Treatment decision of patients with suspected lymphoma is dependent on

- adequate relevant history with emphasis on the presence or not of B-symptoms (fever of unknown origin, weight loss of more than 10% of the body weight and night sweats), the time from the first symptoms or signs, history of infections, pain, vital functions and the clinical performance status
- clinical examination with emphasis on lymph node status and the presence of other masses, spleen and liver enlargement, mental status, signs of neurological disease and vital organ examinations
- adequate sampling of pathological masses for histopathological diagnosis
- bone marrow biopsy and for some entities bone marrow aspirate for immunological assessment by flow cytometry
- Computer tomography (CT) scans of the chest, the abdominal and pelvic regions
- supplementary investigations, particularly of the a) cerebrospinal fluid (cell count, protein, glucose and flow cytometric analysis) in cases of very aggressive lymphomas (lymphoblastic lymphomas, Burkitt's lymphoma) and aggressive lymphomas with risk factors for CNS relapse, and combined with magnetic resonance imaging (MRI) examinations in cases with mental deterioration or other CNS related symptoms like seizures and neurological findings b) alimentary tract examinations in cases of GIT-related symptoms and signs like hematemesis, melena and diarrhoea and in specific histological diagnosis often involving the alimentary tract.

Patients are staged according to the Ann Arbor system (Carbone et al. 1971, Lister et al. 1989). For extranodal disease, the Nordic countries have used a Nordic classification system from 1997, but as this classification system is unpublished, paper III and IV classifies the gastric lymphomas according to Musshoff et al. (1977).

### **4.4 Clinical risk factors**

Given the same histological entities, patients with younger age and limited disease have generally a better prognosis than patients at higher age and with more extensive

disease. Other clinical and biological risk factors (like assessment of the proliferation rate of the tumour assessed by the activation antigen Ki67) have been published, but did not achieve general acceptance. In 1994, however, an international consortium undertook a retrospective examination of clinical risk factors in aggressive lymphomas (The International non-Hodgkins lymphoma prognostic factor project, 1994). During the last ten years, these risk factors named International Prognostic Index, IPI, have been used widely in risk stratification of patients with aggressive lymphomas and in comparing treatment results of new regimens. Similarly, another international group performed a similar retrospective analysis in follicular lymphoma (Solal Séligny et al. 2004) with similar impact worldwide. This index is called Follicular Lymphoma International Prognostic Index. Although these prognostic indexes have not been applied in the papers of this thesis, they are shown in table 1 and 2.

Table 1. International Prognostic Index for aggressive lymphomas

<u>All ages</u>	<u>Patients &lt; 60 years</u>
<u>Risk factors</u>	<u>Risk factors</u>
Age > 60 years	-
Serum LDH above normal	Serum LDH above normal
> 1 extranodal site	-
WHO status $\geq 2$	WHO status $\geq 2$
Stage III/IV	Stage III/IV

Table 2. Follicular Lymphoma International Prognostic Index

Age > 60 years
Stage III/IV
Hemoglobin level < 120 g/L
Serum LDH above normal
Number of nodal sites > 4

For both the IPI and the FLIPI scores, the individual risk factors are largely of the same relative risks. For estimating the total risk, the individual factors are simply added.

#### **4.5 Summary of general treatment recommendations**

The first line treatment recommendations at the Norwegian Radium Hospital for the period 1990 – 2000 are briefly summarized as follows:

Indolent lymphomas (or low grade lymphomas according to the Kiel classification), stage I and stage II for those patients with adjacent lymph node involvement were given high energy radiotherapy, 40 Gy / 20 fractions. Patients with extensive disease without symptoms requiring therapy were observed until treatment requirements were met: B-symptoms, cytopenias or lymph node enlargement with symptoms of discomfort or with impaired organ function like medullary compression or urethral obstruction. When these requirements were met, patients were most often given chlorambucil monotherapy (for some patients in combination with steroids).

High grade lymphomas stage I and stage II as defined on page 8 were given 3 – 6 courses of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone), followed by radiotherapy, 40 Gy. Patients with extensive disease were generally given CHOP chemotherapy alone.

Very aggressive lymphomas (lymphoblastic lymphomas and Burkitt lymphomas) were until 1990 given CHOP chemotherapy, 4 courses with intrathecal methotrexate and high dose i.v methotrexate, 2 g /m<sup>2</sup> with folinic acid rescue at week 2 between 3-weekly CHOP. Patients achieving a good partial remission were consolidated with high dose therapy with autologous stem cell support (HDT with ASCS). After 1990, patients with lymphoblastic lymphomas were given induction chemotherapy with regimens as given for acute lymphoblastic leukemias and those with Burkitt lymphomas a regimen adopted from a German protocol for children with Burkitt leukaemia / lymphoma. Both of these very aggressive lymphomas were still consolidated with HDT with ASCS.

##### **4.5.1 Treatment recommendations for patients with systemic lymphoma with CNS involvement at diagnosis**

Most of these patients had aggressive or very aggressive lymphoma and were treated as for very aggressive lymphomas. Patients with aggressive lymphomas with progression in the CNS or CNS relapse were also generally given the same treatment regimen with intensified i.t. therapy combined with systemic therapy with CNS

penetration (high dose methotrexate in some cases combined with high dose cytarabine). The few patients who received a complete remission were consolidated with HDT with ASCS and irradiation to the CNS axis.

Earlier studies (Herman et al. 1979, Litam et al. 1979, Ersboll et al. 1985, Wolf et al. 1985, Liang et al. 1990) have described specific organ involvement as risk factors for CNS relapse (ocular orbit, paranasal sinuses, bone, testis and bone marrow). Patients with these risk factors were given i.t methotrexate prophylaxis, in younger patients combined with high dose methotrexate with folinic acid rescue.

#### 4.5.2 Patients with primary CNS lymphomas

These patients were not included in this thesis. They were for the first time period treated with high dose methotrexate, 2-3 g/m<sup>2</sup> 4-6 courses and consolidated with high energy radiotherapy to the brain, 40 Gy/20 fractions. During the later time periods, these patients were included in a Nordic protocol for PCNSL (Goldkuhl et al. 2002) or treated according to a protocol developed at Memorial Sloan-Kettering Cancer Centre. (Abrey et al. 2000).

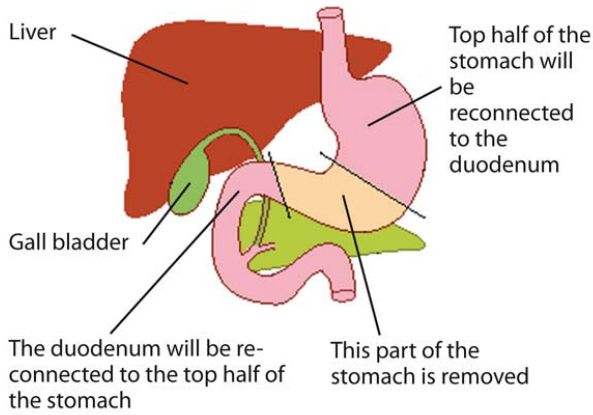
#### **4.6. Primary surgery for gastric lymphomas**

Patients with primary extranodal lymphomas followed generally the outlines described above. However, a different approach was used for patients with lymphomas involving the gastric ventricle. Due to reports of high frequency of serious bleeding or gastric perforations after initiation of primary chemotherapy (Fleming et al. 1982) a protocol was initiated in 1990, involving primary gastric surgery when technically feasible. The inclusion criteria and the treatment are outlined in paper III and IV. Most patients with indolent lymphomas with only superficial gastric wall involvement were generally not operated on.

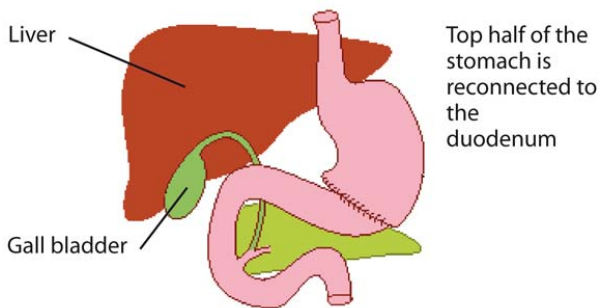
There are different surgery procedures, and the chosen method depends on where the lymphoma is localized. If the lymphoma is distal, partial gastrectomy can be performed, Bilroth I or Bilroth II (figure 1 and figure 2). The stomach will be smaller after the operation, but the cardiac sphincter will be preserved. If the lymphoma is in the middle of the stomach, the entire stomach is removed, but the bile duct and pancreatic duct continues to drain into the duodenum. The total gastrectomy operation is called Roux-

en-Y (figure 3). (Cancer Research UK 2002, Cancer Research UK Charity Number 1089464).

### Bilroth 1 (before)



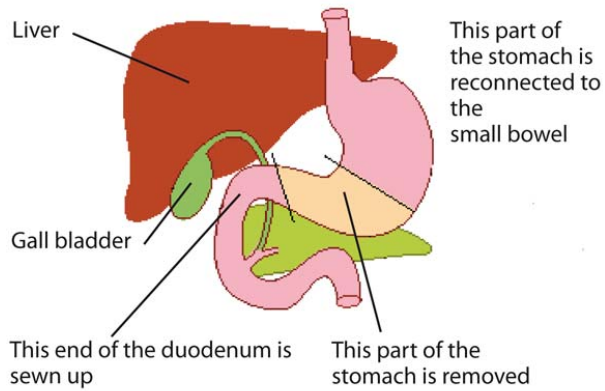
### Bilroth 1 (after)



This operation removes part of the stomach

Figure 1. Partial gastrectomy ad modum Bilroth 1.

### Bilroth 2 (before)



### Bilroth 2 (after)

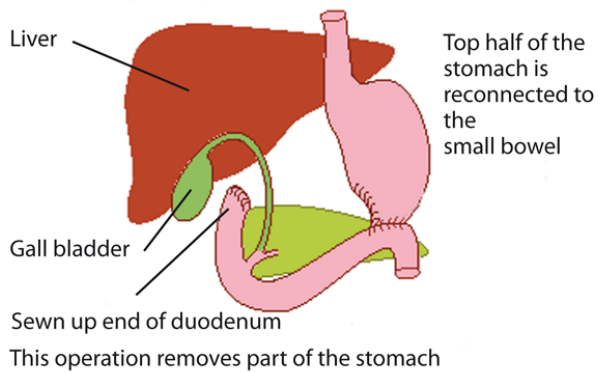
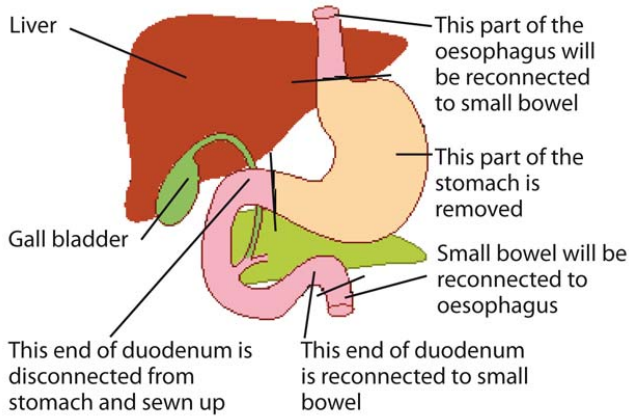


Figure 2. Partial gastrectomy ad modum Bilroth 2.



### Roux-en-y (before)



### Roux-en-y (after)

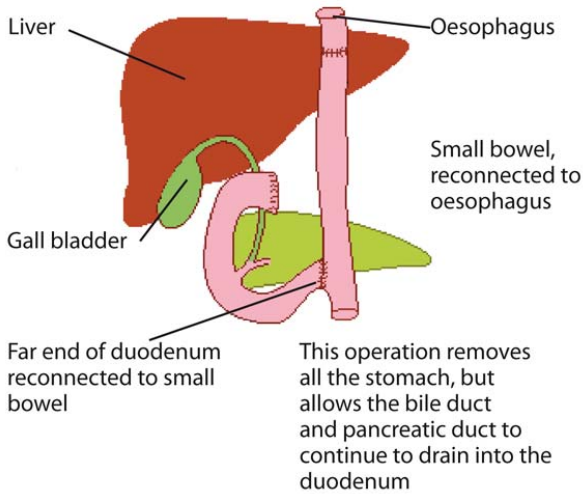


Figure 3. Total gastrectomy ad modum Roux-en-Y.

#### 4.6.1 Examinations of long term side effects after primary surgery for gastric lymphomas

Recently, the recommendation of performing primary surgery in gastric lymphomas has been largely abandoned due to several reasons as described in paper III and IV:

1. The risk of gastric perforation or serious bleeding after primary chemotherapy seems to be lower than previously described. Furthermore, the effect of chemotherapy alone seems as effective as combined surgery and radiotherapy (Al Akwaa et al. 2004, Yoon et al. 2004, Koch et al. 2001 and 2005, Binn et al. 2003).
2. In marginal zone lymphoma, stage IE the association of the disease with H. pylori infection and the effect of H.pylori eradication with antibiotics is effective in two thirds of the cases (Bertoni et al. 2005).
3. Long term morbidity after primary gastric surgery has evolved as a major concern in carcinoma patients operated for gastric carcinomas.

There was, however, no study which had studied the long term health status of gastric lymphoma patients after surgery. Consequently, we undertook a cross-sectional follow up examination of the patients several years after they were treated according to the protocol, examining the patients' nutritional status and quality of life. In addition, a gastroscopy was performed, and the overall results of the treatment protocol were investigated. The patients were informed of the results of the investigation, and advices as to supplementary therapy were given by mail when indicated.

#### 4.7 Health related quality of life in cancer patients

During the two last decades, there has been an increasing focus on health related quality of life (HRQOL) after treatment for cancer. HRQOL focuses on the subjective experiences of the disease, the treatment and its side effects. Quality of life (QOL) studies gives a more comprehensive view of the lives of cancer patients than remission rates and survival analyses alone. In many phase III studies, comparing established therapy with a new and hopefully better therapy, QOL analysis is often integrated in the protocols.

HRQOL is defined as a multidimensional concept, consisting of at least physical, psychological and social phenomena (Aaronsen 1991, Cella et al. 1993). The domains are further divided into various dimensions (physical, social and occupational function, emotional well-being, intimacy issues). The patient is the most reliable source for the HRQOL concept, which is subjective in its nature (Aaronson 1991, Cella et al. 1993). A low correlation between the nurses and the doctor's conception of the well-being of the

patient and the patient's own rating has been documented (Slevin et al. 1988, Sprangers et al. 1992). HRQOL is therefore usually investigated by using validated questionnaires.

#### **4.8 Examinations of the nutritional status after primary surgery for gastric lymphoma**

The most common deficiencies after total gastrectomy (TG) and partial gastrectomy (PG) is related to iron, folic acid, vitamin B<sub>12</sub> and fat indigestion with steatorrhoea, weight loss, vitamin D and vitamin K loss. Except for vitamin K status, these factors were all examined.

The metabolic deficiencies developing two or more years after total gastrectomy continually aggravates, i.e. anaemia, osteoporosis / osteomalaci and loss of body weight (Murawa et al. 2006). In addition to disturbance of the absorption in the gastrointestinal tract, the patients also have a problem with inadequate calorie intake – due to absence of hunger, dyspepsia secondary to agastria, alteration of intestinal mobility, and early satiety (Braga et al.1990).

Most studies concerning the nutritional status after gastrectomy have been studies on gastric cancer as these are more frequent than gastric lymphoma. Gastric cancer has a disease-specific 5 year survival less than 30% (Paimela et al. 2005). Patients with lymphoma in the gastric ventricle live for a considerably longer time; 70-80 % are alive after five years when the disease is limited at diagnosis. It is thus important to take care of and follow up the nutritional status for these lymphoma patients with dietary education and – advices for many years.

##### **4.8.1 Albumin**

The plasma level of albumin is a common nutritional index. Albumin is however, not a sensitive indicator of early malnutrition, and in addition, there are several mechanisms that compensate for low level of serum albumin (Waterlow 1972).

##### **4.8.2 Body Mass Index**

The nutritional status of the patients was also examined by estimation of body mass index (BMI, body weight / square height in m), which is another measure of general nutrition status. As the body weight and height was available from the time of the diagnosis, we were able to measure the gain or loss in BMI.

#### 4.8.3 Vitamin B<sub>12</sub> / folic acid / homocysteine

The absorption of vitamin B<sub>12</sub> (cobalamin) is dependent on binding to the intrinsic factor, a glycoprotein produced in the mucosa in the gastric ventricle. The complex is absorbed in the small intestine. 1-3% vitamin B<sub>12</sub> can be absorbed by simple diffusion without the intrinsic factor (reviewed in Nes et al. 1998). Regularly injections of vitamin B<sub>12</sub> are recommended after gastric surgery. Deficiency of vitamin B<sub>12</sub> leads to megaloblastic anaemia, which also can be caused by lack of folic acid. In that case, it is very important never to give folic acid alone, but always together with vitamin B<sub>12</sub> to avoid neurological symptoms, as folic acid may cover the symptoms of vitamin B<sub>12</sub> deficiency.

Homocysteine is an endogen amino acid, made in the cells by transformation from the essential amino acid methionine. The intracellular turnover of homocysteine depends mainly on folic acid, vitamin B<sub>12</sub> and vitamin B<sub>6</sub>. If one or more of the homocysteine metabolizing pathways are inhibited due to enzymatic defects or vitamin deficiencies, homocysteine accumulates, thereby causing an increased level of homocysteine in the plasma (reviewed in Refsum et al. 1998). Homocysteine is a highly reactive substance, and high levels can damage the endothelium and contribute to development of atherosclerotic coronary heart disease (reviewed in Stakkestad et al. 2000). Refsum et al. (1998), has reviewed the literature on homocysteine in relation to cardiovascular disease. They conclude that an elevated level of total homocysteine in blood is a prevalent and strong risk factor for atherosclerotic vascular disease in the coronary, cerebral, and peripheral vessels, and for arterial and venous thromboembolism. Elevated homocysteine confers a graded risk with no threshold, is independent of but may enhance the effect of the conventional risk factors, and seems to be a particularly strong predictor of cardiovascular mortality.

Nygard et al. (1997) prospectively investigated the relation between plasma total homocysteine levels and mortality among 587 patients with angiographically confirmed coronary artery disease. They concluded that plasma total homocysteine levels are a strong predictor of mortality in these patients.

#### 4.8.4 Iron

Intact epithelial cells in the GIT and normal production of gastric acid are important in the absorption of iron in the small intestine. Most of the non-heme iron in the food exists as a salt with Fe<sup>3+</sup>. In the acid environment, the inorganic iron salt will be ionized into

Fe<sup>3+</sup>, and when reduced to Fe<sup>2+</sup> (with help from i.e. vitamin C ) it is more easily absorbed.

According to Roviello et al. (2004), iron deficiency following a gastrectomy is due to accelerated passage of food through the intestine, resulting in an insufficient time of contact between the absorbing mucosa and the contents of the lumen (Murawa et al. 2006, Stael von Holstein et al. 1991). Reduced gastric acidity can also contribute to less absorption (Murawa et al. 2006). In addition, in patients with chronic gastritis of the gastric stump, small but repeated areas of bleeding from lesions of small mucosal vessels increase the loss of iron in the intestines.

#### 4.8.5 Vitamin D and calcium absorption

##### *The photosynthesis of vitamin D in the skin, and vitamin D's biochemistry*

Vitamin D can be made by the influence of ultraviolet (UV) radiation through the sunlight, or supplied through the diet.

7-dehydrocholesterol is made in the skin, the production is decreasing with age due to a thinner skin. 7-dehydrocholesterol absorbs UV radiation and converts into the pre-vitamin D<sub>3</sub> in a thermic reaction. Vitamin D<sub>3</sub> (from the skin or the diet) is transported to the liver and hydrolyzed to 25-OH- vitamin D<sub>3</sub> (calcidiol). This metabolite is a reliable indicator of the vitamin D status, and is thus the recommended metabolite to be measured (normal serum range 30-100 nmol/l). Calcidiol is then transported to the kidneys, and transformed into 1, 25-(OH)<sub>2</sub> vitamin D<sub>3</sub> (calcitriol) by the enzyme 25-hydroxyvitamin D1 alfa-hydroxylase. The activity of this enzyme is stimulated positively by parathormone (PTH), hydrogen-, phosphate- and calcium ions, estrogen, prolactin, insulin, calcitonin, growth hormone and glucocorticoids, and is inhibited by calcitriol itself (reviewed in Moan et al. 2006). Calcitriol is the active hormone in the regulation of calcium and phosphate in the blood. Vitamin D's biochemistry is illustrated in Figure 4 (reviewed in Moan et al. 2006 and Nes et al. 1998).

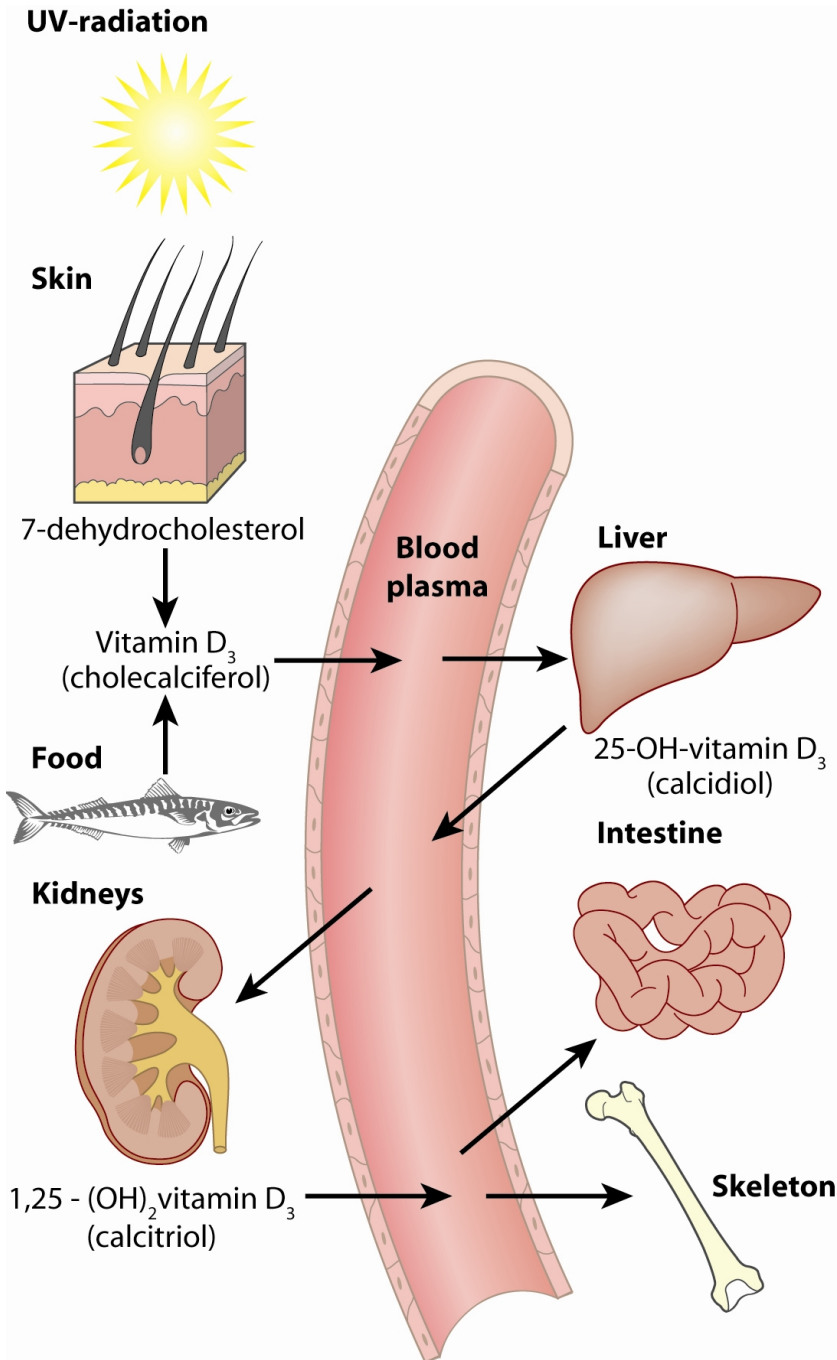


Figure 4. Vitamin D's biochemistry.

### *Functions of vitamin D*

The major function of vitamin D is to maintain calcium homeostasis.

Vitamin D is necessary for normal mineralization of the skeleton, by stimulating the absorption of calcium in the intestine. PTH stimulates the release of calcium from the skeleton (by influencing the osteoclast activity) and thereby raising the concentration of calcium in the blood. A low calcium or phosphate stimulates the secretion of PTH, which in turns stimulates the production of  $1,25(\text{OH})_2\text{D}_3$  in the kidneys (reviewed in Nes et al. 1998 and Moan et al. 2006).

### *Absorption*

Vitamin D in the diet is absorbed together with fat, and is then transported to the liver bound to vitamin D-binding protein. Most of the vitamin D is stored in the fat tissue. For those who are gastrectomized, the malabsorption of fat affects the absorption of vitamin D and thereby reduced calcium absorption. The reason for fat malabsorption is largely unclear. Factors associated with this condition after total gastrectomy are insufficient acid production and insufficient mixing of food and digestive juices, rapid intestinal passage and altered bacterial flora in the small intestine (Stael von Holstein et al. 1991, Bae et al. 1998).

## **5. AIMS**

The thesis focuses on clinical aspects of extranodal manifestations of non-Hodgkin's lymphoma in the CNS and the gastric lymphoma. All patients have been examined, and treated according to protocols at the Norwegian Radium Hospital during the last two decades of the previous century.

The main objectives of the studies were:

- 1) Examine the outcome of the patients with NHL with systemic involvement of the CNS, in order to evaluate our treatment strategy.
- 2) To determine the incidence and risk factors for CNS relapse in patients with NHL.
- 3) For patients with lymphoma in the GIT treated according to a protocol utilizing primary gastric surgery to examine the quality of life at a cross-sectional examination.
- 4) For the same patient cohort as in 3) to examine the nutritional status.

## 6. PATIENTS AND METHODS

### 6.1 Patients

All patients were admitted, examined and treated at The Norwegian Radium Hospital (NRH) during the time period 1980 – 1999. They all had a diagnosis of non-Hodgkin's lymphoma, based on histopathological examinations at the institution. The hospital had the responsibility for lymphoma patients for approximately 2 mill. inhabitants. Patients with a curative treatment intent were admitted, based on the general policy at the Health Region. Patients included in the investigations on systemic CNS manifestations were diagnosed and treated during the period 1980 – 1996 and the patients with gastric lymphoma during the period 1990 – 1999.

#### 6.1.1 Patients with CNS manifestations after a diagnosis of non-Hodgkin's lymphoma

2561 patients with NHL were diagnosed and treated at the NRH from 1980 to 1996. 170 of these patients had CNS involvement (6.6%), 30 of these had primary CNS involvement and the remaining 140 had systemic CNS lymphoma, the latter group being the patients at investigation in paper I. Thirty of these patients had CNS manifestations at diagnosis, 27 patients at relapse and 83 patients at progression.

#### 6.1.2 Patients at risk for CNS relapse or progression

2514 patients were included, excluding patients with PCNSL and with systemic CNS manifestations at diagnosis. The survivors were followed for a median observation time of 94 months.

#### 6.1.3 Cross-sectional follow-up study of patients with primary involvement of the gastric ventricle

A total of 120 patients with involvement of the gastric ventricle were retrieved from the database. The overall treatment results reflect that only 40 patients (33%) had localized disease. The median age of the patients at diagnosis was 63 years. The inclusion criteria for the cross-sectional study were as follows: Patients aged 16-80 years treated according to the standard protocol at NRH during the period from 1990-1999, age below 80 years and in complete remission (CR) at follow up, no prior history of cancer, fluency in oral and written Norwegian and written informed



consent. The study was approved by the institutional review board at NRH and Norwegian Social Science Data Services. A total of 40 patients met the inclusion criteria, 36 patients completed the QOL questionnaires while 33 patients met for the clinical examination.

## **6.2 Methods**

The patients were registered prospectively in a clinical lymphoma database using software from DataEase (DataEase International LTD., Romford, UK, 1991), including the following variables:

- name and birth number
- histopathological diagnosis
- relevant information from staging procedures before treatment initiation including details concerning sites of lymphoma involvement, performance status, blood test results, largest tumour mass, IPI score
- date of and details concerning initiation of primary treatment
- response to primary treatment
- date of first relapse or progression and details concerning second line treatment
- response to second line treatment
- third line treatment with response
- date of and state at last visit
- data on patients lost at followed up were retrieved four times a year from Statistical Norway after consent from The Data Inspectorate. These data told whether the patients were alive or dead from any reason, but not the cause of death or the disease status for living patients.

Updating of the database for patients no longer followed at NRH is a challenge, partly met by continuously registering polyclinic notes and other reports from the local hospital. For patients not longer followed at NRH and for whom no information from the local hospital were available for the last year, these data were asked for at the local hospital during the last 1990'ies.

The statistical analyses in all the studies were performed by using the SPSS for windows (Release 8.0, SPSS Inc., Chicago, IL., USA). The Kaplan-Meier method

(Kaplan et al.1958) was used for survival analysis, and the survival curves were compared by the logrank test (Peto et al. 1973). Multivariate analysis was performed by the Cox regression analysis.  $P < 0.05$  was considered as statistically significant, except in paper II in which  $p < 0.01$  was used due to the high number of variables examined. Comparisons between groups were analyzed by the Mann-Whitney U-test or the qui square test, whichever appropriate (paper III and IV).

### 6.2.1 Patients with CNS manifestations after a diagnosis of non-Hodgkin's lymphoma (paper I)

This is a retrospective analysis. To retrieve information on symptoms at CNS diagnosis, to control and supplement the database on the given treatment and the basis for the CNS lymphoma diagnosis, all patient records were analyzed. As the survival data could be controlled by information from Statistics Norway and as the cause of death in patients with CNS manifestations in systemic lymphoma in nearly all cases were due to death from lymphoma, we used crude survival as the endpoint.

#### Paper II

The incidence and risk factors for CNS progression or relapse were examined retrospectively. Median observation time was 94 months (range 13-202 months) for the survivors. Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) scale. The histological diagnosis was assessed according to the Kiel classification, and was not reviewed for this analysis. The relatively low number of T-cell lymphomas and the high numbers of low grade unclassified and high grade unclassified, reflects that some diagnoses were made before adequate immunohistology was available.

The following factors were registered as potential risk factors for CNS involvement and entered into univariate analysis.

*Clinical variables:* gender, ECOG performance status 0-1 versus 2-4, age below or above 60 years, bulky disease ( $\geq 6$  cm), stage, B- symptoms, IPI (Shipp et al. 1993), age-adjusted IPI, B-or T-cell phenotype.

*Laboratory tests:* erythrocyte sedimentation rate, lymphocyte count, hemoglobin, thrombocytes, LDH, alanine aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, albumin, calcium.

*Lymph node involvement at the following sites (including the spleen):* neck, supraclavicular region, axilla, groin, mediastinum, retroperitoneum, iliacal region, spleen and the mesenterial lymph nodes.

*Extralymphatic involvement:* testicles, lungs, pleura, liver, ventricle, small intestine, colorectal, pancreatic gland, mammary glands, gynecological sites, skin, thyroid gland, bone marrow, skeleton and ear, nose and throat regions, including the paranasal sinuses, parotid and submandibular glands.

The basis for the CNS diagnosis is given in the paper.

#### 6.2.2 Cross-sectional follow-up study of patients with primary involvement of the gastric ventricle (paper III – IV)

The survival analysis of all the 120 patients treated according to the protocol was retrospective. The 40 patients eligible for the study (see patients) were invited by mail to participate in the cross-sectional studies. They received two QOL questionnaires and patient information, and they returned the questionnaires together with the signed informed consent.

The standard baseline questionnaire used in our study as well as in most European HRQOL studies on cancer patients is the EORTC QLQ-C30 (Aronson et al. 1993). The questionnaire is described under Methods in paper III. The questionnaire is not very specific on symptoms like gastrointestinal complaints, fatigue and pain. Accordingly, modules with questions penetrating in depth into specific health problems have been constructed to be used in addition to the EORTC QLQ-C30 questionnaire. Shortly before our study was planned, the gastric module STO22 was released and available as a questionnaire for our patient group. The STO22 questionnaire is also described under Methods in Paper III.

The median observation time for the 33 patients who met for a clinical examination was 102 months (range 34-148). The same patients were examined by case history, clinical examination, upper endoscopy and blood tests as described in paper IV. Surgical procedure performed and weight and height at diagnosis was retrieved from the patient records. The patients received the results from the study by mail and dietary advices if indicated by the blood tests.

## **7. RESULTS AND SUMMERY OF PAPERS**

### **7.1 Paper I**

We examined crude survival from the time of the CNS diagnosis in 140 patients with systemic lymphoma, either at diagnosis of the systemic lymphoma, at progression during therapy or at relapse for patients who had achieved a complete remission. The impact of CNS related symptoms, age, histology and treatment from the CNS diagnosis were evaluated. The overall median survival for the 140 patients with SCNSL was only 2.6 months (95% CI: 2.1-3.2). Only 12 patients were alive in CR at the time of investigation. Patients with CNS involvement at diagnosis had the best prognosis (5.4 months), those who developed CNS disease during treatment the worst with a median survival of only 1.8 months (95% CI: 1.0-2.7). Notably, five of the eight patients consolidated with HDT are in CR. Paresis was the only symptom that predicted a shorter survival for SCNSL. Patients above 60 years of age with CNS involvement at progression or relapse also have a dismal prognosis.

Patients under 60 years of age with chemosensitive disease have better prospects, and they should be offered intensive chemo-radiotherapy including HDT with autologous stem cell support.

### **7.2 Paper II**

The incidence and risk factors for CNS disease in consecutively treated patients were investigated. Among the 2514 patients with NHL, 106 patients (4.2%) developed CNS involvement during primary treatment (n=36) or at relapse (n=70). The percentage CNS recurrence according to the Kiel classification at 5 years were as follows: low grade, 2.8%; high grade, 4.3%; lymphoblastic or Burkitt's lymphoma, 24.4%. Multivariate analysis identified five independent risk factors, each present in > 5% of patients: elevated LDH, serum albumin < 35g/l, < 60 years of age, retroperitoneal lymph node involvement and involvement of more than one extranodal site. If four or five of these risk factors were present, the risk of CNS recurrence was in excess of 25% at 5 years. From 1990 onward, patients less than 60 years of age with lesions in the paranasal sinuses, bone, epidural space, testis and in the bone marrow should receive CNS prophylaxis in the form of i.t methotrexate (some patients additionally received high dose methotrexate). When comparing patients given CNS prophylaxis with those who did not receive

prophylaxis, having the same risk factors, we could not detect any prophylactic effect of i.t. methotrexate.

### **7.3 Paper III**

In the time period from 1990-1999, 120 patients with gastric non-Hodgkin's lymphoma were treated in a protocol involving primary gastric surgery at defined indications. The self-reported QOL (EORTC QLQ-30 and a gastric module) and objective findings from upper GI endoscopy were evaluated in patients less than 80 years of age and in complete remission at a median of 102 months after treatment for primary gastric NHL at the Norwegian Radium Hospital. 36 patients (90%) completed the questionnaire and 33 (83%) met for endoscopy. The median age at follow up was 67 years.

Seventeen of the patients who completed the questionnaires had a partial gastrectomy (PG), ten a total gastrectomy (TG) while nine were not operated on. General QOL was not different from population values according to the EORTC QLQ-30 module. The gastric module showed that patients treated with total gastrectomy reported more emotional problems, had more diarrhoea and more food-related problems ( $p < 0.05$ ) compared with the others. Gastroscopy was normal in 55% of the the patients who did not undergo total gastrectomy, oesophagoscopy in 69%. Four patients had Barret's metaplasia. Conclusion: Total gastrectomy leads to an inferior QOL and should be avoided when possible. When examining QOL, it is important to use the relevant questionnaires.

Survival analysis for the whole cohort of patients showed a disease specific 10-year survival of 88% and 40% for the patients with stage IE-IIE and stage IV, respectively.

### **7.4 Paper IV**

The nutritional status of 33 out of 40 eligible patients treated for gastric lymphoma according to a protocol involving primary surgery was examined at a cross-sectional study. The median observation time was 102 months after initiation of treatment, and the median age at follow up was 67 years.

Seventeen patients had a partial gastrectomy (PG), nine a total gastrectomy (TG) and seven were not operated on. The patients in the TG group had a significant weight loss, lower storage iron content (s-ferritin and s-iron saturation), lower s-

vitamin D, higher s-PTH and homocysteine than the other groups. It was concluded that if surgery is deemed necessary, a TG should be avoided whenever possible. The patients should be followed yearly for nutritional deficiencies and regular intake of vitamin D, vitamin B<sub>12</sub>, calcium, folic acid and iron should be considered.

## 8. DISCUSSION

### **8.1 CNS manifestations in systemic non-Hodgkin's lymphoma.**

CNS manifestations in non-Hodgkin's lymphoma may be seen at diagnosis, during primary therapy or at progression or relapse after primary therapy.

The incidence of CNS manifestations at diagnosis from our series of 30/2651 patients (1.2%) is in line with the results from Bollen et al. (1997). The incidence at diagnosis varies most of all with the histological subtypes, and is highest in Burkitt's lymphoma and Burkitt's leukemia. In a review of three consecutive treatment protocols from the German Adult Acute Leukemia Group, Hoelzer et al (Hoelzer et al. 1996) report an incidence of 8/67 patients (12%) while the incidence in paediatric series of Burkitt lymphoma and leukaemia is reported to be 67/514 patients (13%) from a French study (Patte et al. 2001) and 96/1092 (8.8%) from a German series (Salzburg et al. 2007). Generally, the incidence of CNS manifestations at diagnosis in acute lymphoblastic leukemia (of which Burkitt's leukemia constitutes only a small fraction) is reported to be 3-5% (Chamberlain et al. 2005). A CNS manifestation in follicular and other indolent lymphomas at diagnosis is at best scarce. A report of seven cases of indolent lymphomas includes one case with CNS manifestations at diagnosis, but this case was of small lymphocytic leukemia type (Spectre et al. 2005). The other cases developed at various time points after initial diagnosis, and in four cases, a transformation to aggressive lymphoma was documented. A new entity described only recently, marginal zone lymphoma of the dura is described as a special form of PCNSL, but is located outside the CNS blood-brain barrier. They are usually localized and can be cured in a high percentage of cases by local therapy, surgery or radiotherapy or both (Iwamoto et al. 2006).

There are numerous reports on the incidence of SCNS lymphoma at progression or relapse. Most investigations have been performed in aggressive lymphomas. The incidence amounts to approximately 5% in most series (Bos et al. 1998, van Besien et al. 1998) as in our investigation (Paper I and Paper II). However, some recent reports give lower incidences in the range of 1 – 2% (Boehme et al. 2007, Haioun et al. 2000, Arkenau et al. 2007). Possible explanations for these low figures are effective primary therapy with lower overall relapse rates due to effective therapy (Boehme et al. 2007, Haioun et al. 2000), to systemic and i.t. CNS prophylaxis to all

patients (Haioun et al. 2000) or i.t.methotrexate prophylaxis for high risk patients or shorter median follow up (Arkenau et al. 2007). In addition, Haioun et al. only registered patients with isolated CNS relapses. The incidence of SCNSL progression or relapse in L-NHL in our study was 2.8%. In a report of 7 cases of indolent lymphomas with SCNSL, four cases were related to transformation to aggressive lymphomas (Spectre et al. 2005). In our study, we performed a lymph node biopsy in 14/37 patients with an original diagnosis of L-NHL and found histological transformation in nine (64%) of the cases. It is also well possible that the lymphoma cells of these patients invading the CNS had a more aggressive phenotype.

The diagnosis of CNS manifestations is in the literature documented by cytological or cell count number of the CSF, by parenchymal manifestations by CT or MRI or by CNS-related symptoms like mental deterioration or nerve palsies as in our series. Recently, flow cytometric analysis of the CSF has been used and seems to increase the sensitivity of the leptomeningeal manifestations, at least by a factor of two (Hegde et al. 2005, Bromberg et al. 2007).

CNS manifestations in NHL more often involve the leptomeninges than the parenchyma (Haioun et al. 2000, Kantarjian et al. 1988) as in our series. In a series of primary mediastinal B-cell lymphomas, often involving contiguous extranodal manifestations in the mediastinum and lung metastasis, an increased relative frequency of parenchymal CNS disease was noted. They reviewed the relative frequencies as shown in Table 3 (Bishop et al. 1999).



Table 3. Sites of CNS Involvement in Large-Cell Lymphoma

Study	Total No. of Patients	Leptomeningeal		Parenchymal		Parenchymal and Leptomeningeal	
		No. of Patients	%	No. of Patients	%	No. of Patients	%
Bollen 1997	65	21	32	27	42	17	26
Keldsen 1996	27	9	33	15	56	3	11
Bashir 1991	14	11	79	3	21	0	0
Wolf 1985	44	23	52	20	45	1	2
Johnson 1984	29	23	79	3	10	3	10
Levitt 1980	52	44	85	8	15	0	0
Herman 1979	50	40	80	9	18	1	2
Litam 1979	31	26	84	4	13	1	3
Young 1979	20	16	80	2	10	2	10
Law 1975	20	16	80	1	5	3	15
Total	352	229	65	92	26	31	9

Bishop et al. J Clin Oncol 1999

The relative frequency of leptomeningeal / parenchymal disease of 2:1 is in line with the results from our investigations. In a recent review from the German High-Grade non-Hodgkin's Lymphoma Study Group (DSHNHL) of 1693 patients treated in randomized trials from 1993 – 2000, the relative frequency was inversed with 25 of 37 patients having intracerebral manifestations shown by radiological imaging.

SCNSL may be part of a systemic disease progression or relapse, or alternatively an isolated lymphomatous manifestation. The distinction is important as it is logical to presume that the former manifestation is caused by inadequate primary systemic therapy while the latter manifestation might be avoided by effective CNS prophylaxis. The exact relative numbers is not given in the publications of our series, but is given in Table 4 together with the other six publications from the last decade with a reasonable number of patients at risk.

Table 4. The relative frequency of CNS manifestations as isolated versus part of systemic relapse in patients with aggressive lymphoma (Lymphoblastic and Burkitt excluded)

	<u>Cohort</u>	<u>CNS prophyl.</u>	<u>No of patients</u>	<u>Isolated</u>	<u>Part of systemic</u>	<u>Total</u>
Haioun et al.	CR	both	974	16 (1.6%)	6 (0.6%)	24 (2.2%)
Van Besien	All	systemic	605	20 (3.3%)	5 (0.7%)	25 (4.0%)
Boehme	All	few	1693	15 (0.9%)	22 (1.3%)	37 (2.2%)
Bos et al.	CR	no	193	2 (1%)	8 (4.1%)	10 (5.1%)
Zinzani et al.	CR	not given	175	9 (5.2%)	not given	
Arkenau et al.	All	i.t.	259	0 (0.0%)	3 (1.1%)	3 (1.1%)

### 8.1.1 Symptoms and signs at CNS diagnosis

The symptoms of SCNSL are of course dependent on the site of the manifestations.

In leptomeningeal manifestations, the three domains of neurological disturbances (and their symptoms) are (Chamberlain et al. 2005)

- 1) The cerebral hemispheres (headache, mental status change, seizures, hemiparesis)
- 2) Cranial nerves (double vision and loss of vision, hearing loss, facial numbness)
- 3) Spinal cord and roots (weakness of extremities, most often lower, numbness and pain)

In parenchymal manifestations, the most common symptoms are likely to be similar to those found in primary CNS lymphoma: Mental status change, headache, loss of function.

The most common symptoms in our study (Paper I) are given in Table 3 in the manuscript. Bos et al. (1998) found mental changes in 40% and nerve palsies in nearly 50% of their 25 cases similarly to the findings in two other small series (Hærni-Simon et al. 1987, Mead et al. 1986). Bashir et al. (1991) found personality changes to be the most prominent symptom. Exact relative numbers of symptoms are not given in the recent publications on larger series of patients.

### 8.1.2 Prognosis and treatment of SCNSL.

A CNS manifestation in systemic NHL is considered to be a very serious event. In our retrospective analysis, only 12 out of 140 patients were long-term survivors, and the median survival was only 2.6 months. These figures are in line with other reports (Herman et al. 1979, Levitt et al. 1980, Mackintosh et al. 1982, Recht et al. 1988, Bashir et al. 1991). The prognosis was best for patients with a SCNSL diagnosis from the time of the initial NHL-diagnosis (5.4 months) and worst for those with CNS manifestations evolving during therapy (1.8 months). Slightly better outcome were reported from the French GELA group of 16 patients with isolated CNS relapse (Haioun et al. 2000) with a median survival of approximately 6 months. The German High-Grade non-Hodgkin's Lymphoma Study Group reports of median patient survival of 4.4 months from the time of CNS recurrence. They found CNS recurrence to be an independent adverse risk factor for survival (Boehme et al. 2007). Furthermore, in the report from Spectre et al. (2005) on CNS manifestations in indolent lymphomas, the median survival was in the order of 2 years, implicating that the histology is important for the prognosis. In our study, we have not examined the prognostic value of L-NHL compared to H-NHL, partly because several of the low grade lymphomas had transformed to aggressive lymphomas at the time of CNS diagnosis. A comparison of the lymphoblastic and Burkitt's lymphomas versus the rest showed, however an inferior prognosis for the former category.

Treatment of SCNSL is a difficult theme. The treatment is bothersome in that it may have considerable side effects and it requires long hospital admittances at a time many want to spend the time at home with their families. The clinically relevant impact of the treatment on survival is questionable for many of the patients, but a few patients become long term survivors. It is therefore important to identify the patients with the best prognosis.

We have not found other studies which have examined whether clinical symptoms predict survival. In the multivariate analysis of our study (Paper I) age, paresis or sensory loss, histology and time of CNS involvement were entered as prognostic variables. We found paresis and time of CNS involvement to be independent significant risk factors. Our findings that paresis or sensory loss is an independent risk factor for early death should be confirmed in an independent patient cohort.

Treatment of leptomeningeal disease in systemic NHL has been reviewed by Chamberlain et al. (2005). Effective CNS directed therapy includes i.t. routed chemotherapy (methotrexate, prednisolone and cytarabine or combinations), high dose methotrexate with folic acid rescue, high dose cytarabine, high dose chemotherapy with autologous stem cell support (including the agents carmustine and melphalane) and high energy radiotherapy to the CNS axis or total body irradiation (TBI) with stem cell support. In addition, agents like etoposide and idarubicin have a not negligible penetration through the blood – brain barrier. Local, most often palliative radiotherapy given to intracerebral or intraspinal masses is often indicated. In cases where the CNS manifestations appear simultaneously with a systemic disease, the CNS directed therapy is most often combined with the most effective agents against lymphoma as indicated in the National treatment advice in Norway ([www.legeforeningen.no/lymfomgruppen](http://www.legeforeningen.no/lymfomgruppen)). We are not aware of larger prospective trials in this setting, but smaller retrospective and prospective analyses have been performed. In a pilot study from UK, a regimen containing idarubicin, high dose methotrexate with leukovorin rescue, high dose cytarabine, high dose dexamethasone and MTX and cytarabine given i.t. was given to patients with PCNSL and SCNSL (Moreton et al. 2004). Of the 16 SCNSL patients, 12 achieved CR. Seven patients remained in CR at the time of this report with a median duration of follow-up of 24 months (range 18 to 57 months). Small retrospective studies report rather disappointing results (Bokstein et al. 2002, Kawamura et al. 2001). The value of radiotherapy after chemotherapy has been questioned (Magrath et al. 1996). In a retrospective study of 41 patients with SCNSL who all received systemic and intrathecal chemotherapy, a group of patients received additional CNS directed radiotherapy while a comparable group did not. Response to therapy did not differ whether patients received concomitant radiation or no CNS radiation. There were, however, considerably more side effects in the group receiving radiotherapy. In Norway, radiotherapy to the total CNS axis is usually reserved for patients achieving a complete remission after chemotherapy.

In our study, eight patients below the age of 60 years received high dose therapy with stem cell support after achieving a CR from CNS directed chemotherapy. All patients received some form of CNS directed radiotherapy, either as TBI as a part of the high dose therapy (five patients) or as total CNS irradiation (three patients). Five of these patients became long term survivors. Williams et al. (1994) retrospectively analyzed the

EBMT registry for patients given autologous stem cell transplantation with a history of SCNSL. 62 patients were registered, and those with a CNS manifestation at diagnosis had the better prognosis, as had those transplanted in CR. Patients given both i.t. chemotherapy and cranial irradiation had a better prognosis. In the 25 patients with isolated CNS relapse from the GELA study (Haioun et al. 2000), three patients are alive at four years of follow up. Two of these three patients received HDT.

In a retrospective analysis from Stanford University (Alvarnas et al. 2000), 2 patients with PCNSL and 13 patients with SCNSL underwent HDT. Although there was a rather high morbidity and mortality rate, approximately 40% of the patients became long term survivors, and they conclude that “high-dose therapy with autologous stem cell support extended event free survival in patients with secondary CNS lymphoma and possibly in those with primary CNS NHL”.

For most patients, a palliative goal for the treatment is most realistic. In this setting, repetitive i.t. chemotherapy and oral corticosteroid medication combined with local radiotherapy to sites giving rise to symptoms may be the best treatment choice (Chamberlain et al. 2005). To avoid the discomfort of repetitive lumbar punctures, an intraventricular reservoir is most often used in the US, but not in Europe. A new liposomal formulation of cytarabine (DepoCyte®) gives a prolonged CSF concentration of more than two weeks.

In conclusion, the prognosis for patients with SCNSL is still unsatisfactory. Intensive therapy including HDT may improve long term survival, but more effective treatment regimens are needed.

### 8.1.3 Risk factors for central nervous system recurrence in non-Hodgkin's lymphoma and the value of CNS prophylaxis

CNS prophylaxis is clearly warranted in Burkitt's and lymphoblastic lymphomas based on the high CNS relapse rates of 17%-47% reported from several studies (Ersboll et al. 1985, Liang et al. 1990, Keldsen et al. 1996, Bollen et al. 1997, Tomita et al. 2000) and from our study (Hollender et al. 2000 and 2002) and the reduced incidences in studies with both systemic and i.t. prophylaxis both in children and adults (Murphy et al. 1986, Patte et al. 1991, Magrath et al. 1996, Reiter et al. 1992, 1995, 1999, Soussain et al. 1995, Mead et al. 2002, Pees et al. 1992, Smeland et al. 2004). In our study, 20/84

Burkitt's lymphoma and lymphoblastic lymphoma patients (24.4%) had a CNS relapse. For patients with adequate prophylaxis, 19% had a CNS relapse while the number for those 14 patients who did not receive prophylaxis was as high as 78%.

In indolent lymphomas, the CNS recurrence rate is low and prophylaxis is not considered warranted (Ersboll et al. 1985, Liang et al. 1990, Tomita et al. 2000).

Risk factor analysis for CNS recurrence has been carried out in numerous studies on aggressive lymphomas to identify factors which should trigger the use of CNS prophylaxis. Earlier studies found specific sites to be related to a high risk of CNS recurrence like the ocular orbit, paranasal sinuses, bone, bone marrow and testis (Young et al. 1979, Liang et al. 1990, Al-Katib et al. 1984). More recent investigations have claimed that in multivariate analysis, the general extent of disease like elevated LDH, high IPI score and more than one extranodal localization are more important (Tomita et al. 2000, Bos et al. 1998, Haioun et al. 2000). In our study (paper II), the following factors, which all were present in more than five % of the cases, were found to be of prognostic value in multivariate analysis: low serum albumin, elevated serum LDH, involvement of retroperitoneal lymph node, age below 60 years and more than one extranodal site involved. If the patients had more than three of these factors at diagnosis, the risk of CNS recurrence was higher than 25%. CNS prophylaxis was advised for these patients, as well as for patients with testicular involvement with stage IIE or higher and for patients with paranasal sinus involvement. In a recent report from the German High-Grade Non-Hodgkin's Lymphoma Study Group on 1693 patients with aggressive lymphoma, the CNS recurrence rate was as low as 2.2% although i.t. CNS prophylaxis was given to less than five % of the patients. Increased LDH and involvement of more than one extranodal site was confirmed as independent risk factors. The advice for i.t. CNS prophylaxis was cautiously advocated for elderly patients with elevated LDH and specific extranodal organ involvement like the bladder, liver and adrenals. In another recent study from UK on 259 patients with DLBCL (Arkenau et al. 2007), 19.7% of the patients received i.t. prophylaxis, based on site-restricted guidelines (orbit, paranasal sinuses, testis, bone and bone marrow). The CNS recurrence rate was as low as 1.1%. The CNS relapse rate at three years was estimated to be 2.7%. The authors conclude that the i.t. prophylaxis guidelines used in this study are appropriate.

The value and mode of CNS prophylaxis in aggressive non-Burkitt's – non-lymphoblastic lymphomas is however, debated. In one study, the recurrence rate was high (26% at three years) although all patients received i.t. prophylaxis (Chua et al. 2002). In another study, some patients were given i.t. prophylaxis and some not, dependent on the choice of the attending physician (Tomita et al. 2002). All six CNS relapses of 68 treated patients were in the group not receiving prophylaxis. In studies from the GELA group, both i.t. prophylaxis and consolidation with systemic high dose methotrexate, 3 g/m<sup>2</sup> with folinic acid rescue is given, and the relapse rate is low as previously reported (Haion et al. 2000).

Whether i.t. chemotherapy should be given intraventricularly through a surgically applied reservoir (Omayya catheter) or by the lumbar route is also debated. The concentrations acquired intraventricularly when chemotherapy is given through the lumbar route are considered largely inadequate while higher concentrations are found after intraventricular administration (Shapiro et al. 1975).

The recommended dose of high dose systemic methotrexate to achieve adequate concentrations is discussed in paper II, and is considered to be 3 g/m<sup>2</sup>.

#### 8.1.4 Central nervous system chemoprophylaxis in non-Hodgkin's lymphoma: current practice

The practice concerning CNS prophylaxis varies highly between countries. In France, the ACVBP regimen has been used for more than 10 years, including i.t. methotrexate during induction chemotherapy and high dose cytarabine and methotrexate during consolidation for patients younger than 60-70 years (Tilly et al. 2003). In Germany, less than 5% of the patients have been given CNS prophylaxis, and if so only a small number of i.t. methotrexate administrations (Boehme et al. 2007). The practice in UK has recently been surveyed. The majority of centres used i.t. methotrexate prophylaxis, but generally in cases with specific extranodal involvement like the paranasal sinuses, testis, orbital cavity and bone marrow, and not for cases with high IPI score, elevated LDH and > one extranodalsite involved (Cheung et al. 2005). The practice in the Nordic countries was highly variable as surveyed by the Nordic Lymphoma Group (unpublished). Prophylaxis is generally not used in the US. The varying practice in the Western world illustrates the lack of hard data concerning the value and "best practice" concerning CNS prophylaxis in aggressive non-Burkitt's non-lymphoblastic lymphomas.

## **8.2 Primary gastric lymphomas**

The GIT is the primary site of 30-40% of extranodal NHL and constitutes altogether 12% of NHL. The stomach is the most common site of GIT lymphomas (Glass et al. 1997). The most frequent histologies are the indolent marginal zone lymphomas and DLBCL. Marginal zone lymphomas may transform into DLBCL according to the WHO classification (Jaffe et al. 2001). Whether GIT lymphoma in stage IV disease is a primary extranodal disease or not can be discussed and may vary from case to case. We have chosen to include all patients with gastric involvement at the time of diagnosis. As discussed in papers III and IV, primary surgery was largely abandoned at the turn of the century. To investigate whether gastric surgery leads to long term morbidity, we decided to look into HRQOL and the nutritional status of the patients who were included in our protocol for GIT lymphomas. In this protocol, surgery of gastric lymphomas was a central mode of treatment in many cases.

### **8.2.1 Quality of life after surgery for gastric lymphomas**

The quality of life was investigated by inviting the patients to a cross-sectional examination and by asking them to fill in and return by mail two validated questionnaires, the EORTC QLQ-C30, version 3 (Aaronson et al. 1993) and the STO22 (Vickery et al. 2001).

The EORTC QLQ-C30 questionnaire was developed by the EORTC Life Study Group, and has been thoroughly validated in different cancer populations. It is a 30 item questionnaire and is meant to evaluate physical, role, emotional, cognitive and social function as well as global QOL. The EORTC QLC-30 is a rather general questionnaire and may well be supplemented with cancer specific or organ specific questionnaires. The STO22 questionnaire was translated to Norwegian and released only shortly before this study took place. It is also developed by the EORTC QOL Study Group and evaluates the QOL of patients with gastric cancer and focuses on symptoms and side effects of gastric cancer. It encompasses 22 questions related to dysphagia, abdominal pain and discomfort, dietary restrictions, specific emotional problems, dry mouth, hair loss and body image.

Interestingly, the questionnaires gave different results. There was no apparent difference between the categories no surgery, total gastrectomy and partial gastrectomy using the EORTC QOL-30 questionnaire. On the other hand, the results from the STO22 questionnaire showed increased digestive problems in the group of patients for



whom total gastrectomy was a part of the treatment. The study underlines the importance of asking the right questions when HRQOL is assessed; if we had used only the EORTC QOL-30 questionnaire, the conclusion from the study would have been that also patients treated with total gastrectomy have a satisfactory QOL. When adding the STO22 questionnaire, our conclusion was that total gastrectomy should be avoided when possible when treating patients with gastric lymphomas. The results from this study investigating primarily QOL are in line with those of the accompanying study investigating the nutritional status of the same group of patients.

Another aspect included in the study was the objective findings at upper endoscopy. In four patients, Barrett's metaplasia without dysplasia was diagnosed. One should bear in mind the increased frequency of gastric carcinomas at the surgical resection border in cases of Barrett's dysplasia, and controls with upper endoscopy should be performed at least with a three-year interval (Sampliner 2002).

### 8.2.2 Long term effects on nutritional status after surgical treatment of gastric lymphoma and consequences for advice concerning nutritional supplementation

The patients who were operated on with a total gastrectomy, had significant weight loss. They also had a lower storage iron content, lower s-vitamin D, higher s-PTH and homocysteine than those who had a partial gastrectomy or were not operated on.

We have found no literature on this topic for lymphoma patients.

A strength of the investigation is the rather long follow-up period after surgery.

Treatment differed between patients (total versus partial gastrectomy versus conservative treatment), giving small number of patients in each treatment group. On the other hand, this gave us the opportunity to compare the long term effects of the different treatment options. Another advantage for this analysis was the fact that the body mass index and most relevant blood tests were registered for each patient in the patient record at the time of the diagnosis. The demography in Norway made it possible to reach most patients by mail.

After gastric surgery, information concerning dietary intake should be given before the patient leaves the hospital. The information can be given by the doctor, the nurse or the dietician; it is important to have good routines. We also advise that the information is repeated routinely after one year, five and ten years combined with biochemical control

of vitamin D, PTH, calcium, iron, folic acid and homocysteine. If deficiencies or weight loss is detected, the controls should be performed more frequently. Combined oral and written advice is preferable.

#### Vitamin B<sub>12</sub>/folic acid / homocysteine

It is advised to give Vitamin B<sub>12</sub> injections every 3. month for patients treated with total or partial gastrectomy. When partial gastrectomy ad modum Bilroth I has been performed, serum level of vitamin B<sub>12</sub> can be controlled to evaluate whether vitamin B<sub>12</sub> substitution is necessary or not.

Supplementation with B-vitamins, in particular with folic acid, is an efficient, safe, and inexpensive means to reduce an elevated homocysteine level. This may aid in the prevention of cardiovascular disease. (reviewed in Refsum et al. 1998).

Sakuta et al. (2005) compared plasma total homocysteine, vitamin B<sub>12</sub> and folic acid of 31 male patients who had undergone gastrectomy with those of 31 control male subjects. None of them were taking folic acid or vitamin B<sub>12</sub>. They concluded that hyperhomocysteinemia is a relatively common clinical feature of gastrectomized male patients, especially for those who had undergone gastrectomy for stomach cancer. Folic acid of the two groups was comparable. Vitamin B<sub>12</sub> was lower for the gastrectomized patients.

Iron For iron deficiency, we recommend iron supplementation together with vitamin C between meals for better absorption. Tea and coffee contains polyphenol which inhibits the absorption of iron. Calcium, i.e. in milk, also reduces the absorption of iron. Sources of iron in the Norwegian diet are meat, bread, sweet brown cheese made of goat's milk (fortified with iron), liver paste and green vegetables.

#### Vitamin D

##### Vitamin D deficiencies and consequences

##### *Osteopenia / osteoporosis*

Vitamin D deficiency leads to reduced calcium absorption, resulting in hypocalcaemia and increased PTH. The increased PTH induces increased renal secretion of phosphate and hypophosphataemia. Consequently, too little calcium and phosphate will be

deposited in the bone matrix, and the growth and mineralization of the skeleton will be impaired. Small children and the elderly need supplement of vitamin D to avoid rickets (defective mineralization) and osteomalacia (demineralization of the skeleton) respectively. Osteomalacia results in a weak skeleton with less structural support, which easily fractures. Osteoporosis is preceded by osteopenia, and defined as reduced density of the bone, due to loss of the bone tissue. Mosekilde et al. (review article 2005) concludes that vitamin D deficiency is an established risk factor for osteoporosis, falls and fractures. The population of Oslo has the highest incidence reported of hip fracture and forearm fractures. Lofthus et al. (2007) conclude that the reasons for the high incidence of osteoporotic fractures in Norway are not clear, and different mechanisms for the pathogenesis of osteoporosis related to genetics as well as environmental determinants have to be addressed. Kaastad et al. (1998), found differences in the incidence of hip fracture between the different city regions in Oslo corresponding to differences in the mortality and socioeconomic status. They conclude that further studies are needed to investigate the causes for these differences.

#### *Heart disease, diabetes mellitus and cancer*

Chronic vitamin D deficiency may increase the risk of hypertension, multiple sclerosis, cancers of the colon, prostate, breast and type 1 diabetes (Holick 2004). Also Mosekilde (2005) review epidemiological studies suggesting that vitamin D insufficiency is related to breast, prostate and colon cancers, type 2 diabetes, and cardiovascular disorders including hypertension. The mechanisms for this are probably due to vitamin D's influence on cell differentiation and tumour progression (reviewed in Moan et al. 2006, Mosekilde 2005).

Robsahm et al. (2004) studied 115 096 cases of breast-, colon- and prostate cancer, and they observed a significant variation in prognosis by season of diagnosis. Diagnosis during summer and fall, the season with the highest level of vitamin D<sub>3</sub>, revealed the lowest risk of cancer death. They suggest that a high level of vitamin D<sub>3</sub> at the time of diagnosis, and thus, during cancer treatment, may improve prognosis of the three cancer types studied. The results support the suggestion that vitamin D<sub>3</sub> suppresses cancer progression through several growth inhibition mechanisms. The use of UV radiation might be a supplement to cancer treatment without the risk of hypercalcemia (due to vitamin D's hypercalcemic potency). Porojnicu et al. (2007) also finds a higher

survival for summer and autumn diagnosis for Hodgkin's lymphoma in addition to the above mentioned cancers.

The above referred studies indicates that vitamin D is important in cancer biology, and it is of great interest to follow future studies regarding it's role in prevention and treatment of cancer.

#### Recommended daily intake of vitamin D

The Directorate for Health and Social affairs, Department for Nutrition, generally recommend daily intake of vitamin D as follows: 10 µg from 6 to 23 months and for those over 60 years, and 7,5 µg for those between 2 and 60 years. Serum vitamin D should be > 50 nmol/l. These recommendations are based on The Nordic Nutrition recommendation 2004 – integrating nutrition and physical activity.

Vieth et al. (2004) conclude that 25(OH) D concentrations higher than 70 nmol/L is physiological and beneficial to various aspects of human health. According to Moan (2006) optimal levels of calcidiol are probably higher, in the range 100-250 nmol/l.

Vitamin D exists naturally in fatty fish such as salmon, trout, mackerel and herring, cod liver oil and egg yolk. Some food is vitamin D fortified: margarines and extra low fat milk. (Holick et al. 2004). For many people, it is difficult to get enough vitamin D by eating these foods; it is advised to eat fatty fish at least 3-4 times / week. Five ml cod-liver oil contains 10 µg (=400 IU) vitamin D and is a valuable source of vitamin D. Holick et al. (2004) conclude that the recommended intakes for vitamin D are inadequate, and, in the absence of exposure to sunlight, a minimum of 1000 IU vitamin D/d is required to maintain a healthy concentration of 25(OH)D in the blood.

Robsahm et al. (2004) refers to a Norwegian report from the National Council on Nutrition and Physical Activity which concludes that Norwegian healthy adults have an adequate level of vitamin D<sub>3</sub> during the summer, as far as bone metabolism is concerned. However, the level required to reduce the neoplastic progression to cancer is unknown.

#### Calcium

To prevent osteoporosis; a daily intake of calcium 800 mg for young people and at least 1000 mg for the elderly, in combination with vitamin D is recommended. The lack of production of estrogens for menopausal women is the most important cause for the loss

of bone mass. For men, the lack of androgen production, use of glucocorticoids and excess alcohol intake are important factors. Smoking and inactivity also promotes osteoporosis. For those who already have established osteoporosis, a daily intake of calcium (1-1,5 g/day) and vitamin D (800 IU/day = 20 µ/day) is recommended. Bisphosphonates reduces the activity of the osteoclasts and this treatment reduces the incidence of fractures, especially in women ( [www.legemiddelhandboka.no](http://www.legemiddelhandboka.no)). Moyad (2003) also recommends that calcium and vitamin D supplements are taken together because they act synergistically to reduce fracture risk.

### 8.2.3 For which patients with gastric lymphomas should primary surgery still be considered?

According to our protocol, patients with gastric lymphomas were evaluated for primary surgery for the following reasons:

1. Diagnostic workout. According to Fleming (1982) and other authors, a correct diagnosis and stage was at that time made in a minority of the patients before surgery. The biopsies taken at gastroscopy were often too small and of inferior quality.
2. Treat or prevent excessive bleeding or perforation in lymphomas extending to the serosa, either before treatment or as a complication to chemotherapy.
3. Curative treatment of early-stage lymphomas.

Results from studies from the last decade have shed new light on these issues.

1. During the last decades, histopathological diagnosis based on endoscopic biopsies has improved greatly, and today a surgical biopsy is in most cases unnecessary. Immunohistochemistry will in most cases discern better between lymphoma and carcinoma, and ultrasonography adds information to CT scans regarding degree of gastric wall involvement. In some centres, endoscopic ultrasound is used in the staging procedure. In a large randomized study in Mexico, a correct diagnosis was reported established without the use of surgery in all of the 1160 included patient (Avilés et al. 2004). These data are not in concordance with the results from a multicentre study from the German-Austrian gastrointestinal lymphoma study group, in which primary surgery was used for all non-MALT stage IE cases. Endoscopic-bioptic typing and grading and clinical staging were accurate in only 73% and 70%, respectively, based on the

histopathology of resected specimens. If primary chemotherapy is used, the prognostic difference between stages IE and IIE may be of minor importance, however (Avilés et al. 2004).

2. Today, experience from prospective studies has shown that the complications after primary chemotherapy are fewer than in previous studies and may be considered a safe procedure in most cases. In the German multicentre studies 01/92 and 02/96 the complication rates were low (Koch et al. 2001, Koch et al. 2005). In both studies, primary surgery or a non-surgical conservative approach was used according to the choice of the treating physicians. In the former study, there is only one reported death from perforation out of 106 patients treated conservatively, and there were no complication from serious bleeding. In the study of Avilés (2004), primary surgery was not performed to control bleeding or due to gastric wall perforation in any of the cases. In a smaller study, Kochi et al. (2007) treated ten patients with primary gastric lymphoma stage IE-IIE prospectively with primary intensive combination chemotherapy followed by extensive surgery. No gastric complications were seen during chemotherapy. In all resected specimens, a complete histological remission was seen. No relapses have occurred, but surgical complications were seen in three cases. On the other hand, Spectre et al. (2006) report of gastric complication in 18/73 patients during primary chemotherapy for PGL of whom six were operated. The complications were divided between gastric outlet obstruction and bleeding complication. No perforations were seen.
3. Treatment of stage IE and IIE NHL of the gastric ventricle may in principle follow the principles of localized nodal lymphoma: Aggressive lymphomas are in principle curable with combination immuno-chemotherapy. Systemic therapy thereby reduces the risk of a relapse from minimal disease outside the radiation field or the surgically removed macroscopic tumour. For indolent lymphomas, systemic conventional therapy is not curative and is thus usually not given in addition to local treatment (radiation therapy or surgery).  
In aggressive lymphomas, long term follow up of the prospective randomized SWOG study, comparing eight courses of CHOP to three courses plus radiotherapy indicates that radiotherapy does not seem to be advantageous in the long run (Miller et al. 2001) as indicated from the first publication (Miller et al. 1998). Similarly, the French study comparing the more intensive ACVBP regimen

to combined CHOP-radiotherapy showed a better survival for the chemotherapy-only arm (Reyes et al. 2005). Similar results seem to evolve from studies on gastric intestinal lymphomas; chemotherapy only may be at least as good as combined surgery and radiotherapy (Avilés et al. 2004, Al Akwaa et al. 2004, Binn et al. 2003, Koch et al. 2001, Koch et al. 2005). Furthermore, as for histologically aggressive localized nodal lymphomas surgery and / or radiotherapy without chemotherapy is clearly inferior to regimen in which chemotherapy is added.

As for nodal DLBCL, limited disease, one may argue that when intensive combined immuno-chemotherapy is used, there may no longer be necessary to give radiotherapy to limited stage PGL as shown by Avilés et al. (2004) in a randomized fashion and by the excellent results in a phase II study by Raderer et al. (2000). Koch et al. argue that in PGL DLBCL, there is a mixture of up to 1/3 of the malignant lymphoid cells composed of indolent lymphoma, not eradicated by chemotherapy (Koch et al. 2006). Furthermore, in Helicobacter positive DLBCL, antibiotic treatment has in small series been given successfully (Chen et al. 2005) and should be explored further, and may improve the cure rate of this disease.

In indolent PGL, most cases are of the marginal zone type. In stage IE, helicobacter pylori eradication has evolved as the treatment of choice (Bertoni et al. 2005, Fischbach et al. 2007), curing more than two third of the patients while the majority of the remaining ones can be followed without further treatment for years. For stage IIE disease, radiotherapy is the preferred modality among the majority of haemato-oncology experts, further diminishing the role of primary surgery.

The long term morbidity after total gastrectomy shown in our study is in line with results shown after gastrectomy for gastric carcinomas (Horvath et al. 2001, Svedlund et al. 1997), further strengthening the argument for a conservative approach. However, patients having a partial gastrectomy seem to have a decent quality of life, so that surgery should not be avoided for any price if the

indications for operation are strong: profuse bleeding, perforation or obstruction outlet. (Spectre et al. 2006).

## 9. CONCLUSIONS

1. In patients with NHL with systemic involvement of the CNS, the overall median survival was only 2,6 months in our material. Patients above 60 years of age with CNS involvement at progression or relapse, and those with paresis at the time of CNS diagnosis have a dismal prognosis, and supportive therapy only should be considered. Patients under 60 years with chemosensitive disease have better prognosis, and should be offered intensive chemo-radiotherapy including HDT with ASCS.
2. The risk of CNS involvement for patients with NHL was low (2,8%) in low-grade NHL. In high-grade NHL, lymphoblastic and Burkitt's NHL, patients had a high risk of CNS recurrence (24,4 %) at 5 years, for the other patients with NHL the risk was 5,2%. We recommend CNS prophylaxis for patients with either Burkitt's or lymphoblastic lymphoma with intensive chemotherapy including systemic and i.t. methotrexate. Those with other types of H-NHL should receive CNS prophylaxis if four of the five following risk factors are present: elevated serum LDH, serum albumin < 35 g/l, < 60 years of age, retroperitoneal lymph node involvement or involvement of more than one extranodal site.
3. Patients in CR after treatment for primary gastric NHL reported a general QOL not different from population values according to the EORTC QLQ-30 module. In the gastric module (EORTC STO22), however, patients treated with total gastrectomy reported poorer emotional functions, more diarrhoea and more food-related problems, compared to those who had a partial gastrectomy or those who did not undergo surgery. Total gastrectomy should be avoided when possible.
4. Patients with gastric NHL who had a total gastrectomy, had a significant weight loss. They also had a lower storage iron content, lower s-vitamin D, higher s-PTH and homocysteine than those who had a partial gastrectomy or no surgery. If surgery is necessary for gastric lymphomas, a partial gastrectomy should be performed when possible. The patients should receive dietary advice and follow-up concerning intake of vitamin D-and B<sub>12</sub>, calcium, folate and iron.



## 10. ERRATUM

### Paper II

#### Page 1099, Background, results

...the proportion with CNS involvement at 5 years was 4.3% (not 5.2%).

### Paper IV:

#### Page 675, Table I:

Median age (range) wrong: 56 (37-75)

right: 67 ( 47-79)

#### page 676:

wrong: 2-hydroxyvitamin D and PTH

right: 25- hydroxyvitamin D and PTH

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## 12. PAPERS