Primary Central Nervous System Lymphoma in Norway, 1989-2003

Incidence, clinical features, histopathological findings, imaging characteristics, treatment, and outcome in a 15-year national material.

Ingfrid Salvesen Haldorsen

Dissertation for the degree Philosophiae Doctor (PhD) at the University of Bergen, Norway

2008
## Contents

AKNOWLEDGEMENTS ........................................................................................................5

1. ABBREVIATIONS ........................................................................................................7

2. LIST OF PAPERS ........................................................................................................9

3. INTRODUCTION .......................................................................................................11
   3.1 EPIDEMIOLOGY ......................................................................................................11
   3.2 ETIOLOGY, PATHOGENESIS AND RISK FACTORS ............................................12
   3.3 HISTOPATHOLOGY ..........................................................................................14
       3.3.1 Establishing the diagnosis .........................................................................14
       3.3.2 Histopathological findings in immunocompetent patients ......................14
       3.3.3 Histopathological findings in immunodeficient patients .......................15
       3.3.4 Tumor biomarkers and histogenetic origin ............................................15
       3.3.5 Tumor biomarkers as prognostic markers .............................................16
   3.4 CLINICAL FEATURES .......................................................................................17
       3.4.1 Age and gender .......................................................................................17
       3.4.2 Symptoms ..............................................................................................17
       3.4.3 Time from symptoms to diagnosis .......................................................17
       3.4.4 Cerebrospinal fluid findings ....................................................................18
   3.5 IMAGING CHARACTERISTICS .......................................................................19
       3.5.1 Appearance in immunocompetent patients ..........................................19
       3.5.2 Appearance in immunodeficient patients .............................................19
       3.5.3 CT features ............................................................................................20
       3.5.4 MR imaging features .............................................................................20
       3.5.5 Metabolic imaging ................................................................................21
       3.5.6 Differentiation of PCNSL from other diagnoses by imaging ....................21
   3.6 STAGING ............................................................................................................22
   3.7 TREATMENT .......................................................................................................23
       3.7.1 Treatment of non-AIDS PCNSL .............................................................23
       3.7.2 Treatment of AIDS-related PCNSL .......................................................29
   3.8 OUTCOME ..........................................................................................................29
   3.9 PROGNOSTIC FACTORS ...................................................................................30

4. SPECIFIC BACKGROUND AND AIMS OF THE STUDY ........................................33

5. MATERIALS AND METHODS ..............................................................................35
   5.1 PATIENTS ..........................................................................................................35
   5.2 DATA COLLECTION ..........................................................................................38
       5.2.1 Chart review ............................................................................................38
       5.2.2 Histologic review ....................................................................................38
       5.2.3 Imaging review .......................................................................................39
       5.2.4 Follow-up data .......................................................................................40
5.3  **STATISTICAL METHODS**.............................................................................................................. 41

5.3.1  **Associations and tests for trend**.................................................................................................. 41

5.3.2  **Incidence rates** ........................................................................................................................ 41

5.3.3  **Survival analyses** .................................................................................................................... 42

6.  **MAIN RESULTS** ................................................................................................................................. 43

7.  **DISCUSSION** ................................................................................................................................. 45

7.1  **METHODOLOGICAL CONSIDERATIONS** .................................................................................. 45

7.1.1  **Patient series** ............................................................................................................................ 45

7.1.2  **Data on clinical characteristics and cause of death** .................................................................. 46

7.1.3  **Histological material** ................................................................................................................. 47

7.1.4  **Imaging material** ....................................................................................................................... 47

7.2  **DISCUSSION OF RESULTS** ......................................................................................................... 47

7.2.1  **Incidence** ...................................................................................................................................... 47

7.2.2  **Time to diagnosis** ......................................................................................................................... 51

7.2.3  **Imaging findings** ........................................................................................................................ 53

7.2.4  **Treatment** .................................................................................................................................. 55

7.2.5  **Outcome and prognostic factors** ................................................................................................ 56

8.  **CONCLUSIONS** .............................................................................................................................. 59

9.  **REFERENCES** .................................................................................................................................. 61

APPENDIX ................................................................................................................................................. 75
Acknowledgements

The present study was carried out at the Department of Surgical Sciences, Section for Radiology and Institute of Medicine, Section of Oncology, University of Bergen. The work was funded by the Western Norway Regional Health Authority. Further financial contributions were gratefully received from Haakon and Sigrun Ødegaard’s Foundation, L. Meltzers Høyskolefond, Amersham Health AS and the Research Fund at the Department of Radiology, Haukeland University Hospital.

This study was initiated and skillfully drafted in 2001 by Professor Emeritus John Ludvig Larsen at the Department of Surgical Sciences, Section for Radiology. His enthusiasm and optimistic belief in this project was quite contagious, and I am greatly indebted to Professor Larsen for encouraging me to scope into the field of research. Associate Professor Ansgar Espeland at the Department of Surgical Sciences, Section for Radiology has since 2003 been my principal advisor. His contribution to this work has been immense; continuously enthusiastic, wisely guiding the studies, thoroughly revising the manuscripts and generously sharing his time and interest in the project. Without his participation in this study, this thesis would not have existed. Professor Olav Mella at the Institute of Medicine, Section of Oncology has from the very beginning of this project been an excellent co-advisor and has largely contributed to this work. I am greatly indebted to him for his generous sharing of oncologic expertise and scientific skills.

I am very grateful to Associate Professor Jostein Kråkenes at the Department of Surgical Sciences, Section for Radiology for patiently sharing his expertise on neuroimaging and for his dedicated participation in the review of the imaging material. Furthermore, I express my sincere gratitude to statistician Jan Harald Aarseth (PhD) at the Department of Neurology, Haukeland University Hospital for statistical guidance and fruitful discussions; to Bård Kronen Krossnes at the Department of Pathology, Haukeland University Hospital, David Scheie at the Department of Pathology, Rikshospitalet University Hospital and Anne Kristin Goplen (PhD) at the Department of Pathology, Ullevål University Hospital for carrying out the histopathologic revision; to Tom Børge Johannesen (PhD) at the Norwegian Cancer Registry, Institute of Population-Based Cancer Research for validation of the data from the Norwegian Cancer Registry; to Oona Dunlop (PhD) at the Department of Infectious Diseases and Department of Acute Medicine, Ullevål University Hospital and Aase Hollender at the Department of Oncology, the Norwegian Radium Hospital for fruitful scientific discussions.
I would also like to thank numerous institutions in Norway and Tom Erik Lindhjem for the assistance in the collection of medical records, histologic material, and radiological images enabling the thorough reviews performed in this study.

I would like to thank Aslak B. Aslaksen and Anne Margrethe Bassøe, the present and former Head of the Department of Radiology, respectively, for their genuinely positive attitude and for providing time and space to accomplish this thesis. I am also grateful to my colleagues at the Department of Radiology for providing a friendly and flourishing environment and to Associate Professor Jarle Rørvik for his dedicated promotion of research at the Department of Radiology. Special thanks to the colleague with whom I share office, Gesche Neckelmann, for diverting coffee breaks and for her friendship.

Paralleling the work with this thesis, I have had the pleasure of collaborating with excellent researchers at Center for Genetics in Diabetes at the Department of Pediatrics, Haukeland University Hospital. I especially want to thank Professor Pål Njølstad and Professor Anders Molven for enthusiastically introducing me to the interesting field of genetics. The collaboration with this group has been very enjoyable and has broadened my scientific understanding and interest.

My warmest gratitude goes to my dear parents, Ingunn and Christen and my siblings, Hans-Christen, Helga and Øyvind for their caring and for their lovely company since I was a little child. A lot of friends have been enthusiastic and supportive; Bjørg-Tilde and Rønnaug are especially thanked for their continuous support and for their friendship since our early childhood.

Finally, my uttermost gratitude goes to my dear husband and best friend, Magnus, for his endless support and love and to our wonderful children; Ingunn, Øyvor, Benjamin, and Yngvild for the daily joy and meaning they bring into my life.

_Bergen, August 2008_                   _Ingfrid Salvesen Haldorsen_
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>ASCT</td>
<td>Autologous Stem-Cell Transplantation</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood-Brain Barrier Disruption</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion-Weighted Imaging</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr Virus</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluorodeoxyglucose</td>
</tr>
<tr>
<td>GC</td>
<td>Germinal Center</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HD</td>
<td>High-Dose</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>IELSG</td>
<td>International Extranodal Lymphoma Study Group</td>
</tr>
<tr>
<td>IT</td>
<td>Intrathecal</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>NHL</td>
<td>Non-Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td>PCNSL</td>
<td>Primary Central Nervous System Lymphoma</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PWI</td>
<td>Perfusion-Weighted Images</td>
</tr>
<tr>
<td>PYAR</td>
<td>Person Years At Risk</td>
</tr>
<tr>
<td>REAL</td>
<td>Revised European-American Lymphoma</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-Photon Emission CT</td>
</tr>
<tr>
<td>SPET</td>
<td>Single Photon Emission Tomography</td>
</tr>
<tr>
<td>WBRT</td>
<td>Whole Brain Radiation Therapy</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
2. List of papers

The thesis is based on the following papers, which will be referred to by their Roman numerals:


3. INTRODUCTION

3.1 Epidemiology

Primary central nervous system lymphoma (PCNSL) is a relatively rare type of primary brain tumor. It is defined as lymphoma occurring in the brain, leptomeninges, spinal cord or eyes without evidence of lymphoma outside the central nervous system.\(^1,2\) Prior to the 1980s PCNSL reportedly comprised approximately 1% of all brain tumors\(^3-5\) and 1% of all non-Hodgkin lymphomas.\(^6\) From early 1980s increasing incidence rates of PCNSL were reported both among acquired immunodeficiency syndrome (AIDS)-patients\(^7,8\) and in the non-AIDS population.\(^4,7-10\) However, increasing incidence rates were not found in all parts of the world. While increasing incidence rates were observed in the United States,\(^4,7-10\) the United Kingdom,\(^11\) the Netherlands,\(^12\) and Japan,\(^13\) stable incidence rates were found in Canada,\(^14\) Denmark,\(^15\) Scotland,\(^16\) Hong Kong,\(^17\) and India.\(^18\) Although most of these studies are population-based,\(^4,7,8,10-17\) none of the studies are based on the population of an entire country. No etiological factors that may explain the observed differences in incidence rates have yet been defined. Furthermore, some of the studies are based on recordings in registries without a review of the medical records.\(^4,7,8,10,11\) This may potentially have reduced the validity of their data; two studies report exclusion rates of above 50% after review of medical records.\(^14,15\)

During the last decades there have been discrepant reports concerning the relative frequency of PCNSL compared to primary brain tumors in general. Of all primary malignant brain tumors, PCNSL accounted for 1.2% at a hospital in India in 1985-1999,\(^18\) 1.6% in a region of Denmark in 1983-1992,\(^15\) 5.1% in Southeast Netherlands in 1989-1994,\(^12\) and 6.6% at Massachusetts General Hospital in the US in 1978-1989.\(^9\)

Non-AIDS PCNSL

The reported average annual incidence rate of non-AIDS-related PCNSL ranges from 1.0-4.8 per million in different studies during the last two decades. In a region of Denmark it was 1.6 per million in 1983-1992,\(^15\) in Hong Kong 1.0 per million in 1982-1997,\(^17\) and in Canada (Alberta) 1.1 per million in 1975-1996.\(^14\) In the US increasing incidence rates have been reported; 0.8 per million in 1982-1984 (Surveillance, Epidemiology and End Results program; covering approximately 10% of the US population),\(^4\) 2.0 per million in 1986-1989 (California, Florida, New Jersey and metropolitan Atlanta),\(^7\) and 4.8 per million in 1985-1997 (Surveillance, Epidemiology and End Results program;
excluding never-married patients and patients of unknown marital status to avoid possible human immunodeficiency virus (HIV)-infection. In Southeast England the average annual incidence rate of PCNSL was 2.1 per million in 1985-1990, and in Southeast Netherlands 2.7 per million in 1989-1994. These two studies from England and Netherlands included some HIV-positive patients; 21% of the patients with available HIV status were HIV-positive in the study from England, whereas <15% of the patients were HIV-positive (estimated indirectly) in the study from Netherlands. As many studies are based on recordings in registries only, and some materials may have included patients with HIV-infection, former estimates on incidence rates may have been inaccurate.

**AIDS-related PCNSL**

PCNSL is an AIDS-defining disease, and it represents approximately 20% of all AIDS-related non-Hodgkin’s lymphomas (NHL). The absolute incidence rate of PCNSL per 1000 person-years among AIDS patients in the US was reportedly 4.7 in 1981-1990 and 8.4 and 1.1 in 1988-1995 and 1996-2000, respectively. Incidence rates of PCNSL per 1000 person-years among HIV-infected individuals in Europe were 0.3-5.3 in 1983-2002, 0.4-8.3 in 1994-2000, and 2.8 and 1.0 in 1993-1994 and 1997-1998, respectively. PCNSL is diagnosed in approximately 2% of individuals infected with HIV, and in 9-14% of AIDS-autopsies. During the last decade, in the era of highly active antiretroviral therapy (HAART; introduced in 1996), the incidence of PCNSL among HIV infected patients has been reported to decline. However, few former studies on AIDS-related PCNSL are population-based, and very few studies have presented findings in an entire country.

### 3.2 Etiology, pathogenesis and risk factors

Immunocompromised patients have an increased risk for developing PCNSL. In this setting, PCNSL is typically secondary to AIDS, to iatrogenic immunosuppression for transplantation or for autoimmune diseases such as rheumatoid arthritis, or to congenital immunodeficiency syndromes. The life time risk for developing PCNSL is reported to be 1-5% for transplant patients, 1-2% for renal transplants recipients, and 2-7% for cardiac, lung or liver transplant recipients. Patients with congenital immune deficiency have an approximate 4% life time risk for developing PCNSL. The etiology of PCNSL differs based on whether the affected patients are immunocompromised or immunocompetent. In the context of an immunocompromised patient, PCNSL normally arises from Epstein-Barr virus (EBV) infection of B lymphocytes. Affected B-cells proliferate unchecked by...
the immune system and have a propensity to form tumors in the immuno-privileged environment of the central nervous system (CNS). The pathogenesis is unclear, but may involve cellular transformation by Epstein-Barr virus gene products, resulting in over-expression of bcl-2, a protein that inhibits apoptosis (programmed cell death).\textsuperscript{13} The association between lymphoma and EBV is striking in AIDS patients with PCNSL, and EBV is detected in almost 100% of the cases. This association with EBV is less pronounced in AIDS-related systemic non-Hodgkin’s lymphomas (20-75% associated with EBV, depending on histological subtype).\textsuperscript{26} In AIDS patients, advanced disease with severe immunodeficiency with a very low CD4 cell count (less than 50/µL) is the most important predisposing factor for PCNSL.\textsuperscript{25,38} Among HIV-infected individuals in the French Hospital Database on HIV (for the time periods 1993-1994 and 1997-1998), the incidence rate of PCNSL was 9.7 and 0.15 /1000 person year at risk (PYAR) in patients with CD4 count <50/µL and >350/µL, respectively.\textsuperscript{25}

In contrast to immunocompromised patients, immunocompetent patients have no well-established cause of PCNSL. EBV and the human herpes viruses have been investigated, but no association with PCNSL has been discovered.\textsuperscript{31,37} As B-cells have no known role in the brain, it is puzzling how these neoplasms may develop. Some have proposed that PCNSL arises secondary to a systemic malignancy that is eliminated by the immune system, suggesting that neoplastic tumor cells have a propensity for the CNS since CNS offers immune protection.\textsuperscript{2,41} Others have hypothesized that trauma or infectious processes may attract lymphoid cells that proliferate locally to a monoclonal neoplastic state.\textsuperscript{41,42} Finally, it has been proposed that lymphomatous cells generated in other tissues might develop adhesion molecules and acquire selective homing receptors for cerebral endothelia.\textsuperscript{41,42} So far, no convincing data to support or refute any of these mechanisms have been published.

Different from other lymphomas, there is no evidence to propose a hereditary component in the pathogenesis of PCNSL.\textsuperscript{40} However, PCNSL developing as a second neoplasm is reported in 8-13% of PCNSLs.\textsuperscript{43,44} This may represent an inherent individual predisposition to cancer, or it may be a consequence of the carcinogenic effect of the antineoplastic therapy administered for the first malignancy.\textsuperscript{40} PCNSLs among immunocompetent patients have a slight propensity for the male gender\textsuperscript{37,39} and the elderly population;\textsuperscript{37} there is no known disproportionate representation by race.\textsuperscript{37}
3.3 Histopathology

3.3.1 Establishing the diagnosis

Confirmation of PCNSL is extremely important to facilitate early and optimal treatment. However, establishing the diagnosis may sometimes be difficult due to sites of involvement that are dangerous to biopsy or because of poor performance status of the patients. Modern immunohistochemical and molecular techniques make a diagnosis possible with a minimum of tissue sampled by stereotactic biopsy. There is broad consensus that if PCNSL is suspected, stereotactic biopsy is the diagnostic procedure of choice, since open neurosurgical resection does not add to survival and may increase functional deficits. Lymphoma cells may sometimes be detected through cytology of cerebrospinal fluid (CSF); reportedly tumor cells are detected in 5-35% of the cases. However, the diagnosis of PCNSL is normally established by cytological findings in less than 20% of PCNSLs, and the diagnosis of PCNSL, thus, mainly relies on histological analysis of tissue samples. In some patients, the first stereotactic or open biopsy is unrewarding and a second biopsy has to be done. In these cases, pre-biopsy treatment with systemic corticosteroids may have obscured the diagnosis. For this reason, the diagnosis should be established before the initiation of steroid treatment. For a subset of patients with ocular symptoms, vitrectomy or choroidal/retinal biopsy may sometimes establish the diagnosis of intraocular PCNSL, making stereotactic or open biopsy unnecessary.

AIDS-related PCNSL may occasionally be diagnosed without biopsy, based on the detection of CSF EBV DNA, but this test is not completely specific. Biopsy is normally needed, but should be weighted against its relatively high procedural risk in AIDS patients, with a reported postbiopsy morbidity of 8% and postbiopsy mortality of 3%.

3.3.2 Histopathological findings in immunocompetent patients

Histologically, PCNSLs resemble systemic lymphomas, although a greater proportion of PCNSLs are high-grade lymphomas. More than 95% of the PCNSLs are B-cell lymphomas. Intraparenchymal lymphomas, representing the majority of cases, are nearly always diffuse in architecture. Different classification systems including the Kiel-, the Working Formulation-, the Revised European-American Lymphoma- (REAL) and the WHO-classifications have been applied to PCNSL during the last decades, but none of these classifications specifically deals with PCNSLs. The application of The Kiel Classification (common PCNSL subtypes: immunoblastic, centroblastic, lymphoblastic or low-grade lymphomas) and the Working Formulation Classification (common
PCNSL subtypes: diffuse large cell, diffuse large cell immunoblastic, diffuse small cleaved cell, small non-cleaved cell/non-Burkitt’s, unclassifiable, and diffuse mixed small and large cell), has proved unreliable and unsuitable for PCNSL. When using the REAL or closely related WHO classification schemes, diffuse large B-cell lymphomas account for 90-95% of all PCNSLs. Rare pathological variants include low-grade PCNSL of either B- or T-cell origin found in approximately 3% of PCNSLs and T-cell lymphomas found in 2-4% of PCNSLs in Western countries. The proportion of T-cell lymphomas might be somewhat higher in Asia; T-cell lymphomas represented 9% and 17% of PCNSLs in studies from Japan and Korea, respectively. Other rare histological subtypes of PCNSL include Burkitt PCNSL, lymphomatosis cerebri, primary intraocular lymphoma, neurolymphomatosis (infiltration of the peripheral nervous system by lymphoma), pituitary PCNSL, solitary intracranial plasmacytoma, Hodgkin lymphoma, intravascular lymphoma (involving the small vessels of the brain exclusively), and dural low grade B-cell marginal zone lymphoma (MZL), also denoted mucosa-associated lymphoid tissue (MALT) lymphoma of the intracranial dura.

3.3.3 Histopathological findings in immunodeficient patients

In the context of immunodeficiency, PCNSL is almost always associated with EBV, whereas in immunocompetent individuals, EBV-associated PCNSL is very rarely seen. In immunodeficient PCNSL patients the lesions are more often multifocal and necrotic compared to lesions in immunocompetent patients. Histopathologically the EBV-related PCNSLs are quite similar to non EBV-related PCNSLs; both are most often high-grade diffuse large B-cell lymphomas. Low grade lymphomas occur less frequently in AIDS patients than in immunocompetent individuals.

3.3.4 Tumor biomarkers and histogenetic origin

The expression of different tumor biomarkers and its impact on survival in PCNSL have been increasingly explored during the last decade. The histogenetic origin of PCNSL with respect to stage of B-cell differentiation has been elucidated by using panels of immunohistochemical markers. CD10 and Bcl-6 are expressed in germinal center B (GCB) cells whereas MUM1 (multiple myeloma-1) and CD138 are expressed in activated B-cells. High expression of Bcl-6 has been linked to a likely GCB origin. Genetic studies have also suggested PCNSL to be derived from a late GCB cell. The majority of PCNSLs express MUM1 and Bcl-6. Based on these findings of antigens characteristic of late GC and early post GC, a histogenetic origin of PCNSL in a “time-slot” overlapping late GC and early post GC has been postulated (Figure 1).
3.3.5 Tumor biomarkers as prognostic markers

Different tumor biomarkers have been explored in PCNSL, to identify any prognostic impact of the expression of these markers. The antiapoptotic protein Bcl-2 is associated with poor outcomes in systemic NHL, but not in PCNSL. In systemic NHL, expression of GC phenotype (Bcl-6 and/or CD10) is associated with favorable outcome whereas in PCNSL, Bcl-6 expression has been associated with better outcome in some studies, but not in all. P53 and Ki-67 have no prognostic impact in PCNSL in two reports, but they were associated with poorer survival in one study. Vascular endothelial growth factor (VEGF) and endoglin (CD105) are markers of angiogenesis in PCNSL; VEGF expression was associated with longer survival, and low intratumoral microvessel density (IMVD) using CD105 immunostaining, was a favorable prognostic factor.
3.4 Clinical features

3.4.1 Age and gender

In immunocompetent patients, the median age at diagnosis of PCNSL is 55-60 years.\textsuperscript{37,38,40,45,46,61,81} Among AIDS patients, PCNSL presents earlier at a median age of 35-39 years\textsuperscript{21,33,39} and a mean age of 31-37 year.\textsuperscript{33,38,39,65,81} Pediatric cases of PCNSL are rare and constituted 1.5% and 1% of PCNSLs in Japan (Brain Tumor Registry; 1969-1990)\textsuperscript{82} and the US (the Surveillance, Epidemiology and End Results program; 1973-1998),\textsuperscript{83} respectively. As in adults, PCNSL occurs more frequently in immunodeficient children.\textsuperscript{84}

A male predominance with a male/female ratio of 1.2-2.0:1 in immunocompetent patients, is reported in most studies,\textsuperscript{11-14,18,38,40,48,60,61,81} however, no male preponderance has also been reported.\textsuperscript{15,17} The male/female ratio of AIDS-related PCNSL is reportedly 7:1.\textsuperscript{65}

3.4.2 Symptoms

As with all lesions in the CNS, the location of the PCNSL lesions determines the clinical presentation. The most common symptoms are neurological deficits, reported in 50-70% of cases.\textsuperscript{40,45,65} Hemiparesis or motor dysfunction are reported in 11-52%.\textsuperscript{46} Cognitive, behavioral, and personality changes are frequently reported (in 24-73%);\textsuperscript{45,46} these symptoms may be somewhat more prevalent in AIDS-related PCNSL\textsuperscript{65} and are related to tumor location in the corpus callosum and deep frontal lobes.\textsuperscript{37} Signs of increased intracranial pressure such as headache, nausea, vomiting, or papilloedema are reported in 14-45% of PCNSLs and ataxia or cerebellar symptoms in 15-42%.\textsuperscript{33,45,46,65} Seizures are relatively uncommon in non-AIDS PCNSLs (in the order of 12-14%);\textsuperscript{45,65} but are more common in AIDS-related PCNSLs (in 22-27%).\textsuperscript{33,65} Symptoms of visual disturbance are present in 8-20% of immunocompetent patients with PCNSLs; these visual symptoms include blurred vision, decreased visual acuity, floaters, and painful red eyes, misleadingly suggestive of uveitis or inflammatory diseases.\textsuperscript{37,38,46} Primary intraocular lymphoma, a rare subset of PCNSL defined by intraocular lymphoma with or without central nervous system involvement, is occasionally diagnosed in the patients presenting with visual disturbance.\textsuperscript{54,55}

3.4.3 Time from symptoms to diagnosis

The reported median duration of symptoms prior to the histological diagnosis of non-AIDS PCNSL is 1.5-5 months\textsuperscript{47,85,86} while mean duration from debut of symptoms to histological diagnosis of
PCNSL is 3 months in non-AIDS patients and 2 months in AIDS patients. Administration of corticosteroids may delay or confound the diagnosis due to cytolysis of lymphoma cells.

### 3.4.4 Cerebrospinal fluid findings

A lumbar puncture for CSF examination should be performed on patients with suspected PCNSL, but only in patients having no increased risk of cerebral herniation due to increased intracranial pressure. An examination of CSF includes: 1) basic studies of white blood cell count, protein and glucose concentrations; 2) cytology and flow cytometry; and 3) polymerase chain reaction (PCR) for clonal immunoglobulin gene rearrangements - or in AIDS patients, PCR for EBV DNA.

Basic CSF parameters, such as white blood cell count and protein and glucose concentrations, may be normal or slightly abnormal, indicating non-characteristic changes. White blood cell count, total protein, albumin, IgG, or lactate are elevated in 40-85% of the patients, and decreased glucose concentrations are found in 0-13%.

Cytological studies of CSF may in some instances be sufficient to confirm the diagnosis of PCNSL. Lymphoma cells in CSF are identified in 5-35% of immunocompetent patients with PCNSL. Serial CSF samples may be required to make a diagnosis of PCNSL through CSF cytology since the initial cytology is negative in two thirds of the patients who finally have a positive CSF cytology. Treatment with steroids prior to CSF sampling may induce a falsely negative CSF cytology. In AIDS-related PCNSL with leptomeningeal dissemination (in 25% of AIDS-related PCNSLs), 50% and 85% of the cases have positive CSF cytology after one and three samplings, respectively, and positive cytology of CSF has been found in 23% (3/13 patients) in one study. The value of DNA flow cytometry in the diagnosis of PCNSL is limited by the low cell count of most CSF specimens, and this test rarely adds additional diagnostic information.

PCR examination of the CSF is an important complement to cytology, as it sometimes provides the correct diagnosis when conventional cytology only yields ambiguous results. Demonstration of clonal rearrangements of immunoglobulin genes can establish monoclonality of the lymphocyte population, and can thus make the diagnosis of PCNSL. However, the sensitivity and specificity of CSF PCR as diagnostic tool for non-AIDS PCNSL is uncertain. In AIDS patients, detection of EBV DNA in CSF may establish the diagnosis of PCNSL and obviate the need for biopsy. A sensitivity of 80-100% and a specificity of 79-100% of CSF PCR testing for EBV DNA have been reported. Positive EBV PCR in CSF may also be found in patients with AIDS-related systemic lymphoma; it may be detected preclinically, several months prior to the symptoms of AIDS-related
PCNSL or systemic AIDS-related lymphoma with CNS disease. Further, PCR detection of Toxoplasma gondii DNA in CSF may be helpful in differentiating PCNSL from cerebral toxoplasmosis; the most common cause of intracranial mass lesions in adult AIDS patients. 

3.5 Imaging characteristics

PCNSL may have a characteristic appearance on both CT and MR imaging. This is due to its hypercellularity, high nuclear/cytoplasmic ratio, disruption of the blood-brain barrier, and its predilection for the periventricular regions.

3.5.1 Appearance in immunocompetent patients

Previous studies indicate that PCNSL typically presents as a solitary, homogeneously enhancing mass. Multiple lesions are reported in 20-40% of non-AIDS PCNSLs, and ring-like enhancement is observed in 0-11% of the patients. Perifocal oedema is usually present but less prominent than in malignant gliomas or metastases. Most lesions are located central hemispheric or periventricular in cerebral white matter. Frontal lobe location is reported in 20-30% of PCNSLs, and the basal ganglia are affected in 12-33% of the patients. The brain stem and/or cerebellum are affected in 9-13%, the spinal cord in only 1-2% of the patients. Hemorrhage within the tumor is reported in 0-4%, but has been reported in 21% (4/19 lesions) in one small study. Internal calcification within the PCNSL lesion is observed in 2-3% in some studies on primary imaging.

Imaging findings in non-AIDS PCNSL have mostly been investigated in single- or multicenter studies. In immunocompetent patients, population-based studies on such findings are scarce. Also, with increasing incidence of PCNSL and advancing imaging technology, typical appearance at CT and MR imaging may have changed. However, no previous study has explored temporal trends in imaging findings in non-AIDS PCNSL.

3.5.2 Appearance in immunodeficient patients

Compared to immunocompetent patients with PCNSL, immunodeficient patients with PCNSL are more often diagnosed with multifocal lesions, which are reported in 30-80% of patients with AIDS-related PCNSL. Since many lesions exhibit necrotic regions, contrast enhancement is commonly irregular or peripheral, and ring-like enhancement is reported in as much as 50% of the
cases in some reports. The basal ganglia and corpus callosum are frequently involved. Spontaneous hemorrhage in PCNSL lesions may be more frequent in AIDS patients than in non-AIDS patients, and was identified in as much as 35% (7/20) of the AIDS patients at MRI in one study. Imaging findings in AIDS-related PCNSL reported in the literature are all based on single or multi-center studies; no study has been population-based.

### 3.5.3 CT features

In both immunocompetent and immunodeficient patients with PCNSL, unenhanced computerized tomography (CT) typically reveals hyper- or isodense lesions, and virtually all lesions show enhancement after administration of contrast. Negative findings from CT examinations, however, do not exclude PCNSL since false-negative initial CT examinations are also reported. Whether CT findings of PCNSL have changed with advancing CT technology has not formerly been studied.

### 3.5.4 MR imaging features

In both immunocompetent and immunodeficient patients with PCNSL, lesions are typically hypo- or isointense on unenhanced T1 weighted MR imaging. On T2 weighted images, most papers describe lesions as iso- to hyperintense; some studies also report hypo- or isointense lesions to be a frequent finding. Most lesions show marked contrast enhancement at MR imaging. No enhancement at contrast enhanced MR imaging or isolated white matter hyperintensity on T2 weighted MR imaging has also been described in some rare cases of PCNSL. Traditional MR imaging findings in PCNSL may have changed in the era of increasing incidence of PCNSL and improved MR imaging technology; this issue has not been previously addressed.

Due to the relative restriction of water diffusion within PCNSLs, lesions typically appear hyperintense on diffusion-weighted images (DWI) and hypointense on apparent diffusion coefficient (ADC) maps. This characteristic is shared by acute ischemic stroke, brain abscess and high-grade neoplasms. The diffusion within a PCNSL lesion is typically more restricted than in most other brain malignancies, demonstrated by lower ADC values in PCNSL lesions compared to high-grade gliomas and metastases. Intracranial abscesses normally have lower ADC values than most brain tumors. Proton (hydrogen-1) MR spectroscopy has demonstrated elevated lipid resonances with high choline (Cho)/creatinine (Cr) ratios in PCNSL. Perfusion-weighted images (PWI) in PCNSL demonstrate low maximum cerebral blood volume ratios in tumor
and a characteristic intensity time-curve that is related to a massive leakage of contrast media into the interstitial space.\textsuperscript{114,128}

3.5.5 Metabolic imaging

F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) demonstrates increased uptake of FDG in non-AIDS PCNSL.\textsuperscript{95,129-131} After steroid treatment the degree of hypermetabolic activity in PCNSL decreases and resembles that of malignant glial tumors.\textsuperscript{132} FDG-PET may be suitable for early evaluation of therapeutic response.\textsuperscript{129,130} High N-isopropyl-p-[123I]-iodoamphetamine retention on single-photon emission CT (SPECT) is identified in non-AIDS PCNSL lesions; this may reportedly aid in the diagnosis of PCNSL.\textsuperscript{133}

Thallium-201 SPECT, single photon emission tomography (SPET) and FDG-PET may be useful adjuncts to MRI in patients having AIDS and focal intracranial lesions.\textsuperscript{134,135} While infections normally are hypometabolic, PCNSLs are hypermetabolic with a high Thallium-201 uptake ratio on SPECT and SPET\textsuperscript{26,134,135} and high FDG uptake on PET.\textsuperscript{26,136-138}

3.5.6 Differentiation of PCNSL from other diagnoses by imaging

Non-AIDS PCNSL

In immunocompetent patients, the typical characteristics of PCNSL at standard CT and MRI are not always present; even when present, none of these characteristics will unequivocally differentiate PCNSL from other neoplasms (e.g. metastases, malignant gliomas, meningiomas) or non-neoplastic diseases (e.g. multiple sclerosis, stroke, pyogenic abscess). Newer MR imaging methods that may help to differentiate PCNSL from other lesions of the brain are DWI,\textsuperscript{95,122,123} PWI,\textsuperscript{114,122,128} and MR spectroscopy.\textsuperscript{125,126} A new MR imaging contrast agent (iron oxide nanoparticles) seems promising in the differentiation of malignant neoplasms from multiple sclerosis.\textsuperscript{139} Furthermore, FDG-PET and N-isopropyl-p-[123I]-iodoamphetamine SPECT may aid in the identification and differentiation of PCNSL from malignant gliomas and meningiomas.\textsuperscript{129,131,133}

AIDS-related PCNSL

The traditional CT and MR imaging findings of AIDS-related PCNSL are similar to those in cerebral toxoplasmosis.\textsuperscript{26,26,109,111} Diffusion weighted MR imaging shows significantly overlapping ADC ratios in toxoplasmosis and lymphoma, making DWI unreliable in the differentiation of PCNSL from cerebral toxoplasmosis.\textsuperscript{118} MR spectroscopy has proved to aid in the differentiation of focal brain lesions in
AIDS patients in some studies, but not in all. PWI has been rather disappointing in this aspect. T1-201 SPECT and SPET have been shown to be very accurate in the differentiation of AIDS-related PCNSL from toxoplasmic encephalitis in some studies, but less reliable for this differentiation in other studies. SPECT loses accuracy when the lesions are small (<6-8mm), located leptomeningeal, subependymal, or near the base of the skull, or when the patient has been treated with steroids. FDG-PET is a promising adjunctive diagnostic tool that may aid in the differentiation of infectious and non-infectious brain masses in AIDS.

Although some of these newer imaging methods can help to differentiate PCNSL from other lesions both in immunocompetent and immunocompromised patients, none of these methods have a well-defined role in the diagnosis of PCNSL. Further studies are needed to fully explore the diagnostic potential of these imaging methods as well as their ability to monitor therapeutic response in PCNSL. Furthermore, although the methods seem promising, they are not generally available at most medical centers. Thus, in most clinical settings, diagnostic imaging of PCNSL still relies on traditional CT and MR imaging.

### 3.6 Staging

By definition, PCNSL implies the absence of systemic lymphadenopathies and other extracranial localizations of lymphoma. Therefore, PCNSLs are stage I_E (single extralymphatic organ) according to the Ann Arbor staging system. However, large or multifocal masses are normally classified as stage IV (diffuse or disseminated involvement of one or more extralymphatic organs or tissues).

After the diagnosis of PCNSL has been established, based on biopsy specimen or analysis of CSF or vitreous aspirate, a staging evaluation should be performed (Table 1). This should include a comprehensive physical and neurologic examination. Staging for extent of central nervous system involvement includes: 1) Contrast enhanced MR imaging of the brain and of the spine when clinically indicated. 2) Ophthalmologic evaluation, including slit-lamp examination, to detect ocular involvement. 3) CSF cytology, cytometry, and analysis of total protein, for the identification of leptomeningeal involvement. CSF tumor markers such as lactate dehydrogenase (LDH) isoenzyme 5, β-glucuronidase, and β2-microglobulin may also be evaluated.

Occult systemic lymphoma has been reported in up to 13% of patients initially thought to have isolated PCNSL, and a complete systemic staging is therefore warranted. CT of the chest/abdomen/pelvis and a bone marrow biopsy should be performed routinely to rule out systemic
All patients should be tested for HIV since a diagnosis of PCNSL in the setting of HIV has important implications for treatment and prognosis. $^{18}$FDG PET may be more sensitive than conventional staging with body CT and bone marrow biopsy for detection of systemic lymphoma; and $^{18}$FDG PET may be incorporated into the evaluations of systemic disease in the future. Testicular ultrasound may be performed to rule out testicular lymphoma that has metastasized to the brain, and serum LDH may be measured since this parameter may be a prognostic factor in PCNSL. Recently, subclinical systemic disease in PCNSL was detected by PCR of the rearranged immunoglobulin heavy-chain (IgH) genes in 8% (2/24) of the patients. However, the clinical implication of this occult systemic involvement, not detectable by routine staging, remains unknown.

Table 1
Recommended diagnostic evaluation at time of histological diagnosis of PCNSL

<table>
<thead>
<tr>
<th>CNS staging</th>
<th>Systemic staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast enhanced MRI of the brain</td>
<td>Computed tomography of chest/abdomen/pelvis</td>
</tr>
<tr>
<td>Contrast enhanced MRI of the spine when clinically indicated</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>Lumbar puncture for CSF protein and cytology</td>
<td>HIV testing</td>
</tr>
<tr>
<td>Ophthalmologic evaluation with slit lamp</td>
<td>Serum LDH</td>
</tr>
</tbody>
</table>

3.7 Treatment

3.7.1 Treatment of non-AIDS PCNSL

Corticosteroids
Corticosteroid therapy may result in rapid resolution of cerebral mass lesions in PCNSL and is often associated with clinical improvement. Corticosteroids are potent inducers of apoptosis in lymphoid cells, resulting in cytotoxic effects rather than a reduction of cerebral edema. A marked improvement or resolution of lesions after the start of corticosteroids occurs in at least 40% of PCNSL patients. Neuroimaging response may be dramatic, sometimes demonstrating complete
remission of contrast-enhancing lesions within a few days of glucocorticoid treatment.\textsuperscript{53} However, most responses are temporary, and recurrence of PCNSL normally occurs during glucocorticoid withdrawal or during chronic glucocorticoid treatment.\textsuperscript{53}

Although a marked glucocorticoid response may be suggestive of PCNSL, it is not diagnostic of PCNSL since other processes, such as multiple sclerosis or neurosarcoïdosis, can respond similarly to corticosteroids.\textsuperscript{53,153,154} Furthermore, treatment with corticosteroids prior to biopsy/cytology may obscure the diagnosis; thus, steroids should be avoided in suspected PCNSL until the diagnosis has been established.\textsuperscript{2,46,52,53,153,155} When increased intracranial pressure necessitates therapy, osmotic agents such as mannitol, should be considered prior to histological diagnosis.\textsuperscript{53} When the histological diagnosis of PCNSL has been established, glucocorticoid treatment may relieve symptoms. The lowest possible dose should be given for as short a period as possible to avoid the prominent side effects of long-term glucocorticoid treatment.\textsuperscript{37}

**Surgery**

There is no known survival benefit to debulking surgery other than in patients who have masses large enough to cause herniation.\textsuperscript{37} Furthermore, surgical resection may increase functional deficits.\textsuperscript{45,46} The primary role of surgery, therefore, is to obtain an appropriate and adequate sample of tissue with stereotactic needle biopsy; this method is ideal for evaluating malignancies that lie in or adjacent to deep structures of the brain.\textsuperscript{2}

**Radiotherapy**

Radiotherapy is a fundamental part of PCNSL therapy. Based purely on CT and MR imaging, one would presume that PCNSL is a well-circumscribed disease suitable for focal radiotherapy. However, autopsy studies have demonstrated that PCNSL extensively infiltrates the brain microscopically; this microscopic tumor probably exists behind an intact blood-brain barrier.\textsuperscript{156} MR imaging has also been shown to underestimate the tumor burden of PCNSL compared to autopsy findings, since microscopic tumor infiltration of lymphoma at autopsy was seen as isolated T2 hyperintensity or was completely normal at MR imaging.\textsuperscript{116} Consistent with these findings, patients receiving focal radiotherapy may experience recurrence of the disease within and outside the radiation field.\textsuperscript{157}

Throughout the 1980s whole brain radiation therapy (WBRT) was the mainstay of treatment for non-AIDS PCNSL.\textsuperscript{158-162} Whole brain irradiation as sole treatment normally induces temporary tumor regression with a reported median survival time of 12-18 months\textsuperscript{153,158,161,163,164} and 5-year survival
below 20%. The addition of chemotherapy to standard radiotherapy has had an appreciable positive impact on tumor response and patient survival. The optimal dose of radiotherapy, as sole treatment or combined with chemotherapy, is however, not definitely established. Patients receiving less than 40 Gy may have shorter survival, whereas patients receiving more than 50 Gy may have higher risk of late neurotoxicity. The addition of focal boost towards tumor has not proved beneficial for survival. A dose of 45 Gy whole brain irradiation with no boost is currently recommended by some authors. Combined treatment with WBRT and chemotherapy may cause an unacceptably high incidence of severe permanent neurotoxicity, particularly in patients aged > 60 years. In older patients, deferred whole brain radiotherapy does not seem to compromise overall survival; this has made some authors suggest deferring radiotherapy in elderly in an effort to minimize this treatment related neurotoxicity. Ongoing protocols are further examining the option of either deferring radiotherapy or using a lower dose in the elderly and in patients with complete response on chemotherapy.

Chemotherapy

PCNSL is an exquisitely chemosensitive tumor, and the addition of chemotherapy to radiotherapy has substantially improved survival. Different chemotherapeutic regimens have been applied with chemotherapeutic agents from a variety of classes; antimetabolites (cytarabine, methotrexate), corticosteroids (dexamethasone, hydrocortisone, methylprednisolone), alkylating agents (busulfan, carmustine/BCNU, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine, temozolomide, thiopeta), topoisomerase inhibitors (etoposide, teniposide, topotecan), microtubular poisons (vincristine), mitotic inhibitor (vinodesine), antitumor antibiotics (idarubicin), and monoclonal antibodies (rituximab). Early reports used common systemic NHL regimens like cyclophosphamide, doxorubicin, vincristine, and prednisone/dexamethasone (CHOP/CHOD). However, post- or preirradiation chemotherapy with CHOP/CHOD did not significantly improve survival over radiotherapy alone and tended to give short-lived responses. Furthermore, patients experienced significant treatment related toxicities. This lack of benefit of CHOP/CHOD may be partially attributed to the poor penetration of the blood-brain barrier by these agents, and this chemotherapy regimen has no longer any role in the treatment of PCNSL.

High-dose methotrexate

The history of chemotherapy for PCNSL to date has culminated in the finding that intravenous (IV) high-dose methotrexate (HD-MTX; dose $\geq 1\text{g/m}^2$) is the most effective drug against PCNSL. HD-MTX based regimens are the only regimens with a significant advantage over radiotherapy alone, and most neurooncologists advocate utilizing HD-MTX as a platform for the
chemotherapy treatment of PCNSL. Several HD-MTX based combinations have been assessed in trials, but the superiority of additional drugs over HD-MTX alone is not unequivocally demonstrated. However, in a large multicenter study of treatment of PCNSL, the addition of HD-cytarabine to HD-MTX significantly improved survival. During the last decade, a large number of different regimens have been reported in which HD-MTX is used as initial treatment. Varying treatment regimens and differences in patient selection, however, make the comparisons of survival in these clinical trials difficult.

HD-MTX as single agent with a dose of 8g/m² without WBRT has been applied with median survival rates of 25-55 months. Single agent HD-MTX at lower doses (1-3.5g/m²) combined with WBRT has resulted in a median overall survival of 20-41 months in older studies. Treatment with HD-MTX (1-5g/m²) combined with a variety of chemotherapeutic drugs, with or without radiotherapy, has given a reported median survival of 12-60 months in different recent studies. The choice of additional drugs for these regimens has been based on their activity in non-Hodgkin lymphoma and their ability to penetrate an intact BBB.

There is almost a complete lack of prospective randomized trials on PCNSL, and the optimal chemotherapy treatment remains controversial. Furthermore, as patients participating in clinical trials often are highly selected with younger age and better performance status than the general patient population, the results from these trials may not be applicable to a standard clinical setting. Retrospective studies exploring treatments and outcome in population-based materials of non-AIDS PCNSL are scarce, but such studies may be valuable since they evaluate outcomes in a standard clinical population-based setting unaffected by any clinical study.

Chemotherapy dose intensification
Much of the focus of current research is on optimizing chemotherapy and allowing patients to defer radiotherapy and its sequelae. In an attempt to enhance the delivery of therapeutic agent to the brain while preserving neurocognitive function, treatment with intra-arterial (IA) HD-MTX in conjunction with blood-brain barrier disruption (BBBD) with hyperosmolar agents (mannitol) has been studied in PCNSL. Response rates are comparable to treatment with IV HD-MTX, and WBRT might be obviated or postponed in a substantial number of patients. Furthermore, long term survival with preserved cognitive function is possible. However, this treatment is only feasible at specialized centers and is procedurally very intensive with intraarterial catheterization under general anesthesia, monthly, over a year.
Myeloablative doses of chemotherapy, inducing a severe or complete depletion of bone marrow cells, followed by autologous stem cell rescue (ASCR) has proved to be successful in systemic NHL. The aim of such treatment in PCNSL is to attain cure with cytotoxic therapies alone, allowing patients to avoid radiation-induced long-term neurotoxicity. Recent studies of HD chemotherapy supported by autologous stem cell transplantation (ASCT) in PCNSL report median survival of 20-63 months.

**Intrathecal chemotherapy**

The need for intrathecal (IT) chemotherapy for PCNSL is controversial. Some successful regimens have included the use of intrathecally delivered MTX and/or cytarabine, but this is associated with significant morbidity due to arachnoiditis, infection, bleeding, leuкоencephalopathy, and other complications related to Ommaya reservoir placement or repeated lumbar punctures. IV high-dose MTX and cytarabine are known to produce tumoricidal levels within the CSF, and it has been questioned whether IT drug administration is a crucial part of PCNSL therapy. Some studies have failed to demonstrate any benefit from IT MTX when added to HD IV therapy, but these findings have not been validated in prospective randomized studies. Some authors reserve IT chemotherapy for patients with a positive CSF cytologic examination. However, as the sensitivity of cytological examinations of CSF is low, negative CSF cytology may be a rather unreliable parameter for treatment decisions.

**Salvage therapy**

More than half of the patients achieving remission on primary treatment eventually relapse. At recurrence the patients should be re-staged and considered for salvage therapy which has been shown to improve survival in relapsing PCNSL. The optimal salvage treatment is, however, not yet established. Available options for refractory or recurrent PCNSL include WBRT, chemotherapy, and ASCT. The type of first-line treatment used provides important therapeutic and prognostic implications in relapsing PCNSL. Patients relapsing after a chemotherapy-only initial treatment may respond to salvage radiotherapy, although this gives an increased risk of neurotoxicity. In patients achieving complete response at initial treatment with HD-MTX based chemotherapy, salvage HD-MTX at relapse may be effective with a reported median survival of 62 months from first relapse, but this treatment is normally only feasible in younger patients with good performance status. Various non-MTX based regimens including single agent temozolamide or topotecan, combined chemotherapy regimens, or intraarterial chemotherapy with BBBD have been tried as salvage treatment for PCNSL, resulting in median survival rates of 4-32 months.
**Acute and chronic toxicity**

Therapy for PCNSL may be well tolerated in the acute setting, but all therapies are associated with some side effects. During radiotherapy some patients experience significant fatigue, and some patients experience worsening neurologic deficits due to edema. Common acute side effects of chemotherapy are related to bone marrow suppression (leading to anemia, leukopenia, and thrombocytopenia) and nephrotoxicity (leading to acute renal failure). IV MTX may cause transient encephalopathy characterized by mental status changes, lethargy, and somnolence several days after treatment, and IT MTX may lead to arachnoiditis.

During the last decades there has been an increasing concern regarding the disabling long term effects observed in patients treated for PCNSL. Neurotoxicity, which is considered the most frequent complication in long-term survivors, is a syndrome characterized by rapidly progressive subcortical dementia with psychomotor slowing, executive and memory dysfunction, behavioral changes, gait ataxia, and incontinence. Neurotoxicity reportedly affects 24-58% of the patients treated with the combination of chemotherapy and radiotherapy. Chemotherapy and WBRT may both cause CNS damage, but there is a synergistic toxic effect when these two modalities are combined. The prevalence of neurotoxicity appears to increase with age and radiation dose. In patients aged >60 years, neurotoxicity following combined chemo- and radiotherapy may affect up to 90% of those undergoing treatment. Given this great risk of neurotoxicity in the elderly, patients above 60 years of age are often treated with chemotherapy alone.

Neuroimaging in patients with treatment-related neurotoxicity often shows diffuse leukoencephalopathy, atrophy, and communicating hydrocephalus with white matter hyperintensity on T2-weighted MR imaging. In patients treated with MTX-based chemotherapy without WBRT, the risk of long-term neurotoxicity is very low, and the MTX-induced white matter changes detectable on MR imaging in these patients do not seem to be associated with a cognitive decline.

In order to effectively monitor and compare the extent of neurotoxicity in different clinical trials, it is strongly recommended that baseline neuropsychological tests are performed before, during, and after treatment of PCNSL.
3.7.2 Treatment of AIDS-related PCNSL

With supportive care only the median survival in patients with AIDS-related PCNSL is 1-1.5 months. Palliative WBRT has been the mainstay of treatment in AIDS patients resulting in median survival of 2.0-5.5 months. HAART should be considered in all patients with AIDS-related PCNSL as prolonged survival has been observed with the administration of HAART. The role of chemotherapy in AIDS-related PCNSL has so far been very limited since most AIDS patients are ineligible to chemotherapy due to factors such as concurrent infections, progressive neurologic deterioration, and poor performance status. Survival of more than one year is, however, occasionally achieved in selected patients who are eligible to chemotherapy. Lately, there has been a considerable interest in EBV-targeted therapies in AIDS patients, but their application in AIDS-related PCNSL is not yet fully established.

3.8 Outcome

Non-AIDS PCNSL

The prognosis of non-AIDS PCNSL in patients receiving only symptomatic therapy is extremely poor with a median survival of 2-3 months. Patients treated with whole brain irradiation as sole treatment have a reported median survival time of 12-18 months and 5-year survival below 20%. Combined radiotherapy and chemotherapy has substantially improved survival during the last decades with reported median survival of up to 63 months. Chemotherapy alone has also a well-documented effect on non-AIDS PCNSL with reported median survival of up to 55 months. To minimize treatment related neurotoxicity, deferred whole brain radiotherapy in older patients might be a favorable option as this does not seem to compromise overall survival. In younger patients, however, chemotherapy-only regimens seem to be associated with shorter progression free survival times and decreased potential for cure, supporting the use of WBRT in addition to chemotherapy in younger patients.

Survival rates reported in the literature are mostly from clinical trials with highly selected patient populations. Reports on survival rates from population-based materials of PCNSL are scarce. Whether the observed improved survival in clinical trials is reproducible in population-based materials of PCNSL, is largely unknown.
AIDS-related PCNSL

The prognosis of PCNSL in AIDS patients is poorer than in immunocompetent patients. With supportive care only the reported median survival of AIDS-related PCNSL is 1-1.5 months. Patients treated with WBRT have a median survival of 2.0-5.5 months and in a few selected patients eligible for chemotherapy, survival of more than one year has been achieved. Furthermore, some patients receiving HAART have survived with PCNSL for more than two years. However, in spite of the improved survival observed in these promising reports, a significant prolongation of survival has not yet been observed in epidemiological studies of AIDS-related PCNSL, and the prognosis remains dismal in most patients.

3.9 Prognostic factors

Non-AIDS PCNSL

Age and performance status are universally accepted prognostic factors for non-AIDS PCNSL in the literature. Prognostic models serving as guidelines to determine patient prognosis and appropriate therapy have been developed for PCNSL by different research groups. In these models, the presence of risk factors with a known independent impact on survival is used to identify different risk groups among PCNSL patients. The International Extranodal Lymphoma Study Group (IELSG) designed a prognostic scoring system based on five variables (age >60 years, Eastern Cooperative Oncology Group (ECOG) performance status >1, elevated LDH, elevated level of CSF protein, and involvement of deep regions of the brain) and identified three different risk groups with significantly different survival rates (Table 2). A simpler prognostic model was developed at Memorial Sloan-Kettering Cancer Center. This model was based purely on the two prognostic factors: age (≤ 50 years) and Karnofsky performance score (<70), identifying three risk groups that display significantly different survival rates (Table 2). The Nottingham/Barcelona prediction score identifies 4 risk groups based on the presence of 3 risk factors (age ≥60 years, ECOG performance status >1, and multifocal tumors and/or meningeal disease); these risk groups also display different survival rates (Table 2).

There has been some discussion as to which of these scoring systems that are most adequate and reliable. A prerequisite basis of these models is the inclusion of only the factors with an independent impact on survival. The prognostic role of the variables: elevated LDH, elevated CSF
### Table 2
Different prognostic scoring models for PCNSL

<table>
<thead>
<tr>
<th>IELSG&lt;sup&gt;60&lt;/sup&gt;</th>
<th>MSKCC&lt;sup&gt;248&lt;/sup&gt;</th>
<th>Nottingham/Barcelona&lt;sup&gt;188&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prognostic factors</td>
<td>Poor prognostic factors</td>
<td>Poor prognostic factors</td>
</tr>
<tr>
<td>Age &gt; 60 y</td>
<td>Age &gt; 50 y</td>
<td>Age ≥ 60 y</td>
</tr>
<tr>
<td>ECOG performance status &gt; 1</td>
<td>KPS &lt; 70</td>
<td>ECOG performance status &gt; 1</td>
</tr>
<tr>
<td>Elevated serum LDH</td>
<td></td>
<td>Multifocal tumors and/or meningeal disease</td>
</tr>
<tr>
<td>Elevated CSF protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor located in deep structures</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk group</strong></td>
<td><strong>Risk group</strong></td>
<td><strong>Risk group</strong></td>
</tr>
<tr>
<td>Group 1: 0 or 1 factors present</td>
<td>Group 1: Age &lt; 50</td>
<td>Group 1: 0 factors present</td>
</tr>
<tr>
<td>Group 2: 2 or 3 factors present</td>
<td>Group 2: Age &gt; 50, KPS ≥ 70</td>
<td>Group 2: 1 factors present</td>
</tr>
<tr>
<td>Group 3: 4 or 5 factors present</td>
<td>Group 3: Age &gt; 50, KPS &lt; 70</td>
<td>Group 3: 2 factors present</td>
</tr>
<tr>
<td><strong>Survival: 2-Year Survival ± SD</strong></td>
<td><strong>Median survival; y (95% CI)</strong></td>
<td><strong>Median survival; y</strong></td>
</tr>
<tr>
<td>Group 1: 80% ± 8%</td>
<td>Group 1: 8.5 (4.8-16.8)</td>
<td>Group 1: 4.6</td>
</tr>
<tr>
<td>Group 2: 48% ± 7%</td>
<td>Group 2: 3.2 (2.6-4.3)</td>
<td>Group 2: 3.4</td>
</tr>
<tr>
<td>Group 3: 15% ± 7%</td>
<td>Group 3: 1.1 (0.7-1.6)</td>
<td>Group 3: 2.7</td>
</tr>
</tbody>
</table>

CI, confidence interval; CSF, cerebrospinal fluid; ECOG PS, Eastern Cooperative Oncology Group performance status; IELSG, International Extranodal Lymphoma Study Group; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; MSKCC, Memorial Sloan-Kettering Cancer Center; SD, standard deviation; y, years.

Protein, involvement of deep brain regions (included in the IELSG model), and number of lesions and or meningeal disease (included in the Nottingham/Barcelona model) has not been consistently reproduced by different groups<sup>248,250</sup> whereas age and performance status are consistently identified as independent prognostic factors in a wide variety of studies<sup>45,60,61,170,188,246-248</sup>. Information regarding age and performance status is normally easy to obtain in retrospective series whereas information on serum LDH, CSF protein, and lesion number/location and or meningeal disease may be incomplete or missing; as a result, in retrospective studies, many of the patients can not be categorized using the IELSG score<sup>60,248,249</sup>. The application of a uniform scoring model in the design and reporting of clinical trials may facilitate the critical comparison of therapeutic results from different trials, and may facilitate the selection of more promising therapeutic strategies for future trials<sup>247</sup>.

Biochemical markers proposed as prognostic indicators are expression of Bcl-6, CD10, CD105, Ki-67, p53, VEGF, and c-Myc; results are, however, conflicting and the findings need to be validated in larger studies (See also section 5.3.4).<sup>64,68,69,69-71,71,72,76-80,169</sup> Also, pharmacokinetic variables such as
area under the curve of methotrexate and plasmatic creatinine clearance have been identified as prognostic factors in PCNSL. 251

**AIDS-related PCNSL**

As in non-AIDS PCNSL, good performance status has favorable impact on survival in patients with AIDS-related PCNSL. 252-254 Treatments shown to have a significant impact on survival are whole brain irradiation, 20,21,33,234,235,244 combined chemo- and radiotherapy in selected patients, 20 and HAART. 33,234,235 Higher CD4 lymphocyte count is reported to have favorable impact on survival in some studies, 26,33 but not in all. 21,252
4. SPECIFIC BACKGROUND AND AIMS OF THE STUDY

Specific background

During the last decades discrepant reports have been published on incidence rates of both non-AIDS PCNSL and AIDS-related PCNSL.\textsuperscript{4,7-18} Although many of these reports are population-based,\textsuperscript{4,7,8,10-17} none of the studies comprises the population of an entire country. Furthermore, very few are based on review of medical records of patients recorded in cancer registries.\textsuperscript{14,15} Review of medical records seems essential to ensure the validity of data from cancer registries, as exclusion rates of above 50% after review of medical records are reported.\textsuperscript{14,15} Also, some materials on non-AIDS PCNSL may have included patients with HIV-infections,\textsuperscript{11,12} potentially making the estimates of incidence rates inaccurate.

In the treatment of non-AIDS PCNSL and AIDS-related PCNSL, a large number of different treatment regimens have been reported in the literature during the last decade.\textsuperscript{26,33,168,173,177,188-202} However, there is almost a complete lack of prospective randomized trials on PCNSL,\textsuperscript{184,203} and the optimal treatment remains to be established.\textsuperscript{178} Varying regimens and differences in patient selection between clinical trials make the comparisons of survival difficult. Furthermore, as patients participating in clinical trials often are highly selected with younger age and better performance status, the results from these trials may not be applicable for the general patient population in a standard clinical setting. Very few retrospective studies have explored the treatment received and the outcome in population-based materials of PCNSL,\textsuperscript{12,14,15,162,204} but such studies are important to truly evaluate outcomes in a standard clinical setting. Whether the improved survival observed in clinical trials during the last decade is reproducible in population-based materials of PCNSL, is largely unknown.

To ensure early treatment of PCNSL, early histological diagnosis is essential. Diagnosing PCNSL may be difficult in both AIDS patients and non-AIDS patients. Common debut symptoms such as personality change or symptoms of raised intracranial pressure\textsuperscript{46,47} are non-specific, and findings at CT and MR imaging are variable and may not suggest the diagnosis.\textsuperscript{113} Studies from the 80s and early 90s report median time spans from initial symptoms to final diagnosis of PCNSL of 1.5-5 months in studies of non-AIDS patients\textsuperscript{47,85,86} and mean time spans of 3 months for non-AIDS and 2 months for AIDS patients.\textsuperscript{65} Only few studies reporting such time spans have been population-
and no study has comprised an entire country. Considering the advances in diagnostic imaging technologies during the last decades, these time spans may also have decreased.

Imaging findings in non-AIDS PCNSL have mostly been investigated in single- or multicenter studies; population-based studies on imaging findings are scarce. Furthermore, with increasing incidence of PCNSL and advancing imaging technology, typical appearance at CT and MR imaging may have changed. Studies exploring temporal changes in imaging findings in non-AIDS PCNSL are to date completely lacking in the literature.

**Aims of the study**


2. To investigate incidence, clinical features, radiological findings, histological diagnosis, treatment, and outcome for all patients with histologically verified AIDS-related PCNSL diagnosed in Norway in 1989-2003 (Paper IV).

3. To assess time from initial symptom to first neuroimaging and final morphological diagnosis in non-AIDS and AIDS-related PCNSL in Norway in 1989-1998. To explore potential associations between these time spans and recorded clinical and neuroimaging characteristics (Paper II).

4. To describe the CT and MR imaging characteristics at presentation of non-AIDS PCNSL in Norway in 1989-2003. To investigate time trends concerning these imaging characteristics the consecutive 5-year periods; 1989-1993, 1994-1998, and 1999-2003. To identify possible associations between radiological findings and other patient characteristics, e.g. whether the patients were diagnosed while alive and time to diagnosis (Paper V).
5. MATERIALS AND METHODS

Approval of the studies was obtained from The Directorate for Health and Social Affairs, The Data Inspectorate, and The Regional Committee for Medical Research Ethics.

5.1 Patients

In Norway, cancer reporting to the Norwegian Cancer Registry has been mandatory since 1952, making the registration of cancer in Norway rather comprehensive for more than 50 years. Lists of all patients diagnosed with PCNSL in Norway in 1989-1998 and 1989-2003 were obtained from the Norwegian Cancer Registry in 2001 (for the time period 1 January 1989 to 31 December 1998; n=101) and 2006 (for the time period 1 January 1989 to 31 December 2003; n=180). In order to go through the complete medical records of the patients, the author of this thesis visited the archives of medical records at the 6 major university hospitals in Norway (Rikshospitalet University Hospital, Ullevål University Hospital, the Norwegian Radium Hospital, Haukeland University Hospital, St. Olavs Hospital, and University Hospital of North Norway). These hospitals diagnosed and treated all but 8 of the 180 patients recorded in 1989-2003. The archives were visited twice; at the first visit in 2002 data were collected for the time period 1989-1998. At the second visit in 2006, data were collected for the time period 1999-2003; due to updated recordings in the cancer registry, data on 12 additional patients diagnosed in 1989-1998 were also obtained. Medical records from other treating hospitals were obtained by mail.

The first review of the medical records was performed to identify all patients with morphologically verified (based on the pathological report) PCNSL in Norway in 1989-1998. There were 58 cases of non-AIDS PCNSL (described in Paper I and Paper II) and 16 cases of AIDS-related PCNSL (described in Paper II). For the time period 1989-2003, the patients were included on the basis of chart review and the results of histologic review of all available specimens in patients having conclusive of possible PCNSL as their primary histologic diagnosis (n=104): 98 cases of non-AIDS PCNSL were identified and described in Paper III. Four non-AIDS patients included in the patient samples from 1989-1998 (Paper I and II) were excluded from the patient sample from 1989-2003 (Paper III, n=98) because of lack of histological verification at review (n=3) and inconclusive pathological report in a patient with no histological material available for review (n=1). Updated recordings at the Norwegian Cancer Registry revealed 3 additional cases of non-AIDS PCNSL and 3
cases of AIDS-related PCNSL diagnosed in 1989-1998 that were included in the patient samples in Paper III (n=98) and Paper IV (n=29), respectively.

Of the 98 non-AIDS patients diagnosed in 1989-2003, 75 patients had radiological imaging prior to diagnosis available for review (Paper V). AIDS-related PCNSL was identified in 23 cases recorded at the Norwegian Cancer Registry, and additionally 6 patients were identified from the autopsy registry of AIDS patients at Ullevål University Hospital. All together we identified 29 patients with AIDS-related PCNSL in 1989-2003 in Norway, described in Paper IV. The inclusion of patients investigated in the different papers in this thesis is specified in Table 3 and Figure 2.

**Table 3**
Study characteristics of the various subgroups investigated in the papers included in this thesis.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Study design</th>
<th>Inclusion of patients based on</th>
<th>Number of cases</th>
<th>Time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper IV</td>
<td>Population-based</td>
<td>Norwegian Cancer Registry and AIDS autopsy registry (Ullevål); chart review, histologic review</td>
<td>29</td>
<td>1989-2003</td>
</tr>
<tr>
<td>Paper V</td>
<td>Population-based</td>
<td>Norwegian Cancer Registry; chart review, histologic review, radiological images available</td>
<td>75</td>
<td>1989-2003</td>
</tr>
</tbody>
</table>
Figure 2
Inclusion of patients based on chart review (paper I-II) and both chart review and histologic review (paper III-V).
5.2 Data collection

5.2.1 Chart review

The review of all medical records was performed by the candidate and information concerning clinical features, primary histological diagnosis, radiological findings, medical treatment, and outcome were registered according to a form designed for the purpose of the present study (Appendix). Briefly, these variables included: age, sex, former diseases, symptoms, diagnostic procedures, performance status at time of diagnosis, findings at examinations undertaken (including imaging), histological diagnosis, treatment (steroid medication, chemotherapy and/or radiotherapy), and outcome. Time of symptoms, examinations, diagnosis, treatment, and death were recorded in all patients.

Performance status was assessed according to the World Health Organization (WHO) performance score which is identical to the Eastern Cooperative Oncology Group (ECOG) performance score and Zubrod score. These performance scores run from 0-5 with the different numbers indicating: 0, no symptoms; 1, symptomatic but completely ambulant; 2, symptomatic, <50% in bed during the day; 3, symptomatic, >50% in bed during the day but not chronically bedridden; 4, chronically bedridden requiring assistance with the activities of daily living; 5, death. Performance status when classified as ECOG 0-1 and 2-4 is equivalent to the Karnofsky Performance scores ≥70 and <70, respectively. Performance status at time of diagnosis was recorded when this was specified in the medical records; when this information was lacking, performance status was estimated retrospectively based on information in the medical record.

5.2.2 Histologic review

For non-AIDS patients, all available and relevant histological and cytological material of patients having conclusive or possible PCNSL as primary histological diagnosis (n=104) in 1989-2003 was collected and reviewed by one pathologist at Haukeland University Hospital, and for patients diagnosed at Rikshospitalet University Hospital (n=38) also by one of their pathologists. The material was reclassified according to the current WHO-classification (2001). Supplementary immunohistochemical and histochemical staining techniques (Giemsa stain, Periodic acid-Schiff and reticulin stain) were performed when required to confirm the diagnosis and/or reclassify the lymphomas. As a minimum the following antibodies were used for immunohistochemistry: CD20, CD79a, CD3, and Ki67. The following markers were used as required: CD45 (leukocyte common
antigen), CD43, CD30, CD138, CD23, CD10 (common acute lymphoblastic leukemia antigen),
CD5, Cyclin D1, CD8, CD4, CD68, CD34, terminal deoxynucleotidyl transferase, CD56 (neural cell
adhesion molecule), Kappa light chain, and Lambda light chain.

A pathologist at Ullevål University Hospital reexamined the histologic material of the 29 patients
recorded with AIDS-related PCNSL. In 2 patients the histologic material was collected from other
hospitals; the remaining 27 had biopsy/autopsy material at Ullevål. The specimens (based on biopsy
in 2 patients and autopsy in 27) were reclassified according to the current WHO-classification
(2001). For immunohistochemistry, the antibodies CD3, CD20, and Ki67 were used as a
minimum. Epstein-Barr virus hybridization was performed in 25 patients.

### 5.2.3 Imaging review

All radiological examinations of the brain in patients diagnosed with non-AIDS PCNSL (n=98) or
AIDS-related PCNSL (n=29) in 1989-2003 in Norway were registered, and all available brain
images were collected from treating hospitals and radiological departments. Film images were
scanned and stored together with electronic images (on CDs/DVDs) in an electronic research
archive.

First CT and/or MRI (no more than 2 months apart) performed at presentation prior to histological
diagnosis were reviewed. Hospitals in Norway are obliged to store radiological images for only 10
years; thus, fewer patients had images available for review the first 5-year period of our study.
Among patients diagnosed in 1989-1993 only 9 out of 31 (29%) had images available for review
whereas 80 out of 96 (83%) patients diagnosed in 1994-2003 had images available for review.
Altogether, 75 non-AIDS patients and 14 AIDS patients had imaging of the brain available for
review.

Among non-AIDS patients, 75 patients (35 male, 40 female) aged 13-83 (mean 64, median 67) years
had primary imaging of the brain available for review (Paper V); 68 (91%) patients had contrast-
enhanced imaging (including non-contrast series in 58 patients) while 7 (9%) had non-contrast series
only. CT images were reviewed in 66 patients (both contrast and non-contrast series in 46, only
contrast series in 9 and only non-contrast series in 11). MR images were reviewed in 52 patients (T1-
weighted contrast and non-contrast series in 47, only non-contrast series in 3, only contrast series in
2; T2-weighed series in 48); in 43 patients both CT and MR images were reviewed. For patients with
both CT and MR images (n=43), median (mean; range) time from first imaging modality (CT in 39
patients, MR imaging in 4 patients) to second imaging modality was 4 (8; 0-36) days. Median (mean;
range) time was 6 (14; 0-206) weeks from first symptom to first imaging and 3 (10; 0-125) weeks from first imaging to histological diagnosis.

Among AIDS patients (Paper IV), CT images were reviewed in 14 patients (both contrast and non-contrast series in 11, only contrast series in 3) and MRI in 4 patients (T1-weighted contrast and non-contrast series in 2, only non-contrast series in 2; T2 weighed series in 4); 4 patients had a review of both CT and MRI.

A neuroradiologist with 25 years experience and a general radiologist with 8 years experience (the author of this thesis) reviewed all CT and MR images in consensus, after first having performed independent reviews. They used a standardized registration form for each modality (Appendix) and had primary imaging reports available. The lesions were characterized (numbers, size, location, margins, oedema, mass effect, hemorrhage, attenuation/signal intensities relative to grey/white matter, and contrast enhancement) and the presence of no lesion, single focal lesion, multiple focal lesions, or disseminated lesions (i.e. irregularly margined innumerable confluent pathological lesions affecting multiple regions of the brain) was registered.

Among patients with non-AIDS PCNSL, the radiological findings at CT (n=66) and MRI (n=52) (Paper V) were analyzed separately for the two modalities. We further composed a dataset intended to reflect findings at CT and/or MR imaging in the whole sample (n=75). For this dataset, findings at MR imaging were used when available. If MR imaging was performed without contrast series (n=3) or after steroid treatment (n=19) (which might have influenced imaging findings), findings at contrast-enhanced CT (prior to steroid treatment) were used instead. In 6 patients (out of 75) only post steroid treatment (median duration 4.5 days; range 2-13 days) imaging (MRI in all) was available. These patients had undergone imaging prior to steroid treatment, but the images were unavailable for review (n=5) or were unenhanced CT images only (n=1).

5.2.4 Follow-up data

Cause of death was established from medical records (available in 98/98 non-AIDS patients and 29/29 AIDS patients), autopsy reports (autopsy performed in 27/98 non-AIDS patients and 27/29 AIDS patients; reports available in all), and death certificates (available in 81/89 deceased non-AIDS patients and in 27/28 deceased AIDS patients). The recorded cause of death reported on the death-certificate, was obtained from the Norwegian Cancer Registry. Follow-up data on long-term survivors concerning whether the patient was still alive was regularly obtained from the Patient...
Information Management System (PiMS) (with access to the National Registry/Folkeregisteret) at
Haukeland University Hospital.

5.3 Statistical methods

All p-values in the analyses are two-sided. The analyses were performed with Stata 9.0 (College
Station, TX), SPSS 14.0 (Chicago, IL), StatXact, and S-plus.

5.3.1 Associations and tests for trend

The examination of associations for dichotomous variables was performed with Fischer’s exact test,
and Mantel-Haenszel exact test was applied to analyze time trends in dichotomous variables for the

For the comparison of continuous variables between different patient groups, the assumption of
normal distribution was avoided, by using the non-parametric test Kruskal-Wallis Test for one way
analysis of variance. Time trends for continuous variables for the 5-year periods 1989-1993, 1994-
1998, and 1999-2003 were analyzed using the non-parametric linear trend test Jonckheere-Terpstra
test.

5.3.2 Incidence rates

We calculated incidence rates of non-AIDS PCNSL based on the number of new cases diagnosed
with non-AIDS PCNSL each year and the population of Norway at Jan.1st the same year (Paper I
and III). Trend test and 95% confidence interval (CI) for incidence was calculated according to the
Poisson distribution. To estimate the average change in yearly incidence rate, estimated annual
percent change (EAPC) was calculated by fitting a least-squares regression line to predict the natural
logarithm of the yearly rates.

We calculated absolute incidence rates of PCNSL among persons with AIDS based on numbers of
newly diagnosed AIDS-related PCNSL and numbers of patients living with AIDS the same year
(person year at risk) (data from The Norwegian Surveillance System for Communicable Diseases;
MSIS) (Paper IV). Trend test and 95% confidence interval (CI) for incidence was calculated
according to the Poisson distribution.
5.3.3 Survival analyses

Duration of survival was calculated as time between date of diagnostic procedure (operation/biopsy/cytology) that led to histological diagnosis and date of death. Survival curves were calculated and plotted using the method of Kaplan and Meier.\textsuperscript{258} Log-Rank test was used for univariate comparison of survival between groups. The Cox proportional Hazard Model was used to study the effect on survival of several variables simultaneously and to estimate hazard ratios.\textsuperscript{259} The proportional hazard assumption was assessed by comparing the Cox model with a time dependent model.\textsuperscript{260}

In the analyses of diagnostic delay (Paper II), the method of Kaplan Meier\textsuperscript{258} was applied to analyze potential associations between different factors and time span and the Log-Rank test was used for univariate comparisons of time spans between groups. The Cox proportional Hazard Model was used to study the effect on time span of several factors simultaneously and to estimate hazard ratios.\textsuperscript{259} In the analyses of time to final diagnosis, patients diagnosed post-mortem were censored.
6. MAIN RESULTS

In **Paper I** we report incidence rate, clinical features, treatment, outcome, and prognostic factors of non-AIDS PCNSL in Norway in 1989-1998. We identified 58 cases of histologically verified non-AIDS PCNSL. The average annual incidence rate was 1.34 cases per million with a non-significant increasing trend (p=0.069). For patients diagnosed while alive (n=45), estimated survival following histologic diagnosis was 55%, 47%, and 23% at 1 year, 2 years, and 5 years, respectively. Good performance status and active treatment had an independent favorable impact on survival.

In **Paper II** we examine the time from first symptom to final morphological diagnosis of non-AIDS PCNSL (n=58) and AIDS-related PCNSL (n=16) in Norway in 1989-1998. The time from initial symptom to final morphological diagnosis of PCNSL had a median (mean, range) of 75 (157, 8-1285) days in non-AIDS patients and 70 (106, 22-330) days in AIDS patients. Among non-AIDS patients, the time to diagnosis was longer in patients with no tumor in the first neuroimaging report after initial symptom (p=0.001). Median (mean, range) time from initial symptom to neuroimaging was 21 (88, 1-1095) days in non-AIDS patients and 14 (25, 1-60) days in AIDS patients. In the non-AIDS group, those presenting with personality change or visual disturbance had more delayed imaging than the others. The time from first neuroimaging examination to final diagnosis in non-AIDS patients had a median (mean, range) of 28 (69, 1-845) days, and was longer when no tumor was indicated in the imaging report (p=0.005) and if first biopsy did not confirm the diagnosis (p=0.02). All AIDS patients had their diagnosis of PCNSL first established by autopsy. The time from first neuroimaging to autopsy had a median (mean, range) of 48 (81, 10-270) days.

In **Paper III** we analyze time trends in the incidence, clinical features, histologic diagnosis, treatment, and outcome of non-AIDS PCNSL in Norway from 1989 to 2003. We identified 98 patients with confirmed, newly diagnosed non-AIDS PCNSL in this period. The incidence rate increased during the consecutive 5-year periods from 0.89 per million during 1989 to 1993, to 1.74 per million during 1994 to 1998, and to 1.82 per million during 1999 to 2003 (p = 0.013). Diagnostic delay and overall survival did not improve with time. Survival decreased from 1999 to 2003 compared with survival from 1994 to 1998, which was explained in part by reduced performance status and fewer patients receiving combined chemotherapy and radiotherapy during 1999 to 2003. In multivariate analysis, age <=50 years, a good performance status, and active treatment (especially combined chemotherapy and radiotherapy) significantly improved survival.
In **Paper IV** we investigate incidence, clinical features, treatment, and outcome of AIDS-related PCNSL diagnosed in Norway in 1989-2003. We identified 29 cases of histologically verified AIDS-related PCNSL in this period. Only 2 of these cases were diagnosed while alive. AIDS patients in Norway had 5.5% lifetime risk of PCNSL, and their incidence rate of PCNSL per 100 person-years (1.7, 95% CI: 1.1-2.4) decreased during the consecutive 5-year periods from 3.6, to 2.5, and to 0.4 (p<0.001). Median survival from initial symptom of PCNSL was 2.3 months; one patient was still alive 4 years after radiotherapy.

In **Paper V** we investigate imaging findings at presentation of non-AIDS PCNSL in Norway in 1989-2003; time trends in imaging characteristics the consecutive 5-year periods (1989-1993, 1994-1998, and 1999-2003); and associations between radiological findings and patient characteristics. Review of CT and/or MRI in 75 patients with non-AIDS PCNSL revealed no lesion in 10 (13%), single focal lesion in 34 (45%), multiple focal lesions in 26 (35%), and disseminated lesions in 5 (7%) patients. All together, 103 lesions were identified: 63% had white matter location, 56% abutted the ventricular surface, and 43% had frontal lobe location; 100% (102/102) enhanced (13% ring-like) on contrast series. Except for smaller median diameter of the lesions observed the last time period (1999-2003), the imaging characteristics were practically unchanged during the consecutive 5-year periods. When imaging findings were grouped into no lesion, single focal lesion, multiple focal lesions, or disseminated lesions, longer delay from imaging to diagnosis was observed in patients with no lesion (p=0.01) and patients with no or disseminated lesions were less often diagnosed while alive (p=0.06).
7. Discussion

7.1 Methodological considerations

7.1.1 Patient series

Our patient series are based on recordings of all cases diagnosed with PCNSL in the Norwegian Cancer Registry in 1989-2003. These recordings were validated by thorough review of medical records and pathological material. This led to the exclusion of 59 (33%) out of 180 cases due to incorrect registration of PCNSL (n=41) or lack of histological verification (n=18). Our resulting patient series consisted of 98 non-AIDS PCNSLs and 23 AIDS-related PCNSLs diagnosed in Norway the current 15-year period.

Despite mandatory cancer reporting to the Norwegian Cancer Registry, some cases may not be reported. A comprehensive search for non-reported cases of AIDS-related PCNSL in the autopsy registry at Ullevål University Hospital, led to the inclusion of 6 non-reported cases giving a total of 29 cases of AIDS-related PCNSL. An effective search for non-reported cases of non-AIDS PCNSL could not be performed, as other large registries of non-AIDS PCNSL do not exist, and these patients are diagnosed and treated at many different hospitals in Norway. By contrast, Ullevål University Hospital treated 59% (423/723) of the new cases of AIDS recorded at The Norwegian Surveillance System for Communicable Diseases (MSIS) and autopsied 67% (186/278) of their AIDS deaths during the studied 15-year period.

Patients with no (n=12) or inconclusive (n=6) histological diagnosis were excluded irrespective of clinical and/or radiological findings suggestive of PCNSL. We can not rule out that some of these patients may have had PCNSL and were faulty excluded.

On the other hand, some included patients may have had occult systemic lymphoma since adequate staging regimens were not performed in all of the patients. However, among non-AIDS patients an autopsy that excluded systemic lymphoma was performed in 28% (27/98). Of the remaining 71 patients, 69 had a negative abdominal CT or ultrasound and 58 had a negative bone marrow biopsy. Among AIDS-patients 90% (26/29) had a complete autopsy of the entire body excluding systemic lymphoma. In the remaining 3 patients none had signs of lymphoma at chest- and abdominal imaging (n=3) or bone marrow biopsy (n=2). Thus, most of the patients not having an autopsy performed,
underwent relevant staging that excluded systemic lymphoma. Furthermore experiences from others indicate that systemic lymphoma masquerading as PCNSL is a relatively rare occurrence (in the order of 4%).\textsuperscript{148,149} All taken together, we consider the diagnosis of PCNSL in our patient series to be fairly well validated.

A substantial proportion (33\%) of the patients recorded as PCNSL in the Norwegian Cancer Registry was excluded. Similar experiences have been reported on PCNSL from other groups in which review of medical records led to the exclusion of above 50\% of the patients recorded in cancer registries.\textsuperscript{14,15} These findings underscore the importance of validating data from registries.

### 7.1.2 Data on clinical characteristics and cause of death

In all patients included in the materials of non-AIDS PCNSL (\textit{paper I, II, III} and \textit{V}) and AIDS-related PCNSL (\textit{paper II} and \textit{IV}), the entire or essential parts of the medical records from one or more treating hospitals were obtainable. Clinical features, histological diagnosis, radiological findings, medical treatment, and outcome were registered. Most of these data were normally easy to extract from the medical records. However, for patients diagnosed with PCNSL while alive (80 non-AIDS patients, 2 AIDS patients), performance status at time of histological diagnosis was specified in the medical records in only 39 of the non-AIDS patients, and this variable was therefore estimated retrospectively in 41 non-AIDS patients and 2 AIDS patients. This may have reduced the validity and accuracy of this variable.

Debut of first symptom attributable to PCNSL was specifically dated in the medical records in most cases. However, for some patients, the time of first symptom was more vaguely reported and had to be estimated retrospectively, potentially reducing the validity of the variable. Furthermore, the different symptoms prior to the diagnosis of PCNSL were normally specified in the medical records. In patients having a relatively long time span from symptoms to diagnostic imaging suggesting a tumor and to final histological diagnosis, we can not unequivocally prove that these symptoms actually were attributable to PCNSL. However, most of the patients were formerly healthy and presented with new symptoms not explained by other conditions, making it likely that the symptoms were related to PCNSL.

The cause of death in all included patients was established based on recordings in medical records and death certificates. The cause of death was not always directly stated in the medical records; in these cases, the cause of death was estimated based on clinical course and imaging findings prior to death reported in the medical records. In all cases with obtainable death certificate (81 out of 89
deceased non-AIDS patients, 27 out of 28 deceased AIDS patients), the cause of death given on the
death certificate was in accordance with the cause of death based on recordings in the medical
records. The recordings on cause of death in our material, thus seems quite well validated.

7.1.3 Histological material

The histological review was close to complete in this national material. Furthermore, supplementary
immunohistochemical and histochemical staining techniques were performed when required to
confirm the diagnosis and/or reclassify the lymphomas. In only two patients (both non-AIDS) no
histological or cytological material was available for review. One of these patients was included
based on the primary histological diagnosis (Precursor B-lymphoblastic lymphoma) recorded in the
primary histological report; the other patient was excluded due to inconclusive diagnosis recorded in
the primary histological report.

7.1.4 Imaging material

Most radiological images from 1989-1993 were unavailable, and this may have biased our analyses
on imaging findings. However, the availability of images in patients diagnosed in 1994-1998 and
1999-2003 was quite good, making this imaging rather representative for the time period 1994-2003.
Furthermore, for non-AIDS patients, results on time trends for imaging findings for the 5-year
periods 1989-1993, 1994-1998, and 1999-2003, were largely unchanged in an analysis restricted to
the two last 5-year periods. This, and the stable imaging findings over time identified in the whole
material, makes it unlikely that unavailable images have substantially biased our analyses on
imaging findings.

7.2 Discussion of results

7.2.1 Incidence

Non-AIDS PCNSL

From the early 1980s increasing incidence rates of PCNSL have been reported in the non-AIDS
population in some studies.\textsuperscript{4,7-10} In \textbf{paper I} and \textbf{paper III} we examined the incidence rates of non-
AIDS PCNSL in Norway in 1989-1998 and 1989-2003, respectively, and found an increasing trend
for the time period 1989-1998 and significantly increasing incidence rates for the time period 1989-
2003 (Figure 3). Our findings are in line with reports from the United States\textsuperscript{4,7-10} (from the time periods 1973-1984, 1981-1990, 1973-1992, 1958-1989, and 1973-1997, respectively), the United Kingdom\textsuperscript{11} (1973-1990), the Netherlands\textsuperscript{12} (1989-1994), and Japan\textsuperscript{13} (1989-2004). Stable incidence rates have, however, been found in Canada\textsuperscript{14} (1975-1996), Denmark\textsuperscript{15} (1983-1992), Scotland\textsuperscript{16} (1991-1995), Hong Kong\textsuperscript{17} (1982-1997), and India\textsuperscript{18} (1985-1999). Although most of these reports are population-based\textsuperscript{4,7,8,10-17} only two studies\textsuperscript{14,15} (reporting stable incidence rates) are based on review of medical records of the patients recorded in cancer registries. Furthermore, two studies\textsuperscript{11,12} (reporting increasing incidence rates) may have included patients with HIV-infections. Thus, the discrepant findings from different parts of the world may be partly explained by methodological factors; nevertheless, true regional differences in the incidence of non-AIDS PCNSL most likely exist. So far, etiological factors explaining these differences remain to be identified.

We found significantly increasing incidence rates of non-AIDS PCNSL in Norway from 0.89 per million in 1989-1993 to 1.74 per million in 1994-1998 and 1.82 per million in 1999-2003 (p=0.013). No changes concerning the registration of PCNSL in the Norwegian Cancer Registry have been carried out that could possibly bias this finding of increasing incidence. The proportion of patients excluded (39-55 \%) did not vary much between the different 5-year periods, indicating no obvious changes in registration practice. The observed peak in new cases of PCNSL in 2003 (Figure 3) was odd but may be due to statistical variation within a rising trend. Omitting 2003 in the analysis, we still found significantly increasing incidence rates in 1989-2002 (p=0.023). The rising trend also seems to continue, as 2004 had the second largest number of cases recorded as PCNSL in the Norwegian Cancer Registry since 1989 (\(n=15\) in 2004, \(n=20\) in 2003).

As immunocompromised patients with transplants or autoimmune conditions are predisposed to PCNSL,\textsuperscript{38} the frequent use of immunosuppressive medication the last years could theoretically account for an increasing incidence of PCNSL. However, in our material only 5 patients received immunosuppressive medication prior to first symptom attributable to PCNSL. When omitting these patients in the analyses, there was still a significant increase in annual incidence rate (p=0.006) and in incidence rates between the 5-year periods (p=0.021).

It has been suggested that the observed increase in incidence of PCNSL may be partly due to improved technologies available for the diagnosis of brain tumors including CT and MRI.\textsuperscript{4} However, Olson et al. reported increasing PCNSL rates in the US that coincided with stable glioma rates when both tumors were being diagnosed with similar imaging technology.\textsuperscript{10} In Norway, the rates of CNS tumors almost doubled from 1970 to 1999.\textsuperscript{261} However, between 1989 and 2003 the increase in primary brain tumors (excluding tumors in meninges, corpus pineale, hypophysis, and cranial
Figure 3

The average annual incidence rate of primary brain tumors was 85.7 (95% CI: 83.4-87.9) per million and the estimated annual percent change (EAPC) was 2.3% (95% CI: 1.7-2.9, p<0.001) (Figure 3). As the corresponding EAPC of non-AIDS PCNSL in our material (n=98) is 7.3% (95% CI: 2.6-12.1, p=0.002), PCNSL increased relatively more than primary brain tumors. Although lack of a review of the medical records and histological material on all primary brain tumors gives a risk of misclassification that limits our ability to truly compare these EAPCs, it seems unlikely that the impact of improved diagnostic tools would explain the increasing incidence of PCNSL in Norway.

The increased incidence of PCNSL also exceeds what may be caused by an increasing incidence of non-Hodgkin lymphomas in general. The average annual incidence rate of non-Hodgkin lymphoma in Norway during 1989-2003 was 143.9 (95% CI: 141.0-146.8) per million with an EAPC of only 1.8% (95% CI: 1.3-2.2, p<0.001); far less than the EAPC of PCNSL (7.3%) (Figure 3).

The average annual incidence rate of non-AIDS PCNSL in Norway in 1989-2003 was 1.49 per million (paper III). The corresponding incidence rates, reported from different parts of the world during the last two decades, range from 1.0-4.8 per million. The relative frequency of PCNSL compared to primary brain tumors in Norway in 1989-2003 was 1.7%. The corresponding figures in the literature range from 1.2-6.6%. These discrepant findings may be due to geographic differences in the epidemiology of PCNSL but also overestimation of incidence rates in some studies. While the study having the highest estimate on incidence rate (4.8 per million) based
their findings on recordings without a review of the medical records,\textsuperscript{10} two studies with lower estimates of incidence rate (1.1 and 1.6 per million) reported that a review of medical records led to an exclusion of above 50\% of the recorded patients.\textsuperscript{14,15} Similarly, the review of medical records led to an exclusion of 59 (33\%) out of 180 patients in our material.

\textbf{AIDS-related PCNSL}

As opposed to the dramatic increase in AIDS-related PCNSL observed in the 1980s and early 1990s,\textsuperscript{7,8} the incidence of PCNSL among HIV infected patients has been reported to decline during the last decade in the era of HAART.\textsuperscript{19,22-25,32-35} In paper IV we examined the incidence of AIDS-related PCNSL in Norway. The absolute incidence rate of PCNSL among AIDS patients per 100 person-years in 1989-2003 was 1.7 (95\%CI: 1.1-2.4) and decreased from 3.6, to 2.5, and to 0.4 the consecutive 5-year periods (p<0.001) with an EAPC of 18.6\% (p<0.001) (Figure 4). The average annual incidence rate of AIDS-related PCNSL among inhabitants in Norway was 0.44 per million (95\%CI: 0.30-0.64), and decreased with an EAPC of 8.9\% (p=0.046) (Figure 4). Previous single- and multicenter studies\textsuperscript{22-24,33,34} have also found decreasing incidence of AIDS-related PCNSL in the era of HAART. However, to our knowledge, the present study is the first national survey to confirm these findings.

The proportion of AIDS-deaths diagnosed with concomitant PCNSL was 5.5\% (28/508). This proportion was stable over time (5.3\% (12/227), 6.0\% (13/215), and 4.6\% (3/66) in 1989-1993, 1994-1998, and 1999-2003). Our figures for incidence rate (1.7 per 100 person-years) and lifetime risk (5.5\%) of PCNSL among AIDS patients are in the upper range of figures in other studies.\textsuperscript{7,20,22,26,111} Lower incidence rates have been reported from the US:\textsuperscript{7,22} the absolute incidence rate of brain lymphoma per 1000 person-years among AIDS patients was 4.7 in 1981-1990\textsuperscript{7} and 8.4 and 1.1 in 1988-1995 and 1996-2000,\textsuperscript{22} respectively. Although not truly comparable with rates among AIDS patients, reported incidence rates of PCNSL per 1000 person-years among HIV-infected individuals in Europe were 0.3-5.3 in 1983-2002\textsuperscript{23} and 0.4-8.3 in 1994-2000.\textsuperscript{24} In the present study, the hospital (Ullevål University Hospital) treating 59\% (423/723) of the reported new cases of AIDS in Norway, autopsied as much as 67\% (186/278) of their AIDS deaths. This high autopsy rate far exceeds what is common in most countries,\textsuperscript{263} and the high autopsy rate led to the identification of formerly missed cases of AIDS-related PCNSL, explaining why our figures on incidence rate are in the upper range.

Autopsy studies of AIDS patients have identified PCNSL in as much as 9-14\% of the patients.\textsuperscript{28-30} The proportion of AIDS-deaths diagnosed with concomitant PCNSL in Norway was 5.5\% (28/508). Among patients diagnosed with AIDS-related PCNSL, 93\% (27/29) had the diagnosis first established by autopsy. None of these patients had a biopsy performed while alive, and 15\% (4/27) of them had no
focal brain lesion on imaging, so PCNSL was unexpected. Furthermore, PCNSL was considered a likely differential diagnosis prior to death in only 35% (8/23) of those with focal brain lesions, whereas cerebral toxoplasmosis was considered likely in 91% (21/23). Autopsy in all AIDS patients is thus needed to truly estimate the incidence of AIDS-related PCNSL in a population.

### 7.2.2 Time to diagnosis

Pitfalls in the interpretation of clinical, neuroimaging, and histological findings as well as indication or non-indication for diagnostic surgical procedures are well-known challenges in the management of possible brain tumors. In paper II we investigated time to diagnosis of PCNSL in Norway in the ten-year period 1989-1998. Among non-AIDS patients (n=58), those presenting with personality change or visual disturbance had more delayed first imaging than patients with other symptoms (epilepsy, cerebellar symptoms, focal neurological symptoms, or headache). Others have found that personality change may be the only symptom of PCNSL for a long time, and it may be
misinterpreted as dementia or neurodegenerative disease. It has also been shown that patients with personality changes as dominating symptoms have delayed diagnosis of malignant glioma. Symptoms and signs of visual disturbance have been reported in 8-10% of PCNSL patients and eye involvement by uveal or vitreal lymphoma often antedates the development of clinically evident brain lymphoma. Personality changes or eye symptoms involving uvea or corpus vitreum should thus, raise awareness of possible PCNSL. In our study the first imaging report indicated tumor in 5 out of 8 non-AIDS patients imaged more than 3 months after the debut of personality change or visual disturbance. These patients might perhaps have profited from earlier imaging.

To our knowledge, no former study of PCNSL has documented a relation between imaging findings and time to diagnosis. Time to diagnosis was longer in non-AIDS patients with no tumor in the first neuroimaging report (CT in 57 of 58 patients) after initial symptom (p=0.001) (paper II). Similarly, in paper V, when based on review of the imaging material in non-AIDS patients (1989-2003), patients with no lesion on imaging experienced a longer time to diagnosis of PCNSL (paper V). Non-diagnostic first biopsy also prolonged the time span from first neuroimaging to final diagnosis in non-AIDS patients (p=0.02) (paper II).

In AIDS patients diagnosed in 1989-1998 (n=16), the time span from initial symptom to neuroimaging was relatively short (median 14 days), which could reflect an active attitude towards diagnosing concomitant disease in AIDS. However, the AIDS patients had strikingly long time spans from first neuroimaging examination to final diagnosis of PCNSL (median 48 days) (paper II). In only 7% (2/29) of the patients diagnosed with AIDS-related PCNSL in 1989-2003, the diagnosis was established while alive (paper IV). None of the remaining 27 patients first diagnosed at autopsy, had a biopsy performed while alive. All but 4 of these 27 patients had focal brain lesion(s) on CT/MR imaging, which should raise the suspicion of PCNSL. Furthermore, of 19 patients with focal lesion(s) who received toxoplasma therapy, only 2 showed a clear response. Nevertheless, none of these 19 patients underwent stereotactic or open biopsy which may be partly explained by the bad performance status (WHO 2-4) in most of them (79%, 15/19).

Delayed diagnosis of AIDS-related PCNSL is a concern with empiric toxoplasma therapy. To reduce this delay, brain biopsy is advised when there is clinical or radiological deterioration during the first week of initial toxoplasma therapy or lack of clinical improvement within 2 weeks.
7.2.3 Imaging findings

Non-AIDS PCNSL

The findings at review of first CT and/or MR images, obtained after debut of first symptoms attributable to non-AIDS PCNSL in our population based material, ranged from no lesion (13% of patients), to single focal lesion (45%), multiple focal lesions (35%), and disseminated lesions (7%) (Paper V). Of the focal lesions (n=103), 63% had white matter location and 56% abutted the ventricular wall. These typical findings of single or multiple focal lesions in periventricular white matter are in accordance with previous single and multicenter studies. Also, our study confirmed that lesions are most frequent in the frontal lobes (in 49% of the patients in our study). We found enhancement in all single and multiple focal lesions examined with contrast series; other studies have shown enhancement in 97-99%. Ring-enhancement was found in 13% of the lesions; this is previously reported in 3-16% of lesions in non-AIDS PCNSL.

Concomitant hemorrhage in tumor was observed in 8% of the patients. One of these had tumor in a large chronic subdural hematoma; the remainder had a small hemorrhage identified at non-contrast T1-weighted MR images. Hemorrhagic lesion is an atypical finding in PCNSL, and it occurred more often in our study than in some materials (in 8% versus 2-4% of the patients). Small intratumoral hemorrhages were most common (prevalence 7%); this was also the case in a smaller study where small hemorrhages occurred in four (21%) of 19 lesions.

Disseminated lesions are a well-known atypical presentation of PCNSL, but it was more prevalent in our study than formerly reported (7% versus 1-3%) and might have been even more prevalent at histological examination. In one series, biopsy and autopsy material showed diffuse meningeal or periventricular involvement in 24%. Compared to autopsy, MR imaging seems to underestimate the tumor burden of PCNSL.

To our knowledge, no former study of PCNSL has documented a relation between imaging findings and whether the patient is diagnosed while alive. In paper V we showed that patients with no or disseminated lesions tended to be less likely to receive the diagnosis while alive. Although not formerly reported in PCNSL, delayed diagnosis following “negative” imaging has been documented in other malignancies. In our study (paper V), 5 of the 10 patients with no lesion underwent non-contrast CT only at first imaging. Thus, relevant lesions might easily have been overlooked, and additional contrast series might have added valuable information. However, negative findings on
contrast enhanced CT do not exclude PCNSL. To ensure early detection and biopsy of lesions in suspected PCNSL, first imaging should include contrast enhanced MR imaging; this is considered the gold standard for imaging of brain tumors in National Comprehensive Cancer Network’s Clinical Practice Guidelines in Oncology. Furthermore, early renewed imaging should be considered when first imaging is negative and symptoms persist.

The relative proportions of patients with no, single, multiple, or disseminated lesions at CT and/or MR imaging did not change significantly over time. The lesions had smaller median diameter (largest) the last 5-year period (p = 0.048); for all other variables regarding location, margins, oedema, mass effect, and contrast enhancement of lesions, no significant time trends were observed (p > 0.05). Thus, our hypothesis of changing imaging findings over time was not confirmed, except for lesion size. The smaller diameter of the lesions, observed the last time period, might be related to improved CT imaging and increased use of MR imaging, aiding in the detection of smaller lesions. Similarly, MR imaging has been shown to be superior to CT in the detection of metastases, with a reported mean maximal diameter of the lesions significantly smaller on MR imaging than on CT imaging.

**AIDS-related PCNSL**

Among patients with AIDS-related PCNSL, multiple brain lesions on CT/MRI were found in 79% (11/14) of the patients having images available for review and 59% (17/29) of the patients based on imaging reports (paper IV). These figures are in the upper range of figures from other studies (31-81%). Ring enhancement was observed in 75% (27/36 at CT and 6/8 at MRI) of the lesions (in 13 of the 14 patients at review). Such enhancement was thus more prevalent in our material than reported (52%) in a review of 32 series of AIDS-related PCNSL from 1980-1992 (n=315), and in a more recent study finding irregular peripheral enhancement in 73% and ring enhancement in only 11% of the lesions. However, as ring enhancement may often be irregular and may resemble irregular peripheral enhancement, these discrepant findings may be due to different interpretations of enhancement patterns.

The MRI/CT findings of AIDS-related PCNSL in our study are similar to those in toxoplasmosis. MRI and CT can seldom differentiate PCNSL from toxoplasmosis. If available, diffusion or perfusion MRI, magnetic resonance spectroscopy, positron emission tomography and SPECT might help to select patients for biopsy versus empiric toxoplasma therapy. So might PCR examination of the CSF to detect Epstein-Barr virus DNA or Toxoplasma gondii DNA, but none of these tests are completely specific. Biopsy is often needed, but should be weighted against its relatively high
procedural risk in AIDS patients. Further research on the combination of less invasive diagnostic procedures is required to reduce the need for biopsy.

7.2.4 Treatment

Prior to 1997, there was no ongoing clinical trial on PCNSL in Norway. In 1997 the Nordic PCNSL Working Group introduced a phase II trial to investigate if durable responses could be obtained by a multiagent chemotherapy regimen. This treatment was based on HD-MTX 6 g/m² in patients < 65 years and HD-cytarabine 3 g/m² in patients > 65 years; both age groups received carmustine, vincristine, dexamethasone and intrathecal treatment (cytarabine and MTX). This study was terminated after the enrollment of 30 patients due to five toxic deaths. In 2006 the Nordic PCNSL Working Group launched a phase II clinical trial on immunochemotherapy in PCNSL using rituximab, HD-MTX, HD-cytarabine, cyclophosphamide, ifosfamide, vincristine, vindesine, temozolomide and intrathecal cytarabine induction therapy in patients aged 18-75 years (followed by maintenance treatment with temozolomide in patients aged 66-75 years); no results on this trial have yet been published.

Only 9 (2 in 1994-1998 and 7 in 1999-2003) out of the 80 non-AIDS patients diagnosed while alive in Norway in 1989-2003 (paper III), participated in a clinical trial. The remaining 71 non-AIDS patients were treated according to the ordinary clinical practice in Norway the current time period. Thus, the treatment of PCNSL in this non-AIDS population reflects the ordinary treatment practice in Norway, practically unaffected by any clinical trials, applied in an everyday clinical setting (Figure 5). The diversity of the treatment regimens applied, the limited size of our series, and the retrospective nature of our studies, did not allow a meaningful evaluation of an optimal treatment regimen for PCNSL. However, treatment with radiotherapy and/or chemotherapy had a significant favorable impact on survival in our study of non-AIDS PCNSL (paper III), as uniformly reported in the literature.

The optimal treatment of non-AIDS PCNSL remains controversial and is not standardized. In spite of numerous studies documenting the effect of chemotherapy and radiotherapy, the almost complete lack of prospective randomized studies on PCNSL makes it impossible to draw valid conclusions on the optimal treatment and the best timing of this treatment. Future prospective multicenter randomized trials are strongly warranted and crucial if these issues are to be addressed in the future.
Figure 5
Therapy received among patients diagnosed while alive with non-AIDS PCNSL in Norway in 1989-2003. Chemotherapy included HD-MTX in 66% (only MTX in 28%; combined with other agents in 38%). Radiotherapy consisted of whole brain irradiation in 100% and focal boost toward tumor in 39%.

Among patients with AIDS-related PCNSL, only two patients (7%; 2/29) had the diagnosis of PCNSL established while alive. These two patients received radiotherapy and were the only receiving adequate treatment for PCNSL. By contrast, in an Australian study of HIV-related PCNSL diagnosed in 1987-1998, more than 40% had biopsy and 49% received radiotherapy.33 This large difference is difficult to explain, but might suggest a more reluctant attitude towards invasive diagnostic procedures and treatment in our material. However, most of the AIDS patients in our study had a poor general condition, which could complicate diagnostic procedures and active therapy.

7.2.5 Outcome and prognostic factors
Among non-AIDS patients diagnosed while alive (n=80), the overall estimated survival from time of diagnosis was 46%, 38%, and 16% at 1, 2, and 5 years respectively, with a median survival of 7 months (paper III). The estimated median survival was 44 months in patients receiving combined chemo- and radiotherapy versus 9 months and 4 months in patients receiving only radiotherapy and only chemotherapy, respectively. These survival rates are in the lower range of those reported by others.61,158,163,168,169,187,248 In our population-based material, fewer patients were ≤ 50 years than in many institution based materials; e.g., 14% of patients in our material compared with 30% of
patients in a material from a tertiary referral center.\textsuperscript{248} As young age is a well-documented favorable prognostic factor,\textsuperscript{45,60,61,247,248} differences in patient age may partly explain the discrepant findings on survival.

The overall survival among non-AIDS patient diagnosed while alive the three 5-year periods did not improve with time (paper III). Considering the therapeutic advances reported in clinical trials during the last decades,\textsuperscript{167,228} this was rather unexpected. However, our findings are in accordance with two recent population-based studies from the US (1975-1999)\textsuperscript{162} and Canada (1990-2003)\textsuperscript{204} reporting stable outcomes in the studied periods. By contrast, a large study from Japan (1985-1999)\textsuperscript{278} reported improved survival with time; this was partly explained by a significantly higher proportion of patients with good performance status treated during 1995-1999. Thus, the improved survival of PCNSL achieved in clinical studies with largely selected study samples, are not convincingly reproduced in population-based studies on PCNSL. Substantial obstacles might exist in the implementation of advanced treatment and care in the ordinary clinical practice in a population-based setting.

In paper III we examined prognostic factors among non-AIDS patients diagnosed while alive. As reported in most other studies, good performance status and young age had favorable independent impact on survival;\textsuperscript{45,60,61,247,248} patients receiving only symptomatic therapy had shorter survival,\textsuperscript{168,169,228} and combined chemo- and radiotherapy was superior to chemotherapy\textsuperscript{178} or radiotherapy alone.\textsuperscript{187} In our study, HD-MTX-containing regimen was highly significant (p=0.006) and year of diagnosis and total radiation dose ($\geq$45 Gy) almost significant (p=0.06 and p=0.08, respectively) prognostic factors in the univariate analyses. However, none of these three variables reached statistical significance when included in a multivariate model. Omission of HD-MTX in the chemotherapy regimen tended to reduce survival (hazard ratio: 1.50, 95% CI: 0.76-2.96, p=0.24) (paper III); two studies have reported significant impact of HD-MTX on survival with hazard ratios of 2.3\textsuperscript{204} and 1.48.\textsuperscript{187} Reducing the radiotherapy dose (from 45 Gy to 30.6 Gy) in patients aged $<$60 years may be associated with an increased risk of recurrence and lower overall survival;\textsuperscript{171} however, in our study the impact of radiation dose on survival was not significant in the multivariate analysis (hazard ratio: 1.33, 95% CI: 0.53-3.36, p=0.55).

In the analyses of prognostic factors, the most common categorization of WHO performance score is 0-1 versus 2-4,\textsuperscript{60,188,248} and this categorization was performed in paper III. Differently, we categorized performance status into 0-2 versus 3-4 in paper I. Nevertheless, also in paper I did good performance status (0-2) significantly improve survival both in the univariate (p<0.001) and in the multivariate analyses (hazard ratio: 2.39, 95% CI: 1.13-5.09, p=0.023).
Among AIDS patients median survival from first symptom attributable to PCNSL was 2.3 (95% CI: 1.5-3.2) months, and only 21% (6/29) and 7% (2/29) were alive at 6 months and 1 year, respectively (Paper IV). The short median survival from first symptom attributable to PCNSL (2.3 months) is similar to survival times in other larger materials (1.0-2.8 months). However, long time survival of more than 4.5 years was achieved in one patient treated with radiotherapy and HAART. Similar cases have been reported by others. The possibility of long term survival should prompt more aggressive diagnostics in suspected PCNSL.
8. Conclusions

We identified an increasing incidence of non-AIDS PCNSL in Norway during 1989-2003 (paper I and paper III). For patients diagnosed while alive, the median survival from time of diagnosis was 7 months, and young age (≤ 50 years), good performance status (WHO 0-1), and active treatment (especially combined chemo- and radiotherapy) significantly improved survival (paper III). For patients diagnosed at death, the median survival from time of initial symptom was 3 months. Despite diagnostic and therapeutic advances over the last decades, neither a reduction in diagnostic delay nor any improvement in overall survival with time was observed during the time period 1989-2003. Survival the last 5-year period (1999-2003) rather decreased compared to the preceding 5-year period (1994-1998), explained in part by worsened performance status and fewer patients receiving combined chemo- and radiotherapy. To achieve improved survival, better treatment and care must be implemented in ordinary clinical practice.

We found decreasing incidence of AIDS-related PCNSL in Norway during 1989-2003 (Paper IV). Only 2 out of 29 patients had the diagnosis of AIDS-related PCNSL established while alive. AIDS patients had a 5.5% lifetime risk of PCNSL, emphasizing the importance of PCNSL as organ-specific manifestation of AIDS. Despite dismal survival in most patients (median survival from initial symptom of PCNSL was 2.3 months), long term survival was achieved in one patient treated with radiotherapy and HAART. The possibility of long term survival should prompt more aggressive diagnostics in suspected PCNSL.

We have identified considerable delays in the diagnosis of PCNSL during 1989-1998; time from initial symptom to final morphological diagnosis had a median (mean, range) of 75 (157, 8-1285) days in non-AIDS patients and 70 (106, 22-330) days in AIDS patients (paper II). Non-AIDS patients with personality change or visual disturbance as initial clinical symptom had particularly delayed first neuroimaging, and those with no tumor reported on initial neuroimaging or with non-diagnostic first biopsy had particularly delayed histopathological diagnosis of PCNSL. Physicians should consider early neuroimaging in patients with personality changes or visual disturbance, early renewed imaging in patients with persistent neurological symptoms but no tumor on initial imaging, and early/repeated biopsy of focal brain lesions in both AIDS patients and non-AIDS patients.

CT and MR imaging at presentation of non-AIDS PCNSL in Norway in 1989-2003, typically revealed contrast-enhancing single (45%) or multiple (35%) focal lesions (paper V). No or disseminated lesions were also common (in 20%) and resulted in later histopathological diagnosis.
We observed a smaller diameter of the lesions the last time period (1999-2003); this might be related to increased use of MR imaging and improved CT imaging, aiding in the detection of smaller lesions. To ensure early diagnosis of PCNSL, first imaging should include contrast enhanced MR series. Early renewed imaging should be considered when first imaging is negative and symptoms persist. In the era of increasing incidence of non-AIDS PCNSL, its features on imaging remain practically unchanged.
9. References


64. Camilleri-Broet S, Martin A, Moreau A et al. Primary central nervous system lymphomas in 72 immunocompetent patients: pathologic findings and clinical correlations. Groupe


Appendix
# Registreringsskjema for primære cerebrale lymfomer

## Patient

<table>
<thead>
<tr>
<th>Fornavn:</th>
<th>Journalen er hentet fra:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eternavn:</td>
<td>Sykehus</td>
</tr>
<tr>
<td>Personnummer:</td>
<td>Avdeling</td>
</tr>
<tr>
<td>Gateadresse:</td>
<td>Også behandlet ved:</td>
</tr>
<tr>
<td>Postadresse:</td>
<td></td>
</tr>
<tr>
<td>Fylke:</td>
<td></td>
</tr>
</tbody>
</table>

### Kjønn:
- Mann
- Kvinne

*Er pasienten i live?*
- Ja
- Nej

*Hvis nej, angi dødsdato:*

### Tidligere sykdommer:

- HIV-infeksjon
- Immunsuppressiv behandling
- Allergi/låsbær

## Familie

*Lymphom i familien?*
- Vet ikke
- Ingen

## Debut

*Debutedato:*

- d.
- m.
- a.

*Debutsymptomer:*

- Personligforandringer
- Neurologiske avtlætt
- Trykksymptomer (bopipine/kvalme/oppkast)
- Anore

## Diagnose

*Diagnosedato:*

- d.
- m.
- a.

*Hvor ble diagnosen stilt (institusjon):*

*Diagnose basert på:*

- Operasjon med histologi
- Autopsi med histologi
- Biopsi med histologi
- Cerebrospinalvaskkfimm
  - Protein
  - vellere
  - molekuleceller

*Kun kliniske/røntgenologiske funn/forløp:*
- Ja
- Nej

*Histologisk funn:*

## Familie
<table>
<thead>
<tr>
<th>CT</th>
<th>MR</th>
<th>IVK</th>
<th>Dato (dag)</th>
<th>Dato (mnd)</th>
<th>Dato (år)</th>
<th>Funn</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annen utredning:</th>
<th>Dato (dag)</th>
<th>Type utredning</th>
<th>Funn</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behandling</th>
<th>Dato (mnd)</th>
<th>Dato (år)</th>
<th>Billedmessig respons:</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Billedmessig respons:</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strålebehandling</th>
<th>Dato (mnd)</th>
<th>Dato (år)</th>
<th>Billedmessig respons:</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Billedmessig respons:</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Lesjoner

<table>
<thead>
<tr>
<th>Nr</th>
<th>Lokalis.</th>
<th>Ax. verreml (x y z) (mm)</th>
<th>Side</th>
<th>Hovedsaklig lokaliseret (G/H/ Bege (B))</th>
<th>Peri. ventr. J/N</th>
<th>Kont. m. hjern.-nerves overflate J/N</th>
<th>Kont. m. ventr. syst. J/N</th>
<th>Kont. m. hjernehull J/N</th>
<th>Avgrens. Skarpe/Moderat skarp (M/ D)</th>
<th>Omkr. I. adven (I) J/N</th>
<th>Masse- effekt J/N</th>
<th>Blod. J/N</th>
<th>Kalk J/N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Læsninger (uten i v/k) hovedsakelig lavere (↓), lik (=) el. høyere (↑) enn:

<table>
<thead>
<tr>
<th>Nr forts.</th>
<th>Grå subst.</th>
<th>Hvit subst.</th>
<th>Homogen attenuasjon (uten i v/k) (J/N)</th>
<th>Kontrastoppladning i tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ingen (I) J/N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Middel (M) J/N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Homogen (H) J/N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kontrastdefekt (K) J/N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ring (R) J/N</td>
</tr>
</tbody>
</table>

### Andre funn (sett ring):

- Meningeval kontrastoppladning: ja (J) / ne (N)
- Største forhornsavstand (mm):
- Største diameter ventrikkelen (mm):
- Kontrastoppladning subependymalt: ingen / mild / utalt
- Ekstracerebral blodning (sett ring):
  - Subarachnoidal: subdural: epidural: ingen
- Ventrikkelsymmetri: ingen / mild / utalt
- Annet: Annet:
- Cortical relief: grovt / normal / upplandet

### Diagnoser: Sett ring rundt de hoveddiagnoser da mener foreligger (1,2 osv) og de mest sannsynlige underdiagnoser (a,b,osv)

1. Tumor
   a. Glion
   b. Meningeum
   c. Metasase
   d. Lymfor
   e. Annet:

2. Infeksjon
   a. Abscess
   b. Encephalitis
   c. Ventriculis

3. Infarkt
   a. Trombotisk <1,5 cm
   b. Embolisk
   c. Venetrukturer
   d. Leukurais

4. Degenerativ sykdom
   a. Sentral arrof
   b. Perifer arrof
   c. General arrof
   d. Epidural

5. Blodning
   a. Subarachnoidal
   b. Subdural
   c. Epidural

6. Inflamm. sykdom
   a. Demyeliniserende
   b. Cerebral vaskulitt

7. Hydrocephalus

8. Normal

9. Annet:

Utfyllt av (init.): Dato for utfylling:
### MR ved PCNSL

<table>
<thead>
<tr>
<th>Løpenummer</th>
<th>Pasientnavn</th>
<th>Dato for MR ms.</th>
<th>Lv. kontrast (+ / + / ±)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lesjonene nummereres (etter avtagende størrelse) og lokalisasjonen anmerkes med en eller flere forkortelser: Frontallapp FL, Parietallapp PL, Temporalallapp TL, Occipitalallapp OL, Insula IN, Basalganglier BG, Corpus callosum CC, Intraventricular IV, Nucleus ovuli BO, Hypostamme HS, Cerebellum CE, Medulla spinalis MS.

<table>
<thead>
<tr>
<th>Nr Lokalis.</th>
<th>Antall:</th>
<th>Areal</th>
<th>Niveau/height (x y z)</th>
<th>Side</th>
<th>Hovedskel</th>
<th>Lokalisert til</th>
<th>Periact.</th>
<th>Kont. m.ventr.</th>
<th>Kont. m.hjernens overflate</th>
<th>Avgrens. Skarp(S)/Moderat Skarp (M)/Diftus (D)</th>
<th>Omkr. lød.</th>
<th>Ingen(l)</th>
<th>Ingen(D)</th>
<th>Young(l)</th>
<th>Young(D)</th>
<th>Masse-effekt</th>
<th>Lett(l)</th>
<th>Moderat (l)</th>
<th>Utalt (l)</th>
<th>Riedning J/N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ved >7 lesjoner benyttes ekstra skjema.

### Lesjoner

<table>
<thead>
<tr>
<th>Nr forts.</th>
<th>Lesjon</th>
<th>Signal (uten i.v.k)</th>
<th>Homogen signal (uten i.v.k)</th>
<th>Kontrastopladien i tumor</th>
<th>Tentativ diagnose: (ex. 2b, jmf. diagnosemøde)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Andet tunn (sett. ring)

<table>
<thead>
<tr>
<th>Meningeval kontrastopladien</th>
<th>ja</th>
<th>nei</th>
<th>Største foromhavstand (mm):</th>
<th>Største diameter 3. ventrikkel (mm):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontrastopladien subependymalt</td>
<td>ingen</td>
<td>mild</td>
<td>utalt</td>
<td>Ekstraaxialt blodning (sei ring):</td>
</tr>
<tr>
<td>Ventrikel asyimetri</td>
<td>ingen</td>
<td>mild</td>
<td>utalt</td>
<td>Epiduralt subdural subarachnoidal</td>
</tr>
<tr>
<td>Cortical relief</td>
<td>grovt</td>
<td>normal</td>
<td>utplanert</td>
<td>Annot:</td>
</tr>
</tbody>
</table>

### Diagnoser: Sekt ring rundt de hoveddiagnoser du mener foreligger (1,2 osv) og de mest sannsynlige underdiagnoser (a,b osv)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>d. Lymphom</td>
<td>d.</td>
<td>d. Epihedral</td>
<td>d.</td>
<td></td>
</tr>
<tr>
<td>e. Annen</td>
<td>e.</td>
<td>e.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Demyeliniserende sykdom</td>
<td>b. Cerebral vaskulitt</td>
<td></td>
</tr>
</tbody>
</table>

9. Annot:_________

Utfylt av (init.): | Dato for utfylding: