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ORIGINAL ARTICLE

Population-based experience on primary central nervous system lymphoma 2000–2012: the incidence is increasing

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ABSTRACT

Background: Primary central nervous system lymphomas (PCNSL) are rare lymphomas with a poor prognosis. Recently, an increased incidence has been reported. The present study is a population-based study of all patients with PCNSL in the Uppsala/Örebro region of middle Sweden.

Patients and methods: All patients diagnosed with a PCNSL at Uppsala University Hospital 2000–2012 were identified. Altogether, 96 patients (50 women and 46 men) were included. The median age at diagnosis was 66 years (17–95).

Results: There was a statistically significant increase in age-standardized incidence during the study period, 30 patients were diagnosed in the first half and 66 in the second half of the period. No patient had an HIV-infection. Two patients had undergone kidney transplantation and were treated with immunosuppressive drugs. A high proportion of the patients, 29%, had a history of an autoimmune or inflammatory disease. The prognosis was poor with a median survival of only four months. In the 70 (73%) patients treated with curative intention the median survival was 12 months. Patients treated with high-dose methotrexate, radiotherapy and/or temozolomide appeared to have a better survival. There was no improvement in survival during the study period or after the introduction of rituximab. There also was no difference in any of the analyzed variables that could explain the increased incidence.

Conclusion: In this population-based study we could confirm the previously described increased incidence of PCNSL. The prognosis remains poor despite the inclusion of treatment with rituximab during the study period. A high proportion of the patients had a history of an autoimmune or inflammatory disease not previously described but there was no increase during the study period.

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Primary central nervous system lymphomas (PCNSL) are rare lymphomas and account for <1% of the lymphomas [1]. During recent decades, an increasing incidence for PCNSL has been described in a non-HIV population in US in the elderly [2–4]. The reason for the increased incidence is unknown but the reduction in immunological surveillance by age or concomitant diseases and their treatment has been suggested.

PCNSL are almost exclusively diffuse large B cell lymphomas (DLBCL) [1]. The PCNSL are derived from post-germinal center B cells and share molecular similarities with other lymphomas of immune privileged sites including loss of the HLA region [5]. Furthermore, a biased usage of VH genes of the immunoglobulin gene, e.g. VH 4-34 suggests antigen stimulation [6]. VH4-34 encodes autoreactive antibodies, which strengthens the association to immune dysfunction as a part of the pathogenesis [7].

PCNSL have a poor prognosis despite intensive treatment with chemotherapy and radiotherapy [8–10]. DLBCL outside the context of PCNSL can, by gene expression profiling, be divided in two major groups, the germinal center (GC) derived and those derived from activated B cells (non-GC). Most of the PCNSL have been assigned to the non-GC type [11], which together with poor penetration of drugs active towards lymphomas to the CNS might contribute to the poor prognosis.

The aim of this study was to investigate if an increased incidence of PCNSL could be confirmed by identifying all patients with a PCNSL in the Uppsala/Örebro health care region in Sweden 2000–2012. Furthermore, the aim was to study how the treatment and survival had developed during the study period and search for possible explanations to the increased incidence, e.g. for relation to autoimmune or inflammatory diseases.

Material and methods

Patients

Patients diagnosed with a PCNSL in the Uppsala/Örebro region of Sweden 2000–2012 were identified via the files of

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the Department of Pathology, Uppsala University Hospital. Patients diagnosed by imaging only where not included in the study. All patients in the study were diagnosed through a neurosurgical biopsy, there were no cases diagnosed on lymphoma of the cerebrospinal fluid only. The Uppsala University Hospital is a referral hospital for all neurosurgery of the region, which covers 2.1 million inhabitants. Information about the extent of the disease, a possible immune impairment or autoimmune or inflammatory disease, initial treatment and survival was retrieved from the patients' records at the Departments of Neurosurgery and Oncology at the Uppsala University Hospital or in some cases from the county hospitals the patients were referred to after neurosurgery. The patients were retrospectively assigned a prognostic score developed by Memorial Sloan Kettering Cancer Center (MSKCC) [12]. Patients $\leq$50 years comprised one group, patients >50 years and Karnofsky performance status $\geq$70 comprised a second group, and patients >50 years and Karnofsky performance status <70 a third group.

The treatment recommendations changed during the study period but always included high-dose methotrexate in patients considered to tolerate intensive treatment. Twelve patients were included in a Nordic trial [13].

All patients were followed until death or 1 December 2014. The median follow-up of living patients was 58 months (25–158 months). The study was approved by the ethical review board of Uppsala University.

Pathology

All diagnostic biopsies were reclassified according to the WHO classification of lymphomas [1] by an experienced hematopathologist and in all cases confirmed to be DLBCL.

Statistical methods

The χ^2-test or Fisher's exact test (when <5 observations) was applied when analyzing categorical data against categories. The Mann-Whitney U-test was used to calculate differences in continuous data between subgroups. Overall survival was defined as time from initial lymphoma diagnosis until death. Survival curves were generated using the Kaplan-Meier method. Differences in survival were calculated using the log-rank test. Univariate analysis was performed using the Cox proportional hazards regression model. Statistical significance was defined as a p value of <0.05. All statistical analyses were performed using Statistica software (version 10, Stat Soft Inc.). Age-standardized incidence was calculated by using the weights from the World Standard Population and its variance was estimated by assuming a Poisson distribution. Weighted linear regression was used to test for change in age-standardized incidence over time by using the inverse of the variance as weights. The same analysis was made with the Swedish population of the year 2000 as a reference population.

Results

Altogether, 96 patients with a median age of 66 years (17–95) were identified, 50 female and 46 male (Table 1; Figure 1). The men were significantly younger at diagnosis, median age 60 years as compared to 66 years for the women ($p < 0.01$). There was a significant increase in age-standardized incidence during the study period both when compared to the Swedish population of the year 2000 ($p = 0.0008$) and the World Standard Population ($p = 0.027$) (Figure 2). In the first 6.5 years (hereafter called the first period) 30 patients were diagnosed as compared with 66 in the last 6.5 years (hereafter called the last period). There was no difference in clinical characteristics between the first and the last study period (Table 1). Although there was a higher proportion of patients above 60 years in the last period; 52 versus 20, the difference was not statistically significant ($p = 0.20$).

Table 1. Clinical characteristics of the included patients. First period refers to the first 6.5 years of the study period 2000–2012 and second period refers to the last 6.5 years.

	Total	First period	Second period	p Value
Total number of patients	96	30	66	
Male/female	46/50	14/16	32/34	0.87
Median age (range)	66 (17–95)	64 (18–74)	66 (17–95)	0.22
17–49	13 (14)	4 (13)	9 (14)	0.35*
50–59	11 (11)	6 (20)	5 (8)	
60–69	41 (43)	12 (40)	29 (44)	
70–	31 (32)	8 (27)	23 (35)	
Histology no. (%)				
DLBCL	96 (100)	30	66	
Site of disease no. (%)				0.78
Cerebral hemisphere	43 (45)	13 (43)	30 (45)	
Deep structure	22 (23)	7 (23)	15 (23)	
Cerebellum	2 (2)	0 (0)	2 (3)	
Multiple lesions	29 (30)	10 (33)	19 (29)	
Positive cerebrospinal fluid no. (%)				0.16
Yes	9 (9)	4 (13)	5 (8)	
No	43 (45)	10 (33)	26 (39)	
Unknown	42 (44)	16 (53)	42 (64)	
Performance status (WHO) no. (%)				0.67
0	16 (17)	3 (10)	13 (20)	
1	32 (33)	12 (40)	20 (30)	
2	26 (27)	7 (23)	19 (29)	
3	17 (18)	6 (20)	11 (17)	
4	4 (4)	2 (7)	2 (3)	
Diagnosed at autopsy	1 (1)	0	1 (2)	
MSKCC score				0.96
1	14 (15)	4 (13)	10 (15)	
2	42 (44)	13 (43)	29 (44)	
3	40 (42)	13 (43)	27 (41)	
Autoimmune/Inflammatory disease no. (%)	27 (28)	9 (30)	18 (28)	0.85

DLBCL: diffuse large B cell lymphoma; MSKCC score: Memorial Sloan Kettering Cancer Center score. * p level for the entire age distribution in age categories.

Immune deficiency and autoimmune disease

There was no patient with HIV infection. Two patients were under treatment with immunosuppressive drugs due to previous kidney transplantation. Of the remaining 94 patients, 27 (29%) had a history of an autoimmune or inflammatory disease preceding the diagnosis of PCNSL (Table 2). The median age in patients both with and without an autoimmune disease was 66 years. A history of an autoimmune disease was significantly more common in women as compared to men, 19 (39%) versus eight (18%) ($p = 0.03$) (Table 2).There was no difference in the frequency of autoimmune

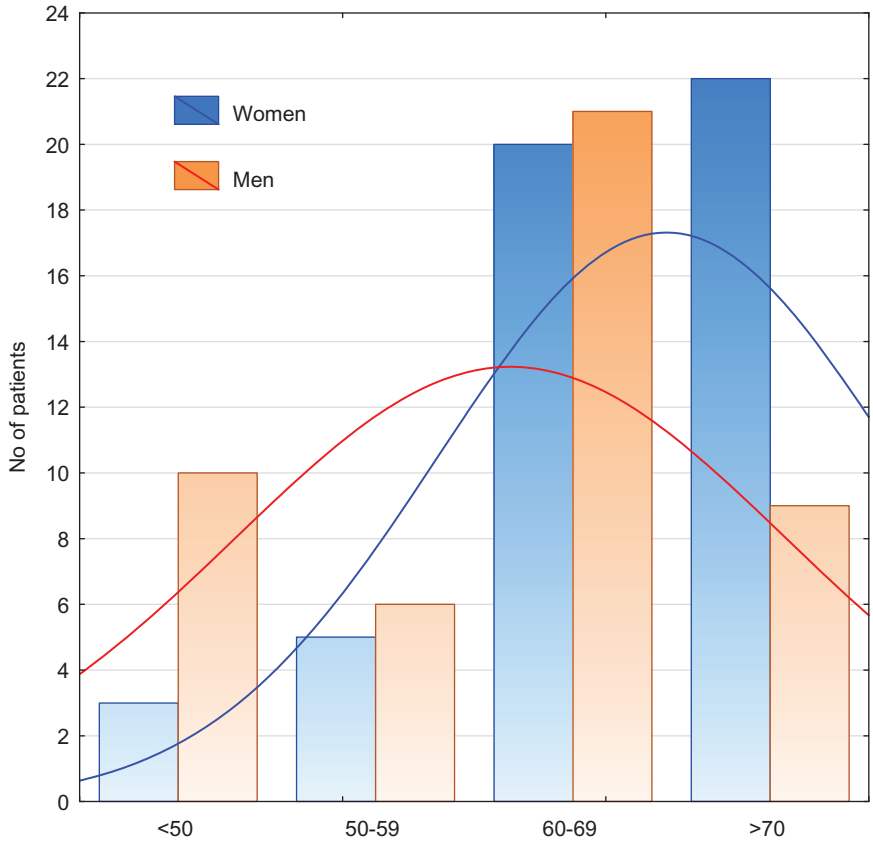

Figure 1. Age and sex distribution of the included patients.

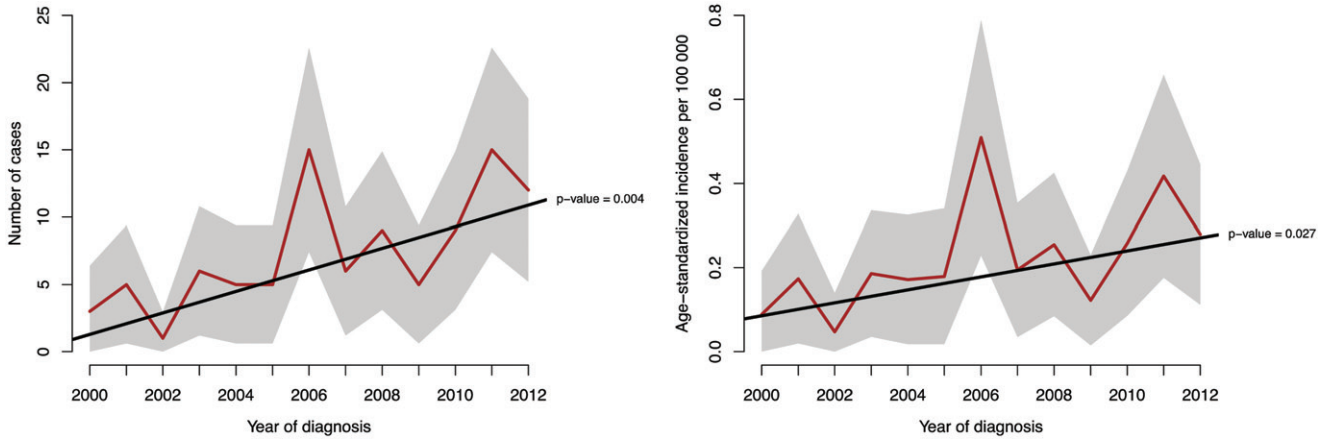

Figure 2. Age-standardized incidence according to the World Standard Population. The red line indicates actual incidence with confidence limits in gray. The black line indicated age-standardized incidence.

or inflammatory disease in the first 6.5 years versus the last 6.5 years of the study (Table 1).

Table 3 summarizes the interval between the diagnosis of the autoimmune or inflammatory disease, and the PCNSL and the immunosuppressive drugs used. In total, seven patients were on, or had been on immunosuppressive drugs, most often corticosteroids.

Seven patients had inflammatory manifestations of the eyes. Four had uveitis, six, seven, 15 and 40 months before the PCNSL diagnosis. In three, an magnetic resonance imaging (MRI) of the brain was performed at the time of the uveitis diagnosis, and found normal. All patients were treated with corticosteroids. Two patients had chorionretinitis, one was not treated and found at the diagnostic work up of the PCNSL. The other patient had his diagnosis six months before the PCNSL diagnosis and a MRI of the brain was normal. The last patient had retrobulbar neuritis 12 months before the PCNSL diagnosis and a MRI was normal.

Treatment

Seventy (76%) were treated with curative intention whereas 24 (25%) patients received palliative treatment or no treatment and data were missing in two patients. Significantly,

Table 2. Autoimmune or inflammatory diseases present in the included patients.

Disease	Total	Men	Women	Median duration (range)	Immunosuppressive treatment
Total	27[a]	8	18		
Uveitis/chorionretinitis	7	2	5	13.5 months (6–40 months)	Corticosteroids
Hypothyroidism[b]	7	2	5	Many years	No
Thyretoxicosis	2		1		No
Inflammatory bowel disease	3	0	3		Corticosteroids, mesalazine
Systemic lupus erythematosus	1	0	1		Azathioprine, methoitrexate, hydroxy-chloroquine, mycophenolate mofetil
Ankylosing spondylitis	1	1	0		No
Primary Sjögren's syndrome	2	1	1		No
Pustolosis palmoplantaris	1	0	1		no
Polymyositis, primary biliary cirrhosis	1	0	1		Azathioprine
Alopecia	1	1	0		No
Lumbosacral plexopathy	1	0	1	3 years	Steroids
Panniculitis	1	1	0		Information missing
Interstital pneumonitis, asculitis	1	0	1	15 months	Prednisone, Azathioprine

[a]A few patients had more than one diagnosis.
[b]No information on preceding thyroiditis.

Table 3. First line treatment of the included patients.

Type of treatment	Total	First period	Second period	*p* Value
Patients	96	30	66	
Curative[a]no. (%)	70 (73)	21 (70)	49 (64)	0.50
High-dose Mtx	50	13 (43)	37 (56)	0.25
High-dose cytarabine	55	16 (53)	39 (70)	0.63
Rituximab[b]	27	3 (10)	24 (36)	0.004
Radiotherapy[b]	21	6 (20)	15 (23)	0.32
HDCT	4	3 (10)	1 (2)	0.04
Temozolamide[b]	21	3 (10)	18 (27)	0.02
Palliative	24 (25)	9 (30)	15 (23)	0.50
Missing data	2 (2)	0	2 (3)	

[a]Many patients received a combination of drugs.
[b]As part of the primary planned treatment.

more men were treated with curative intention 39 versus 31 ($p = 0.02$). The patients treated with curative intention were significantly younger; median age 60 years as compared with 71 years ($p < 0.001$) for those treated without curative intention. Curative treatment varied during the study period.

Fifty patients were treated with high-dose methotrexate of whom 29 were treated with methotrexate, vincristine and procarbazine (MPV) [14] and 12 were treated according to a Nordic study protocol based on high-dose methotrexate and ifosfamide [13]. The remaining nine patients treated with high-dose methotraxate were treated according to an alternating schedule with high-dose methotrexate, radiotherapy and cytarabine adapted and modified from Deangelis et al. [15] (Table 3). In 55 patients, the curative treatment included cytarabine. The planned treatment was an alternating schedule with methotrexate, but in some patients the treatment was started with cytarabine due to poor performance or renal function. In other patients MPV was switched to cytarabine due to toxicity or poor effect. Four patients [two women and two men, median age 54 years (18–61)] were treated with high-dose chemotherapy and autologous stem cell transplantation (HDCT). Two of the patients treated with HDCT are alive and in remission with no further treatment with a follow-up of 105 and 108 months, respectively, and one patient received radiotherapy (RT) at progressive disease and are alive and disease-free 98 months post-RT.

Twenty-one patients were treated with radiotherapy as a part of the primary treatment of whom 19 were treated with curative intention. The radiotherapy was given in 1.8–2 Gy fractions for a maximum dose of 40 Gy.

Twenty-seven (28%) patients received rituximab as part of the primary treatment of which 12 received one dose of rituximab as a part of the Nordic protocol [13]. The remaining 15 patients received a varying number of doses of which the details not was retrievable. Twenty-one patients received temozolomide as a part of the primary treatment of which six received it as a part of the Nordic protocol [13] and 15 outside of protocol, in most cases as maintenance. The patients who received temozolamide had a median age of 69 years as compared to 65 years for those who did not ($p = 0.12$). There was a significantly higher proportion patients treated with rituximab and temozolomide in the last study period (Table 3).

The reason for the choice of palliative treatment or no treatment was in all cases high age, a poor performance status or rapid disease progression.

Survival

The median survival of all patients was four months (range 0–158) (Figure 3(a)). Patients treated with curative intention had a median survival of 12 months (0–158) (Figure 3(b)). Men had a better survival than women; 6.5 months versus 3 months but the difference was not statistically significant $p = 0.06$, hazard ratio (HR) 1.5 [confidence limits (CL) 0.97–2.4]. When patients treated with curative intention were studied men had a median survival of 12 months versus 10 months for women ($p = 0.28$, HR 1.35 (CL 0.78–2.33). Younger patients had a better survival as had patients with lower MSKCC score (Figure 3(c–d)). There was no survival difference between the first and the last time period; the median overall survival in both periods was four months HR 0.94 (CL 0.58–1.54). Patients with good performance status (WHO <2) had a better prognosis, $p = 0.05$, HR 0.64 (CL 0.41–1.0), but S-Lactate dehydrogenase (S-LDH) or the location of the PCNSL had no impact on survival (data not presented). There was no survival difference in patients with or without an autoimmune or inflammatory disease. The median survival for patients without an autoimmune disease was four months

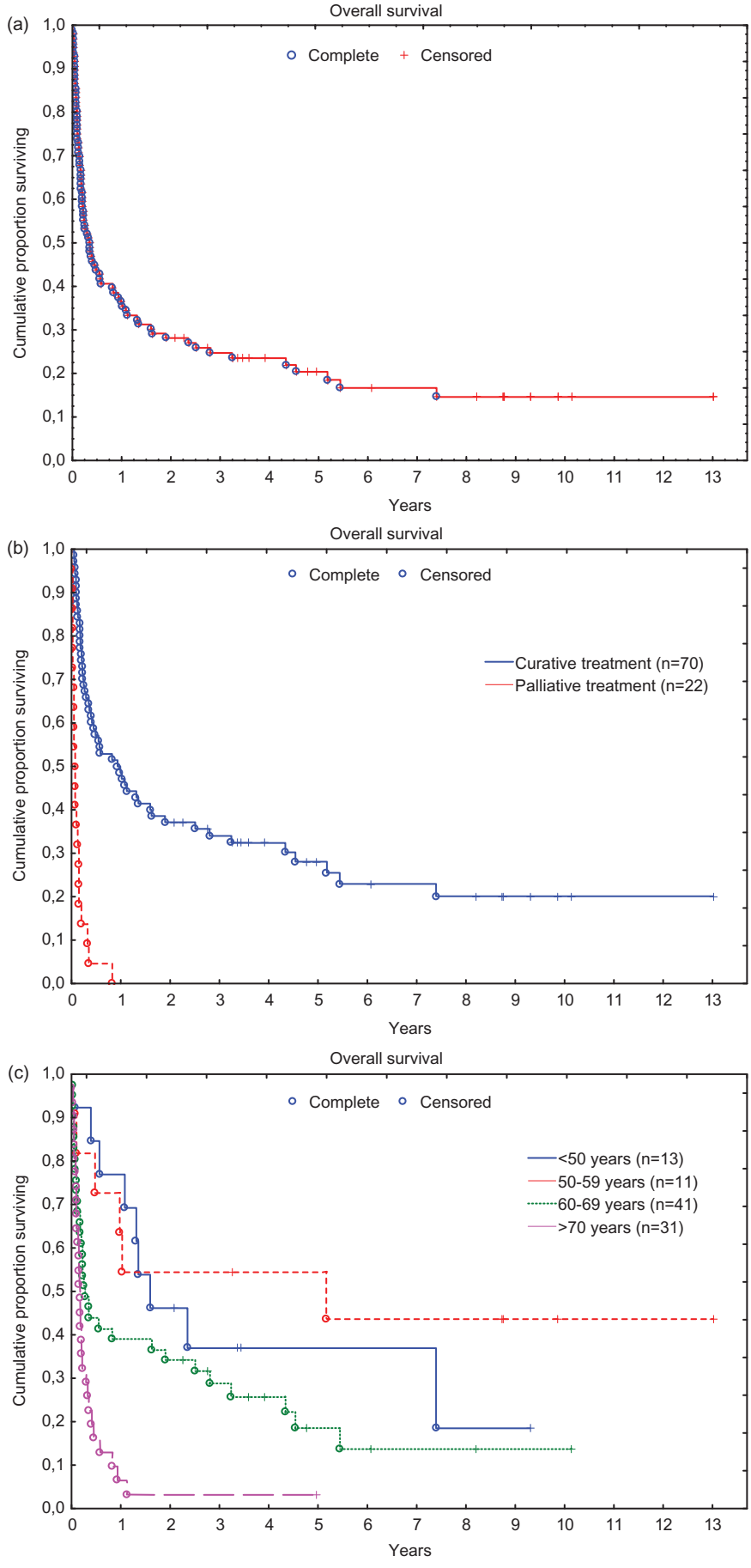

Figure 3. (a–d) Overall survival in all patients and according to treatment intention and risk groups. MSKCC: Memorial Sloan Kettering Cancer Center prognostic score.

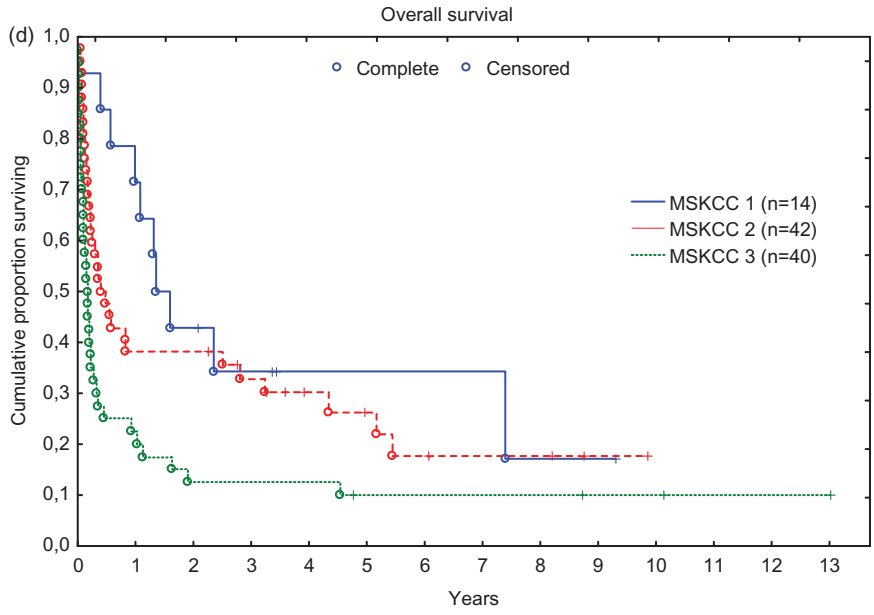

Figure 3 Continued.

versus three months for those with an autoimmune disease, $p = 0.84$, HR 0.95 (CL 0.60–1.56).

The patients whose curative treatment included high-dose methotrexate, radiotherapy or temozolamide all had a significantly better survival (Figure 4(a–c)) whereas cytarabine or rituximab, $p = 0.33$, HR 1.33 (0.74–2.37) did not seem to have an impact on survival.

At the end of follow-up, 78 patients had died. The causes of death were treatment related in 10 (nine infections and one pulmonary embolism).

Discussion

The most interesting finding in the present population-based study from the middle region of Sweden was the significantly increased incidence in PCNSL. In the Swedish lymphoma registry, covering the entire country, PCNSL is not recorded as a separate entity why it is not possible to study if the increased incidence is seen in the entire country through the registry. The increased incidence was mainly found in patients above the age of 60, which is consistent with data from the US where an increased incidence in both men and women was found in patients above 65 [4].

The reasons for the increasing incidence are so far unknown. Increased use of biopsies during the study period could not be entirely ruled out, but all patients in the present study were originally seen by the study team and the hospital policy has been to verify all suspicious PCNSL for many years.

One might speculate that a yet unknown virus or other environmental factors could contribute to the development to PCNSL. The biased use of VH genes of the immunoglobulin gene supports an antigen involved in the pathogenesis [6]. Neuroinflammation with cerebral lesions preceding the diagnosis of PCNSL has been described [16], but was not seen in this study. Autoimmune or inflammatory disease is a risk factor for various types of lymphomas although to our knowledge a specific association to PCNSL has not been described [17,18]. In the present study, 29% of the patients had a preceding autoimmune or inflammatory disease but there was no difference between the first and last half of the study period. Seven patients had inflammatory manifestations to the eye. Primary vitroretinal lymphoma (PVRL) is an intraocular lymphoma often related to or preceding PCNSL [19]. The symptoms mimics uveitis and in the present study the seven cases of inflammatory diseases of the eyes probably in most cases represent lymphoma manifestations although it was not proven in any of the cases. There was no patient with proven ocular manifestation at the diagnosis of the PCNSL. However, ocular investigation was not a part of the routine work up during most of the study period.

Nine patients (9%) had diseases of the thyroid gland (two thyreotoxicosis and seven hypothyroidism) and one patient had an unexplained alopecia. None of these conditions are proven to be inflammatory but the frequency of hypothyroidism seemed to be higher than what would be expected in iodine-replete population where the prevalence of hypothyroidism is between 1% and 2% [20].

Nine patients had inflammatory diseases related to HLAB27 (ankylosing spondylitis, uveitis, pustolosis palmoplantaris and inflammatory bowel disease) but there is no definitive association known between HLAB27 and lymphomas. Immunosuppressive treatment might of course contribute to PCNSL development but there were only seven of the patients (excluding the eye manifestations) with inflammatory disease that had been on immunosuppressive drugs, most often corticosteroids. We have previously shown that treatment with corticosteroids rather reduces the risk of lymphoma in patients with rheumatoid arthritis [21].

There was, however, no patient with rheumatoid arthritis with a known increased risk of lymphoma, particularly DLBCL [17,18]. This could, of course, be explained by chance as the

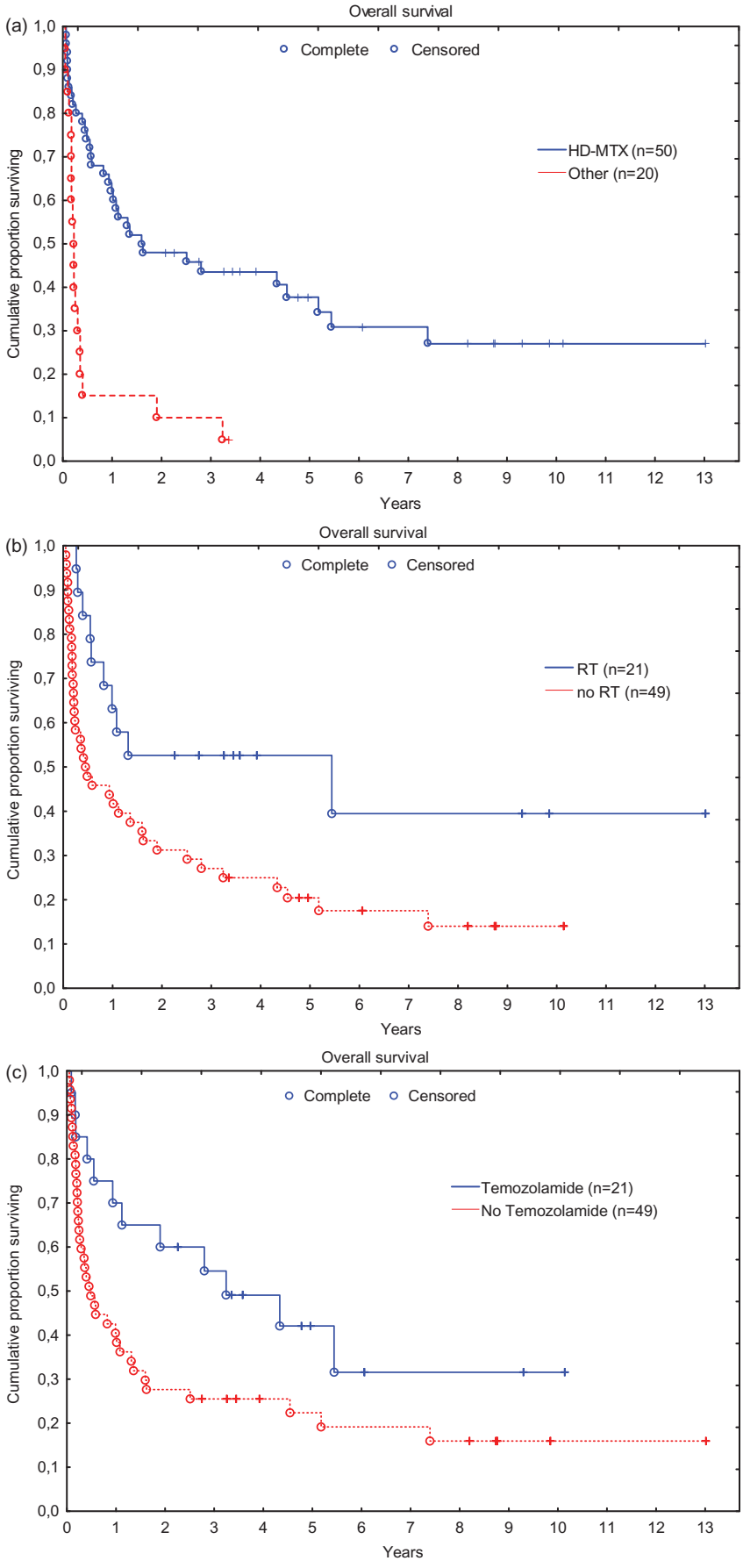

Figure 4. (a–c) Overall survival according to treatment in patients treated with curative intention.

material is limited but complex mechanism between immune dysregulations and PCNSL might be considered.

The overall survival in the present study was poor. However, the material includes all patients diagnosed with a PCNSL in the population, also including patients whose performance was too poor to be considered for treatment. When studying patients treated with curative intention only, the results are in line with a recently published material [10] but worse than in other more specialized centers [22,23]. The present study confirms that high-dose methotrexate is an important component of the therapy for PCNSL. However, rituximab did not seem to improve prognosis, neither was there any improvement between the first and the second half of the study period. However, the number of patients was low and a selection of the sickest patients chosen for rituximab cannot be excluded. Other groups have found increased complete remission (CR)-rate [24] and survival after the introduction of rituximab [25].

In contrast, patients who received temozolamide as a part of the primary treatment appeared to have a better survival. Although, many patients received temozolamide as consolidation, which selected patients who had managed the initial part of the treatment, the results are still promising. A few of the patients in the present study were also included in a Nordic phase II study where temozolamide were used in the elderly group with apparently promising results [13]. Also others have incorporated temozolamide in the treatment of PCNSL with positive results [26].

In conclusion, the present study shows an increased incidence of PCNSL, which require further studies. It also confirms the poor prognosis of these patients despite intensive treatment. There seems to be a relation to autoimmune or inflammatory disease, not previously described.

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