ACTA ONCOLOGICA
2019, VOL. 58, NO. 7, 967–976
https://doi.org/10.1080/0284186X.2019.1599137

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Increasing use of immunotherapy and prolonged survival among younger patients with primary CNS lymphoma: a population-based study

Magdalena Neuhauser[a,b]*, Thomas Roetzer[a,b]*, Stefan Oberndorfer[c], Melitta Kitzwoegerer[d], Franz Payer[e], Julia J. Unterluggauer[f], Johannes Haybaeck[f,g], Günther Stockhammer[h], Sarah Iglseder[h], Patrizia Moser[i], Claudius Thomé[j], Martin Stultschnig[k], Franz Wuertz[l], Tanisa Brandner-Kokalj[l], Serge Weis[m], Dave Bandke[m], Josef Pichler[n], Markus Hutterer[o], Karl J. Krenosz[p], Alexandra Boehm[q], Beate Mayrbaeurl[r], Andrea Hager-Seifert[s], Hannes Kaufmann[t], Martina Dumser[u], Angelika Reiner-Concin[v], Selma Hoenigschnabl[v], Waltraud Kleindienst[w], Markus Hoffermann[x], Karin Dieckmann[b,y], Barbara Kiesel[b,z], Georg Widhalm[b,z], Christine Marosi[b,aa], Ulrich Jaeger[b,aa], Andreas Hainfellner[a,b], Monika Hackl[ab], Johannes A. Hainfellner[a,b], Matthias Preusser[b,aa] and Adelheid Woehrer[a,b]

[a]Institute of Neurology, Medical University of Vienna, Vienna, Austria; [b]Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [c]Department of Neurology, University Hospital St. Poelten, Karl Landsteiner University of Health Sciences, St. Poelten, Austria; [d]Department of Pathology, University Hospital St. Poelten Karl Landsteiner University of Health Sciences, St. Poelten, Austria; [e]Department of Neurology, Medical University of Graz, Graz, Austria; [f]Department of Neuropathology, Institute of Pathology, Medical University of Graz, Graz, Austria; [g]Department of Pathology, Otto-von-Guericke University of Magdeburg, Magdeburg, Germany; [h]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria; [i]Department of Pathology, Medical University of Innsbruck, Innsbruck, Austria; [j]Department of Neurosurgery, Medical University of Innsbruck, Innsbruck, Austria; [k]Department of Neurology, State Hospital Klagenfurt, Klagenfurt, Austria; [l]Institute of Pathology, State Hospital Klagenfurt, Klagenfurt, Austria; [m]Department of Neuropathology, Neuromed Campus, Kepler University Hospital, Johannes Kepler University of Linz, Linz, Austria; [n]Department of Internal Medicine and Neurooncology, Neuromed Campus, Kepler University Hospital, Johannes Kepler University of Linz, Linz, Austria; [o]Department of Neurology, Neuromed Campus, Kepler University Hospital, Johannes Kepler University of Linz, Linz, Austria; [p]Department of Hematology and Oncology, Kepler University Hospital, Johannes Kepler University of Linz, Linz, Austria; [q]Department of Internal Medicine, Hematology and Oncology, Hospital Elisabethinen, Linz, Austria; [r]Department of Internal Medicine IV, Hospital Wels-Grieskirchen, Wels-Grieskirchen, Austria; [s]Department of Neurology, State Hospital Wiener Neustadt, Wiener Neustadt, Austria; [t]Department of Oncology, Krankenanstalt Rudolfstiftung, Vienna, Austria; [u]Department of Pathology, Krankenanstalt Rudolfstiftung, Vienna, Austria; [v]Department of Pathology, Donauspital Vienna, Vienna, Austria; [w]Department of Neurology, Paracelsus Medical University Salzburg, Salzburg, Austria; [x]Department of Neurosurgery, State Hospital Feldkirch, Feldkirch, Austria; [y]Department of Radiotherapy, Medical University of Vienna, Vienna, Austria; [z]Department of Neurosurgery, Medical University of Vienna, Vienna, Austria; [aa]Department of Medicine I, Medical University of Vienna, Vienna, Austria; [ab]Austrian National Cancer Registry, Statistics Austria, Vienna, Austria

ABSTRACT

Background: Primary CNS lymphoma is a highly aggressive and rare type of extranodal non-Hodgkin lymphoma. Although, new therapeutic approaches have led to improved survival, the management of the disease poses a challenge, practice patterns vary across institutions and countries, and remain ill-defined for vulnerable patient subgroups.

Material and Methods: Using information from the Austrian Brain Tumor Registry we followed a population-based cohort of 189 patients newly diagnosed from 2005 to 2010 through various lines of treatment until death or last follow-up (12-31-2016). Prognostic factors and treatment-related data were integrated in a comprehensive survival analysis including conditional survival estimates.

Results: We find variable patterns of first-line treatment with increasing use of rituximab and high-dose methotrexate (HDMTX)-based poly-chemotherapy after 2007, paralleled by an increase in median overall survival restricted to patients aged below 70 years. In the entire cohort, 5-year overall survival was 24.4% while 5-year conditional survival increased with every year postdiagnosis.

Conclusion: In conclusion, we show that the use of poly-chemotherapy and immunotherapy has disseminated to community practice to a fair extent and survival has increased over time at least in younger patients. Annually increasing conditional survival rates provide clinicians with an adequate and encouraging prognostic measure.

ARTICLE HISTORY
Received 20 December 2018
Accepted 17 March 2019

CONTACT Johannes A. Hainfellner johannes.hainfellner@meduniwien.ac.at Institute of Neurology & Comprehensive Cancer Center, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria; Matthias Preusser matthias.preusser@meduniwien.ac.at Department of Medicine I & Comprehensive Cancer Center, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria
*These authors contributed equally to this work

Supplemental data for this article can be accessed here

Introduction

Primary CNS lymphoma (PCNSL) is a highly aggressive and rare type of extranodal non-Hodgkin lymphoma that is confined to the brain, spinal cord, and their coverings without evidence of systemic disease involvement. PCNSL represents only 4% of all primary brain tumors [1] and shows – unlike many other brain tumors – a favorable first response to chemo- and radiotherapy, but compared with extra-cerebral lymphomas survival is notably poor [2]. The prognosis for patients that have failed first-line therapy remains particularly dismal. Although, new therapeutic approaches have led to prolonged survival [3–6], the multimodal treatment of the disease still poses a challenge [7]. Experts agree on high-dose methotrexate (HDMTX) as backbone of chemotherapeutic protocols that frequently include other cytotoxic drugs with or without rituximab immunotherapy and radiotherapy. Important initiatives aim at harmonizing first-line treatment [8], while practice patterns still vary across institutions and countries, and remain ill-defined for subgroups of patients such as elderly, immune-deficient, or relapsing patients.

Due to the rarity of PCNSL and complex patient management, it remains unclear how much of the mounting treatment evidence has disseminated in routine clinical practice. So far, only single studies have documented patient care and outcome in unselected patient populations [9–14]. Together they provided evidence for continued poor outcome of the majority of patients, varying treatment patterns between younger and elderly patients, as well as frequent treatment-related toxicities [1,11,12]. At the same time, they highlight a fraction of roughly 20% of patients in whom a durable remission is achieved [1,13]. For those 'chronic disease' patients conventional survival estimates do not adequately capture their prognosis as it changes over time. In contrast, conditional survival, which takes prior survival into account, offers more dynamic and clinically informative estimates [15]. Conditional survival has previously been reported for malignant brain tumors including PCNSL, but these analyses have been limited to cancer registry data without detailed phenotypic annotation [16,17].

Within this study, we aimed at tracking a large population-scale patient cohort with contemporary patient care and extended follow-up. The cohort stands out by its rich clinical annotation and allows for in-depth analysis of sensitive patient cohorts, treatment-related toxicity data as well as long-term survivors. The herein provided conditional survival estimates aim at guiding doctors in patient counseling and PCNSL survivors in their future planning.

Material and methods

Data source

We selected data from the population-based Austrian Brain Tumor Registry (ABTR) that uses multiple sources for case reporting including pathology records, clinical documentation and mortality statistics to warrant high disease coverage (overall ~1,500 incident brain tumor cases per year in a population of ~ 8,7 Mio). We included data on 205 patients aged ≥18 years, who were newly diagnosed with PCNSL from January 2005 to December 2010 with a last follow-up in December 2016. 16 patients were excluded upon chart review due to prior or concomitant systemic disease or lack of histologic confirmation. Detailed information on prognostic factors, onset of symptoms, diagnostic scan, neurosurgery, adjuvant treatment modality, and treatment response were retrospectively abstracted from medical records using a standardized case report form (Supporting Information Table I). Relapse was defined as disease recurrence after an initial response had been achieved. Gadolinium-enhanced magnetic resonance images were not available for central review. Date of death or last follow-up were provided by the Austrian National Cancer Registry, Statistics Austria. The study was approved by the Institutional Review Board of the Medical University of Vienna (approval no 2091/2015). Informed consent was obtained according to the Declaration of Helsinki.

Variables

We stratified age at diagnosis in two categories, that is, 18–69 and 70+ and defined long-term survival as being alive at 5 years after diagnosis. We defined major first line treatment modalities as receipt of radiotherapy only (RT-only), chemotherapy only (CT-only), or combined treatment (CT-RT). In order to assess changes over time, we stratified patients according to year of diagnosis in two 3-year diagnostic intervals (2005–2007, 2008–2010). Good clinical performance was defined as Eastern Cooperative Oncology Group (ECOG) scores 0–1, whereas ECOG scores 2–4 were summarized as poor functional status. Caseload per hospital was defined as low (1–9 patients), medium (10–19 patients), and high (≥20 patients) during the observational period and centers were categorized into academic and community hospitals. Please note that the Austrian health care system provides virtually complete social health insurance coverage with publicly funded care for all residents irrespective of income or ethnic background. Information on total number of hospitals was obtained from 'Gesundheit Österreich GmbH' available at www.spitalskompass.at and plotted on a topographic map downloaded from Google Earth.

Statistical analyses

Statistical analyses were exploratory and descriptive in nature and included the median (min–max) for continuous variables and percentages for categorical variables. The nonparametric Mann–Whitney *U* test was used to analyze continuous variables and the χ^2- or Fisher's exact tests were used to compare categorical variables. Time to relapse and overall survival (OS) were calculated according to Kaplan–Meier estimates with two-sided log-rank tests for univariate comparisons. Univariate analysis was used to identify predictors of survival and all variables with either a p value <.25 or based on their clinical relevance were selected for the multivariable Cox regression model. All p values quoted are two-sided with a level of significance of .05. The percentages of persons surviving one and five additional

Table 1. Demographic characteristics of the cohort and comparative survival analysis.

			Short-term survival		Long-term survival		
Variable		Total $N = 164$ (100%)	0–12 months $N = 82$ (100%)	12–60 months $N = 42$ (100%)	60–100 months $N = 24$ (100%)	100+ months $N = 16$ (100%)	Log-rank[a] p Value
Gender	Female	86 (52.4)	42 (51.2)	23 (54.8)	14 (58.3)	7 (43.8)	.773
	Male	78 (47.6)	40 (48.8)	19 (45.2)	10 (41.7)	9 (56.3)	
Age	18–69 years	104 (64.6)	38 (46.3)	30 (71.4)	21 (87.5)	15 (93.8)	<.001**
	70+ years	60 (36.6)	44 (53.7)	12 (28.6)	3 (12.5)	1 (6.3)	
Performance	ECOG 0-1	99 (68.8)	42 (58.3)	27 (73.0)	20 (87.0)	10 (83.3)	<.001**
	ECOG 2-4	45 (31.3)	30 (41.7)	10 (27.0)	3 (13.0)	2 (16.7)	
Immune status	Competent	150 (93.8)	73 (91.3)	38 (92.7)	24 (100.0)	25 (100.0)	.006**
	Deficient	10 (6.3)	7 (8.8)	3 (7.3)	–	–	
Surgery	Biopsy	122 (77.2)	58 (74.4)	32 (80.0)	17 (70.8)	15 (93.8)	.233
	Resection	36 (22.8)	20 (25.6)	8 (20.0)	7 (29.2)	1 (6.3%)	
First-line	CT-only	94 (57.3)	41 (50.0)	23 (54.8)	19 (79.2)	11 (68.8)	<.001**
	CT-RT	32 (19.5)	9 (11.0)	13 (31.0)	5 (20.8)	5 (31.3)	
	RT-only	16 (9.8)	12 (14.6)	4 (9.5)	–	–	
	BSC	22 (13.4)	20 (24.4)	2 (4.8)	–	–	
	HDMTX	98 (61.3)	40 (51.3)	25 (59.5)	21 (87.5)	12 (75.0)	<.001**
	Poly-CT	52 (41.3)	17 (34.0)	13 (36.1)	14 (58.3)	8 (50.0)	.012*
	Rituximab	27 (17.0)	10 (13.0)	6 (14.3)	8 (33.3)	3 (18.8)	.031*
Second-line	Any	28 (18.1)	1 (1.3)	18 (43.9)	4 (19.7)	5 (33.3)	(.045*)
	CT-only	15 (53.6)	–	10 (55.6)	2(50.0)	3 (60.0)	.569
	CT-RT	9 (32.1)	–	6 (33.3)	1 (25.0)	2 (40)	
	RT-only	4 (14.3)	1 (100.0)	2 (11.1)	1 (25.0)	–	
Third-line	Any	6 (3.7)	–	3 (7.1)	–	3 (18.8)	(.044*)
	CT-only	3 (50.0)	–	1 (33.3)	–	2 (66.7)	
	CT-RT	1 (16.7)	–	–		1 (33.3)	
	RT-only	2 (33.3)	–	2 (66.7)	–	–	
Diagnostic period	2005–2007	71 (44.7)	38 (48.1)	23 (56.1)	2 (8.3)	8 (53.3)	.031*
	2008–2010	88 (55.3)	41 (51.9)	18 (43.9)	22 (91.7)	7 (46.7)	
Hospital	Community	95 (57.9)	52 (63.4)	20 (47.6)	14 (58.3)	9 (56.3)	.645
	Academic	69 (42.1)	30 (36.6)	22 (52.4)	10 (41.7)	7 (43.8)	
Caseload	Low	50 (30.5)	27 (33.3)	12 (28.6)	9 (36.0)	2 (12.5)	.091
	Medium	83 (50.6)	39 (48.1)	25 (59.5)	10 (40.0)	9 (56.3)	
	High	31 (18.9)	15 (18.5)	5 (11.9)	6 (24.0)	5 (31.3)	
Diagnostic delay	<30 days	90 (57.7)	45 (57.7)	25 (64.1)	12 (50.0)	8 (53.3)	.331
	>30 days	66 (42.3)	33 (42.3)	14 (35.9)	12 (50.0)	7 (46.7)	
Integrated Care	Yes	121 (73.8)	58 (70.8)	33 (78.6)	16 (66.7)	14 (87.5)	.411
	No	43 (26.2)	24 (29.3)	9 (21.4)	8 (33.3)	2 (12.5)	

(.) Cave immortal time bias.
[a]Group comparison based on categories per variable as defined in columns one and two. For HDMTX, Poly-CT and Rituximab, patients who received the given modality were compared with CT-only patients who did not receive the respective modality.
CT-only: chemotherapy-only; CT-RT: induction chemotherapy followed by consolidation radiotherapy; RT-only: radiotherapy only; BSC: best supportive care; HDMTX: high-dose methotrexate; Poly-CT: poly-chemotherapy.

years after a period of 1, 2, 3, and 4 years postdiagnosis were generated along with their 95% CI. Conditional survival rates were generated overall as well as by age group, gender, clinical performance, immune status, treatment modality, and diagnostic interval using the *condSURV* R package [18]. Missing values were excluded from the respective analysis. Statistical analyses were conducted using SPSS® v23, Excel®v14.6.1, and R v3.3.3 [19]. Data visualization was performed with R v3.3.3 and the *ggplot2*-package [20] as well as with the python libraries *matplotlib* [21] and *lifelines* [22].

Results

Basic demographic characteristics and decentralized patient care

The entire cohort consisted of 189 patients with newly diagnosed, histologically confirmed PCNSL with a median follow-up of 12 months (ranging from 0 to 136 months). Median age at diagnosis was 66 years (range 23–84 years) with 50.3% being female and 39.7% being above age 70. The cohort is introduced in Figure 1(A) and demographics detailed in Table 1. Clinical and therapeutic information was available for 164 patients (86.8%). Among those, 142 (86.6%) patients received any tumor-directed therapy, 22 patients (13.4%) best supportive care (BSC). Median time from onset of symptoms to first MR scan was 18 days, while median time from MR scan to surgery was 5 days in the active treatment group versus 11.5 days in the BSC subgroup ($p = .036$). Common presenting symptoms included cognitive impairment (42.1%) and focal neurological deficits (40.2%). Diagnostic delay, that is, time from onset of symptoms to surgery, was shortest in patients with epileptic seizures (median 13 days, range 3–127 days) and longest in those with visual disturbances (median 65.5 days, range 8–272 days). Median time from surgery to start of adjuvant treatment was 14 days (range 1–141 days).

When analyzing patient care at the national level, 23 centers (13.8% of all Austrian hospitals) were involved including 10 hospitals that provided integrated care, i.e., surgery plus adjuvant therapy, while 11 centers performed surgery only (Figure 1(B)). Thus, 26.2% of the patients were

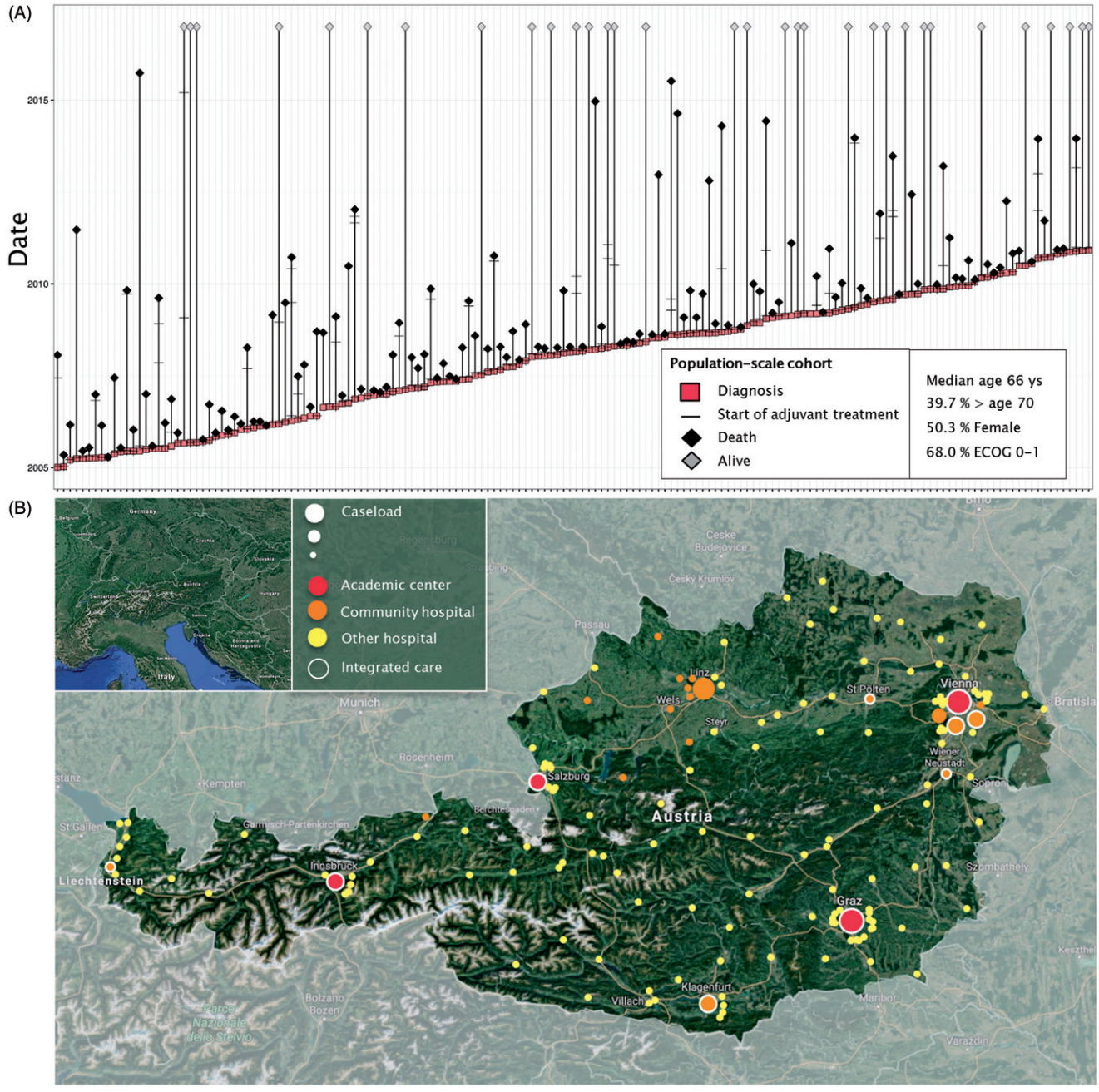

Figure 1. Population-scale cohort and nationwide patient care. (A) Introduction to the cohort throughout the observation period including different lines of treatment and vital status. (B) Decentralized patient care with a total of 23 hospitals involved in PCNSL care (depicted in red and orange) with only few centers that offer surgery and adjuvant therapy (integrated care, white edge).

postoperatively referred to other hospitals. Secondary referral did not significantly defer start of adjuvant treatment (median 15 vs. 10 days, $p = .217$). Baseline patient performance and age did not differ between academic and community hospitals ($p = .717$, $p = .347$) or between high- and low caseload centers ($p = .947$, $p = .532$). More extensive tumor resections were reported from all but one institution and their prevalence remained stable over time.

Patterns of first-line treatment vary considerably

Next, we focused on first-line treatment (detailed in Table 1 and Figure 2(A)) and found increasing use of rituximab after 2007 (from 8.5% to 24.4%, $p = .008$) while RT-only use did not decrease. Mean radiotherapy doses decreased from 44.0 to 40.0 Gy over time though this change was not significant ($p = .106$). The patients' baseline performance did impact adjuvant treatment choice *per se* ($p = .040$) with more prevalent use of CT-only among patients with good clinical performance and RT-only among patients with poor clinical performance.

Chemotherapy-wise, fourteen different substances and one targeted agent, that is, rituximab were in use. The most commonly used substance was HDMTX ($N = 98$, 77.8%), followed by cytarabine ($N = 43$, 34.1%), and rituximab ($N = 27$, 21.4%). The most common drug combination consisted of HDMTX and cytarabine ($N = 34$, 27.0%). Of note, eight

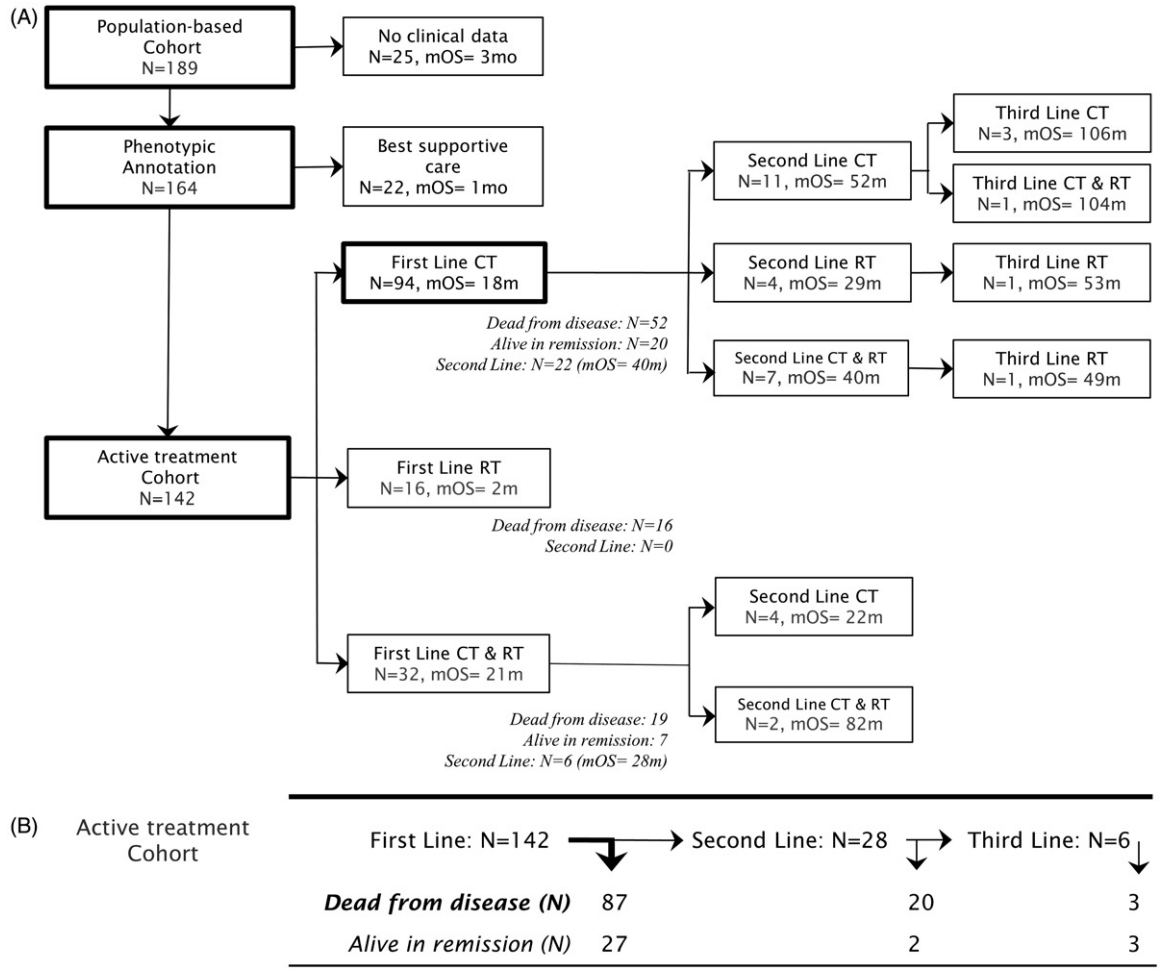

Figure 2. Patterns of care in patients with PCNSL. (A) Decision tree following the cohort through various lines of treatment with CT-only being the most prevalent first-line treatment. (B) Summarizes the total number of patients per line of treatment and vital status.

patients received HDMTX plus cytarabine plus rituximab (as proposed in the newer MATRix regimen [23]). The prevalence of poly-CT use increased significantly over time (from 27.3% to 52.2%, $p = .005$) including two- to four-drug combinations. Overall, 34 patients received intrathecal MTX therapy and 5 patients ASCT as part of their consolidation treatment. Likewise, radiotherapy doses ranged from 2.0 to 54.0 Gy (median 40.0 Gy) being lower in elderly patients (median 30.0 Gy, $p = .023$). Eight patients received local radiotherapy boosts with median doses of 10.0 Gy (range 6.0–20.0 Gy). There was a nonsignificant tendency towards lower radiotherapy doses when used as single treatment as compared with consolidation RT (mean 30 vs. 40 Gy, $p = .052$).

Few patients receive active salvage treatment

Out of 142 patients who started first-line treatment, the majority of patients (61.3%) died from refractory or relapsing disease, while similarly smaller fractions (19.0% and 19.7%) showed either a complete response or received active salvage treatment (Figure 2). Time from first to second line ranged from 6 to 57 months (median 21 months) and patients who qualified for a second line of treatment were considerably younger (58 vs. 66 years, $p < .001$). Again, HDMTX, cytarabine and rituximab were the most commonly used substances. Of note, 14/28 patients received a poly-CT regimen followed by ASCT consolidation in two patients. Radiotherapy doses ranged from 26.0 to 54.0 Gy (median 40.0 Gy) with a local boost of 14.0 Gy in a single patient. Two patients received re-irradiation. After second line treatment only six patients continued on a third line of treatment upon re-relapse (Figure 2(B)). None of them was older than 70 years. Time from second to third line ranged from 3 to 73 months (median 11 months). Four out of six patients received poly-CT – frequently including rituximab.

Treatment-related toxicities occur in roughly a third of all patients

Fifty patients (35.2% overall) experienced treatment-related adverse events (grades 1–5) with 31% being severe adverse events that were most common among patients with CT-only (38.3%) and combined CT-RT (34.4%), followed by RT-only use (12.5%). Common toxicities comprised infectious/inflammatory (30.0%), hematologic (22.0%), and neurologic conditions (18.0%), as well as combinations thereof (22.0%). Severe MTX-associated nephrotoxicity was noted in four patients. Among patients receiving any type of chemotherapy, toxicities were positively correlated with age ($p = .011$) but were not significantly more prevalent among patients

with poly-CT use ($N = 26$ vs. 21, $p = 0.549$). A similar rate and profile of treatment-related adverse events was noted during second-line treatment ($N = 10$, 35.7%) with severe adverse events in three patients. No secondary CNS infections following systemic or intrathecal therapies were reported and late neurotoxicity with white matter changes occurred in two patients. Overall, grade 5 toxicity (toxic death) occurred in three cases and included septic complications. Details on drug-related toxicities are provided in Supporting Information Table II.

Overall survival differs according to clinical characteristics and diagnostic period

Median OS in the entire patient cohort was 10 months with an estimated 5-year survival of 24.4% (95% CI 18.5–31.0; Figure 3). Median OS was significantly higher among younger patients (25 vs. 4 months, $p < .001$), as well as those with good clinical performance (22 vs. 4 months, $p < .001$) and immune-competent status (12 vs. 2 months, $p = .002$). Choice of surgical modality (biopsy vs. resection) was not associated with differential survival ($p = .233$). Interestingly, neither diagnostic delay nor delayed start of adjuvant treatment of more than 30 days did significantly alter median OS

Table 2. Multivariable survival model.

Variable	Hazard ratio	95 % CI	*p*
Age at diagnosis[a]	1.048	1.028–1.069	<.001
ECOG score[b]	1.343	1.126–1.602	.001
HDMTX-based CT versus no HDMTX-containing therapy	0.608	0.403–0.915	.017
Immunodeficiency	2.447	1.134–5.279	.023

[a]Per 1-year increase, [b]Per 1-point increase (ECOG 1-4).

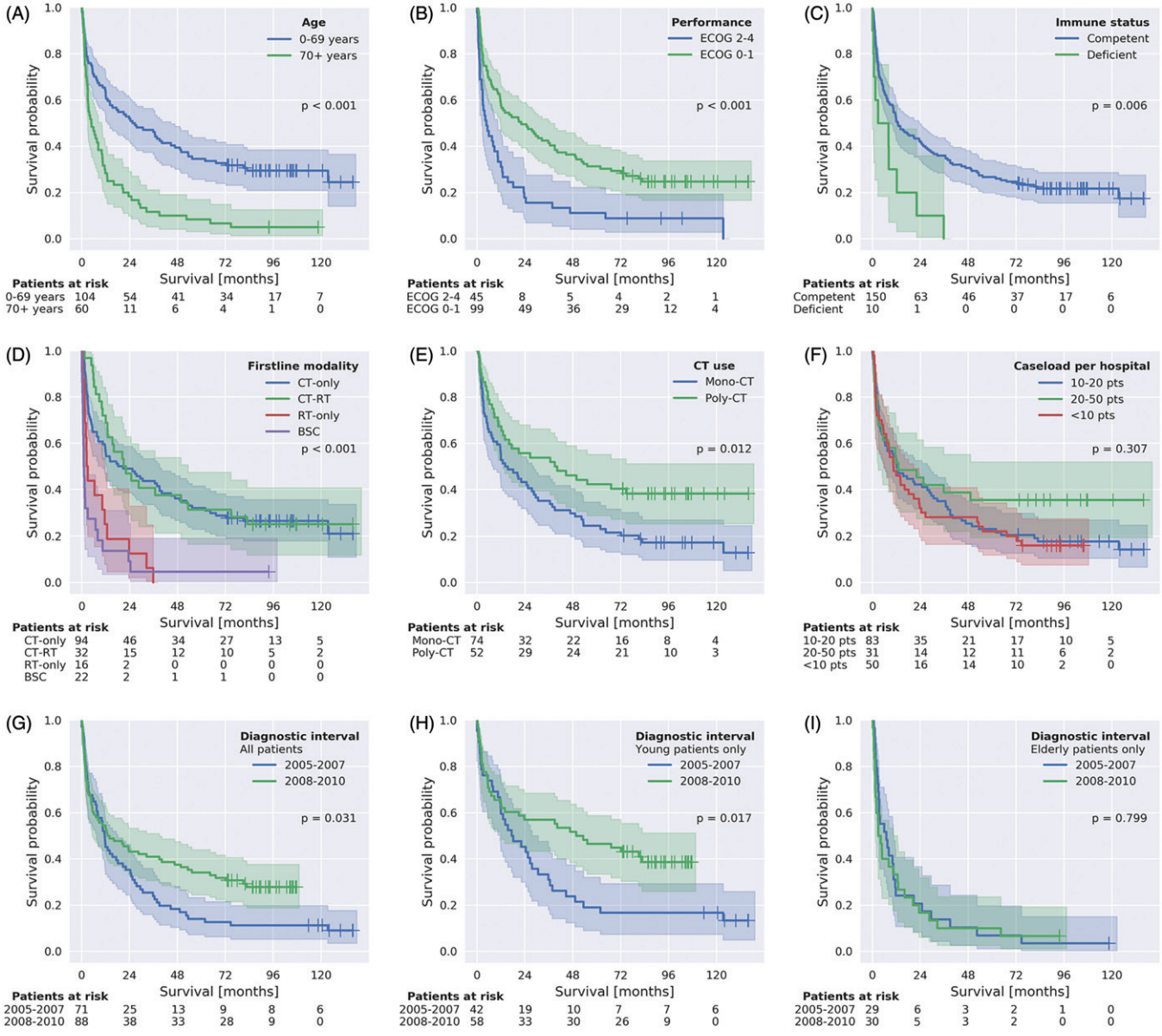

Figure 3. Population-based survival from PCNSL. (A–I) Survival estimates according to Kaplan-Meier for selected clinical parameters (A–C), treatment modalities (D, E), according to hospital caseload (F), as well as for diagnostic intervals (G–I).

($p = .331$, $p = .387$) and the same was true for referral to a secondary hospital for adjuvant treatment ($p = .411$). When stratified according to first-line treatment, median OS was superior in patients receiving CT-containing treatment (20 months) whereas RT-only and BSC yielded similarly poor outcomes (2 months and 1 month, $p < .001$). The use of poly-CT was associated with enhanced survival (39 months, $p = .012$). Likewise, active second-line treatment after relapse was associated with beneficial survival ($p = .045$). There was neither a significant survival difference between academic and community centers ($p = .645$) nor between high- and low-caseload centers ($p = .307$, Figure 3(F)). Instead, we found significantly improved survival in the more recent period from 2008 onwards ($p = .031$). However, this increase in survival was restricted to younger patients ($p = .017$), whereas no improvement was observed among elderly patients ($p = .799$, Figure 3(G–I)).

After adjustment for confounding factors, receipt of HDMTX-based CT, immune-competent status, younger age, and good performance were independently associated with improved OS (Table 2).

Treatment patterns differ considerably in vulnerable patient groups

When focusing on vulnerable patient cohorts we identified a total of 10 patients with immune-deficiency (one patient due to HIV, nine patients due to prior receipt of organ transplants, median age 54 years, range 33–79 years). Eight patients received active tumor-directed treatment (4x CT-only, 2x CT-RT, 2x RT-only). In the HIV-related patient HDMTX and rituximab were initiated but he died soon thereafter without receipt of cART (unknown HIV load and CD4+ cell count). All but one transplant-related patients were treated at high- and medium-caseload hospitals. Overall, the small number of immune-deficient patients limited further comparative analyses.

In contrast, patterns of care differed significantly between younger and elderly patients with a higher prevalence of RT-only use ($p = .001$) and less common use of combined CT-RT ($p = .036$) in the elderly. Both the prevalence of HDMTX-based regimens was lower ($p = .048$) and poly-CT was less likely administered ($p = .001$) with only exceptional patients receiving more than two drugs. While 80% of elderly patients with poor clinical performance received anti-tumor directed therapy, eight patients with reportedly good performance did not. Interestingly, in elderly patients median OS did not differ significantly according to first-line treatment modality ($p = .307$) with a minor tendency to improved outcome for combined CT-RT (median OS 16 months). Significantly fewer elderly patients qualified for salvage treatment upon relapse ($p = .018$) and no poly-CTs were reported.

Predictors of long-term survival

Next, we focused on long-term survivors. For a detailed comparative analysis of long- versus short-time survivors see Table 1. In brief, a total of 40 patients (24.4%) were found alive at 5 years after diagnosis. Those patients were significantly younger, had a better baseline performance, and competent immune status. In terms of treatment, they were more likely to receive CT-containing therapy with 75.0% receiving CT-only upfront. In particular the use of HDMTX ($p = .001$) and poly-CT ($p = .033$) was associated with long-term survival. Overall, long-term survivors were less likely to suffer from treatment-related toxicity ($p = .016$) but equally likely to experience early relapse, that is, within 12 months from diagnosis ($p = .601$). Three long-term survivors were encountered even upon re-relapse. In the entire cohort, relapses became rare after 3 years from diagnosis. We observed a significantly higher fraction of long-term survivors after 2007 ($p = .006$).

Conditional survival increases with increasing years postdiagnosis

Finally, we calculated 1- and 5-year conditional survival for patients who had already survived 1–4 years postdiagnosis (Table 3). The probability of surviving one additional year increased modestly over time showing the most pronounced step between years 1 and 2 (from 80.0% to 86.1%) leveling off soon thereafter. Increases were seen irrespective of patient age, gender, or clinical performance. In contrast, 5-year conditional survival rates showed a more pronounced and steady increase over time ranging from 47.8% (95% CI 37.4–58.1) at 1 year to 70.8% (95% CI 57.8–82.9) at 4 years postdiagnosis. After 3 years 5-year conditional survival estimates were well over 50% for the entire cohort.

Discussion

In this large observational study, we describe patterns of care and outcome in an unselected population of patients with PCNSL, a prototypic example for an ultra-rare and difficult-to-treat type of cancer. Due to the absolute rarity of the disease evidence-based treatment has been largely based on nonrandomized or smaller phase II trials, whereas only a single phase III trial has been conducted, so far [24]. However, as a large proportion of patients with PCNSL are above age 70, trial participants are not fully representative of the unselected patient population. The present study is one of the few to evaluate PCNSL therapy and outcome in a large unselected patient population. Our nationwide data provide insights into how the evolving treatment guidelines have translated into community practice and uncover previously unappreciated associations and disparities.

Most previous studies in unselected patient populations were based on cancer registry data with no or limited therapeutic information [1,10,14,25,26]. They reported almost identical cornerstones with consistently poor median overall survival of roughly 11 months. Only a single population-based study reported longer survival of 18 months in patients diagnosed after 2000 [2]. Even fewer patterns of care studies have documented real-life patient management over the last decades at the population level [9,11,27,28]. Together they suggested a gradual increase in HDMTX-

Table 3. Conditional survival estimates.

		Percent surviving 1 additional year				Percent surviving 5 additional years			
Variable	Years after diagnosis	1 (95% CI)	2 (95% CI)	3 (95% CI)	4 (95% CI)	1 (95% CI)	2 (95% CI)	3 (95% CI)	4 (95% CI)
Overall		80.0 (71.4–88.0)	86.1 (77.6–93.6)	85.5 (75.9–93.7)	86.8 (77.0–94.9)	47.8 (37.4–58.1)	52.1 (40.4–63.8)	60.5 (47.7–73.1)	70.8 (57.8–82.9)
Gender	Female	78.7 (66.0–90.0)	81.1 (67.5–93.1)	90.0 (77.8–100.0)	85.2 (70.4–96.6)	48.9 (34.9–63.4)	51.1 (34.8–67.6)	63.0 (45.0–80.0)	70.0 (51.9–86.9)
	Male	81.4 (69.0–92.5)	91.4 (81.1–100.0)	81.3 (66.7–93.8)	88.5 (75.0–100.0)	46.5 (31.7–61.9)	54.2 (37.5–70.6)	59.4 (42.3–76.5)	73.1 (55.0–89.7)
Age	18–69 years	82.9 (73.4–91.0)	89.7 (81.1–96.6)	84.6 (74.2–93.8)	88.6 (78.6–97.5)	52.9 (41.2–64.6)	56.3 (43.1–69.5)	62.7 (48.6–76.1)	74.1 (59.9–86.8)
	70 + years	70.0 (47.8–89.5)	71.4 (45.5–93.3)	[a]	[a]	30.0 (10.5–50.0)	35.7 (11.1–62.5)	[a]	[a]
Performance	ECOG 0-1	85.0 (75.8–93.4)	84.3 (73.9–93.6)	88.4 (78.0–97.4)	84.2 (71.8–94.9)	50.0 (37.1–62.5)	48.0 (33.9–62.0)	56.9 (41.6–72.0)	64.4 (48.2–79.9)
	ECOG 2-5	56.3 (30.0–81.3)	[a]	[a]	[a]	25.0 (5.9–47.6)	[a]	[a]	[a]
Immune status	Competent	81.5 (72.5–89.7)	86.4 (77.8–94.0)	84.2 (74.1–93.2)	85.4 (74.5–94.7)	46.9 (36.3–58.0)	49.3 (37.2–62.0)	57.1 (43.6–70.0)	67.8 (53.4–80.7)
	Deficient	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Surgery	Biopsy	82.1 (72.3–90.7)	85.5 (75.5–94.2)	83.0 (71.4–92.9)	84.6 (72.2–94.9)	49.3 (37.3–61.3)	54.3 (40.9–67.9)	63.5 (49.6–77.1)	76.5 (62.0–89.4)
	Resection	70.6 (46.7–92.3)	[a]	[a]	[a]	35.3 (13.3–58.9)	[a]	[a]	[a]
First-line	CT-only	86.8 (77.1–94.9)	89.1 (79.5–97.6)	82.9 (70.6–93.5)	88.2 (76.5–97.4)	50.9 (37.5–64.6)	53.8 (39.0–68.2)	60.4 (45.1–75.4)	72.8 (56.8–87.2)
	CT-RT	65.2 (45.0–84.0)	86.7 (66.7–100.0)	92.3 (75.0–100.0)	83.3 (60.0–100.0)	43.5 (23.5–64.0)	53.3 (27.3–80.0)	61.5 (33.3–87.5)	[a]
	RT-only	0	[a]	[a]	[a]	0	[a]	[a]	[a]
	BSC	0	[a]	[a]	[a]	0	[a]	[a]	[a]
	HDMTX	84.5 (74.5–93.2)	91.8 (83.3–98.1)	82.2 (70.2–92.7)	89.2 (78.1–97.6)	51.7 (38.9–64.4)	54.2 (40.0–68.6)	59.0 (44.0–73.7)	71.8 (56.4–86.1)
	Poly-CT	82.9 (69.4–94.3)	96.6 (88.6–100.0)	85.7 (71.4–96.7)	91.7 (78.9–100.0)	60.0 (43.3–76.2)	68.6 (51.5–85.2)	71.1 (53.3–87.2)	82.9 (66.2–96.0)
	Rituximab	76.5 (53.8–94.4)	[a]	[a]	[a]	64.7 (41.2–86.7)	[a]	[a]	[a]
Diagnostic period	2005-2007	78.9 (64.9–91.2)	73.3 (56.7–88.5)	77.3 (58.1–94.4)	76.5 (54.5–94.4)	31.6 (17.1–47.2)	33.3 (17.2–50.0)	45.5 (24.0–66.7)	58.8 (33.3–82.4)
	2008–2010	80.0 (68.6–90.5)	95.0 (87.2–100.0)	92.1 (82.5–100.0)	91.4 (81.1–100.0)	60.0 (46.0–73.5)	66.0 (50.0–80.6)	69.5 (53.9–84.4)	[a]

[a]Rate suppressed due to less than 15 cases at start or end of survival period.

containing CT as treatment of choice, which is confirmed by our data. In fact, we found fair dissemination of treatment recommendations [8] to community practice including increasing use of poly CT and rituximab. At the same time, we document a non-negligible fraction of patients in whom undertreatment seems a concern. In line with previous reports [12] this was especially true for a fraction of elderly patients who were less likely to receive chemotherapy despite adequate clinical performance. Whether this reflects responsible patients' refusal, obsolete treatment practices, or errors in clinical documentation remains unclear. However, those patients who tolerated intense treatment achieved similar outcomes as compared with a recent multicenter study [29]. Alerting though, only very few patients above age 70 years qualified for active second-line treatment and not a single patient received a third line. Of note, we did not observe a significant difference in survival between RT only and BSC in contrast to single other series [11], which might, however, be due to the low sample size of the subgroups.

The systematic documentation of real-life patterns across second and third lines of treatment constitutes a major strength of our approach. So far, the probably largest and most detailed analysis of salvage therapy has come from the French LOC network [30]. Therein, the authors found poor overall survival for refractory/relapsed patients with many patients not receiving active salvage therapy upon relapse, and the relatively longest survival for those treated with induction CT and ASCT [30]. While we similarly found receipt of active salvage therapy the major bottleneck, our cohort differs from the French one in several aspects. First, we found a significantly higher proportion of refractory/relapsed patients (81.0 vs. 45.5%), which is, however, in line with previous studies with similarly extended follow-up times [31,32]. Second, in the Austrian cohort consolidation consisted mostly of whole-brain RT while the use of ASCT was much less prevalent, which is most likely due to a previous diagnostic period, that is, before 2010. Thus, it will be of special interest to prospectively follow the changing use of ASCT in light of newer trial results that advocate its safety and efficiency [3,33,34]. The same will be true for newer treatment approaches including PD-1 blockade [35]. Of interest, temozolomide, which is the drug of choice for many primary brain tumors such as glioma and which is being increasingly recognized also for the treatment of PCNSL [36], was rarely used in our patient population.

Despite treatment-associated toxicities being retrospectively assessed with inherent potential bias, we noted toxicities in roughly a third of all patients, which is comparable to clinical trial data (26–58%) [4,6,23,34,37–39] with similar side effect profiles in the unselected population. In line with those data, predictors of toxicity included HDMTX and older age. Of note, late neurotoxicity was reported in only few patients but longitudinal MR imaging data were not available to objectively assess white matter changes. In addition to common treatment-related toxicities we identified a relatively large proportion of patients who did not qualify for tumor-directed therapy upfront and this fraction seemed considerably higher as compared with an unselected cohort of

patients with glioblastoma (13.4 vs. 7.0%) in the same underlying population [40]. Regarding immune-deficient patients our data contrast a recent report from the US [26] by indicating that transplant-related cases have already outnumbered HIV-related ones and meanwhile constitute the leading cause of immune deficiency-related PCNSL burden.

Another major strength of our approach is the extended patient follow-up ranging until 13 years postdiagnosis that allowed us to focus on long-term survivors. In line with recent studies, our multivariable model found age, performance, immune status, and HDMTX as independent predictors of survival [41]. Importantly, we further confirm a several months' increase in survival over time as observed by recent studies [9,10,26], which however seems restricted to younger patients [2,42]. In light of the encouraging proportion of patients in whom a durable remission is achieved, we calculated conditional survival estimates. In contrast to overall survival statistics, these provide more practical and useful information for cancer survivors, particularly in cancers with low 1-year overall survival such as PCNSL. Thereby we found that the longer patients survive, the higher the chances of surviving further years with variations according to age, clinical performance, treatment, immune status, extent of surgery, and diagnostic period.

Ultimately, we found PCNSL patient care being highly decentralized across scattered academic and community centers of variable caseload. Interestingly and in contrast to recent US data [9], when tackling eventual disparities we did not observe a significant difference in patient outcome across academic and community centers. However, we did see a tendency towards enhanced survival in high caseload centers (albeit not reaching statistical significance), which might reflect differences in expertise when treating this rare malignancy. Thus, further centralization of care in high caseload centers with adequate resources may be warranted.

The present study has limitations. First, clinical data were retrospectively abstracted from medical records. In order to address the inherent problem of missing values, we designed a specific case report form aiming at more standardized data reporting. Still, our experience with cross-sectional, population-scale data suggests that documentation in real-life patients is less detailed and standardized as compared with those in clinical trials (missing values in 13.2% of cases). Among parameters of limited availability were date and method of response assessment such that we were not able to differentiate between complete and partial responses. Moreover, pertinent data on MR imaging, progression-free survival, patients' quality of life, major comorbidities and other medications, as well as neuropsychological function in particular of long-term survivors were not available for this study. However, such data are urgently needed and future approaches will benefit from including them in their outcome measures. Similarly, despite being one of the larger PCNSL cohorts to date, subgroup-specific analyses were limited by sample size constraints.

In conclusion, we present a large population-based cohort of PCNSL patients with detailed phenotypic annotation and extended follow-up. We find that the use of HDMTX-based poly-CT and rituximab has disseminated to community practice to a fair extent but undertreatment remains a concern especially in a fraction of elderly patients, and frequent treatment-related toxicities further complicate the picture. Nevertheless, survival from PCNSL has improved at the population-level over time – a finding that is restricted to patients below 70 years of age. Conditional survival estimates increase with every year postdiagnosis and provide clinicians and PCNSL survivors with a more adequate and encouraging prognostic measure during their follow-up.

Acknowledgments

We thank Dr. Johanna Klughammer, Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna for help with graphical representations using R© software and Dr. Harald Heinzl, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna for statistical advice. Part of the samples and/or data used for this research project were kindly provided by Biobank Graz.

Author contributions

AW designed the study. MN, SO, MK, FP, JJU, JH, GS, SI, PM, CT, MS, FW, TBK, SW, DB, JP, MH, KJK, AB, BM, AHS, HK, MD, ARC, SH, WK, MH, KD collected the data. MN, TR, and AW performed the statistical analyses. AW, MN, TR, JAH, and MP wrote the manuscript with contributions from all authors.

Disclosure statement

MP has received research support from Roche and honoraria for lectures, consultation or advisory board participation from Roche and AbbVie. The other authors declare no conflict of interest.

Funding

This study was supported by the Anniversary Fund of the Oesterreichische Nationalbank under grant agreement 16725 to AW. Additional funding for ABTR was provided by unrestricted research grants of Roche, the Austrian Society of Neurology, and AbbVie.

ORCID

Thomas Roetzer http://orcid.org/0000-0001-8875-7304

References

[1] Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer. 2011;105:1414–1418.

[2] Mendez JS, Ostrom QT, Gittleman H, et al. The elderly left behind—changes in survival trends of primary central nervous system lymphoma over the past four decades. Neuro Oncol. 2018;20:687–694.

[3] Kasenda B, Ihorst G, Schroers R, et al. High-dose chemotherapy with autologous haematopoietic stem cell support for relapsed or refractory primary CNS lymphoma: a prospective multicentre trial by the German Cooperative PCNSL study group. Leukemia. 2017;31:2623–2629.

[4] Omuro A, Correa DD, DeAngelis LM, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood. 2015;125:1403–1410.

[5] Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol. 2013;31:3061–3068.
[6] Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol. 2013;31:3971.
[7] Grommes C, DeAngelis LM. Primary CNS Lymphoma. J Clin Oncol. 2017;35:2410–2418.
[8] Hoang-Xuan K, Bessell E, Bromberg J, et al. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. Lancet Oncol. 2015;16:e322–e332.
[9] Fallah J, Qunaj L, Olszewski AJ. Therapy and outcomes of primary central nervous system lymphoma in the United States: analysis of the National Cancer Database. Blood Adv. 2016;1:112–121.
[10] Norden AD, Drappatz J, Wen PY, et al. Survival among patients with primary central nervous system lymphoma, 1973-2004. J Neurooncol. 2011;101:487–493.
[11] Haldorsen IS, Krossnes BK, Aarseth JH, et al. Increasing incidence and continued dismal outcome of primary central nervous system lymphoma in Norway 1989-2003: time trends in a 15-year national survey. Cancer. 2007;110:1803–1814.
[12] Panageas KS, Elkin EB, Ben-Porat L, et al. Patterns of treatment in older adults with primary central nervous system lymphoma. Cancer. 2007;110:1338–1344.
[13] Hao D, DiFrancesco LM, Brasher PM, et al. Is primary CNS lymphoma really becoming more common? A population-based study of incidence, clinicopathological features and outcomes in Alberta from 1975 to 1996. Ann Oncol. 1999;10:65–70.
[14] Krogh-Jensen M, D'Amore F, Jensen MK, et al. Clinicopathological features, survival and prognostic factors of primary central nervous system lymphomas: trends in incidence of primary central nervous system lymphomas and primary malignant brain tumors in a well-defined geographical area. Population-based data from the Danish Lymphoma Registry, LYFO, and the Danish Cancer Registry. Leuk Lymphoma. 1995;19:223–233.
[15] Zabor EC, Gonen M, Chapman PB, et al. Dynamic prognostication using conditional survival estimates. Cancer. 2013;119:3589–3592.
[16] Farah P, Blanda R, Kromer C, et al. Conditional survival after diagnosis with malignant brain and central nervous system tumor in the United States, 1995-2012. J Neurooncol. 2016;128:419–429.
[17] Porter KR, McCarthy BJ, Berbaum ML, et al. Conditional survival of all primary brain tumor patients by age, behavior, and histology. Neuroepidemiology. 2011;36:230–239.
[18] Meira-Machado L, Sestelo M. condSURV: An R package for the estimation of the conditional survival function for ordered multivariate failure time data. R J. 2016;8(2):460–473.
[19] R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; Available from https://www.R-project.org/. 2017.
[20] Wickham H. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag, New York; 2016.
[21] Hunter JD. Matplotlib: a 2D graphics environment. Comput Sci Eng. 2007;9:90–95.
[22] Davidson-Pilon C. Lifelines Github repository. Available from: https://github com/CamDavidsonPilon/lifelines. 2016.
[23] Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3:e217–e227.
[24] Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol. 2010;11:1036–1047.
[25] Panageas KS, Elkin EB, DeAngelis LM, et al. Trends in survival from primary central nervous system lymphoma, 1975-1999: a population-based analysis. Cancer. 2005;104:2466–2472.
[26] Shiels MS, Pfeiffer RM, Besson C, et al. Trends in primary central nervous system lymphoma incidence and survival in the U.S. Br J Haematol. 2016;174:417–424.
[27] Enblad G, Martinsson G, Baecklund E, et al. Population-based experience on primary central nervous system lymphoma 2000-2012: the incidence is increasing. Acta Oncol (Stockholm, Sweden). 2017;56:599–607.
[28] van der Sanden GA, Schouten LJ, van Dijck JA, et al. Primary central nervous system lymphomas: incidence and survival in the Southern and Eastern Netherlands. Cancer. 2002;94:1548–1556.
[29] Schorb E, Fox CP, Fritsch K, et al. High-dose thiotepa-based chemotherapy with autologous stem cell support in elderly patients with primary central nervous system lymphoma: a European retrospective study. Bone Marrow Transplant. 2017;52:1113–1119.
[30] Langner-Lemercier S, Houillier C, Soussain C, et al. Primary CNS lymphoma at first relapse/progression: characteristics, management, and outcome of 256 patients from the French LOC network. Neuro Oncol. 2016;18:1297–1303.
[31] Reni M, Ferreri AJ. Therapeutic management of refractory or relapsed primary central nervous system lymphomas. Ann Hematol. 2001;80:B113–B117.
[32] Jahnke K, Thiel E, Martus P, et al. Relapse of primary central nervous system lymphoma: clinical features, outcome and prognostic factors. J Neurooncol. 2006;80:159.
[33] Ferreri AJM, Cwynarski K, Pulczynski E, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. Lancet Haematol. 2017;4:e510–e523.
[34] Illerhaus G, Kasenda B, Ihorst G, et al. High-dose chemotherapy with autologous haemopoietic stem cell transplantation for newly diagnosed primary CNS lymphoma: a prospective, single-arm, phase 2 trial. Lancet Haematol. 2016;3:e388–e397.
[35] Nayak L, Iwamoto FM, LaCasce A, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. Blood. 2017;129:3071–3073.
[36] Glass J, Won M, Schultz CJ, et al. Phase I and II study of induction chemotherapy with methotrexate, rituximab, and temozolomide, followed by whole-brain radiotherapy and postirradiation temozolomide for primary CNS lymphoma: NRG oncology RTOG 0227. J Clin Oncol. 2016;34:1620–1625.
[37] O'Brien PC, Roos DE, Pratt G, et al. Combined-modality therapy for primary central nervous system lymphoma: long-term data from a Phase II multicenter study (Trans-Tasman Radiation Oncology Group). Int J Radiat Oncol Biol Phys. 2006;64:408.
[38] Herrlinger U, Schabet M, Brugger W, et al. Primary central nervous system lymphoma 1991-1997: outcome and late adverse effects after combined modality treatment. Cancer. 2001;91:130.
[39] Blay JY, Conroy T, Chevreau C, et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol. 1998;16:864–871.
[40] Oberndorfer S, Marosi C, Payer F, et al. ABTR-SANO real-world pattern of care study on glioblastoma in the Austrian population. Neuro-Oncol. 2016;18:iv21.
[41] Roth P, Martus P, Thiel E, et al. Long-term survival in patients with primary CNS lymphoma: Results from the G-PCNSL-SG1 trial. J Clin Oncol. 2015;33:2032–2032.
[42] van der Meulen M, Dinmohamed AG, Visser O, et al. Improved survival in primary central nervous system lymphoma up to age 70 only: a population-based study on incidence, primary treatment and survival in the Netherlands, 1989-2015. Leukemia. 2017;31:1822–1825.