

Clinical manifestations of, diagnostic approach to, and treatment of neurolymphomatosis in the rituximab era

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Key Points

- Overall outcomes of neurolymphomatosis have improved in the rituximab era.
- Treatment of neurolymphomatosis remains individualized as presentation and outcomes vary based on lymphoma type and presentation setting.

Neurolymphomatosis (NL) is a rare manifestation of lymphoma, with limited evidence for optimal management. The largest patient series, 50 cases of lymphoma and leukemia, was published in 2010 with limited rituximab exposure. This study aims to evaluate the clinical presentation, diagnostic testing, and outcomes of NL in the rituximab era. Forty biopsy-proven cases of NL, in association with non-Hodgkin lymphoma (NHL), at the Mayo Clinic were retrospectively evaluated. B-cell NHL was associated with 97% of NL cases, of which diffuse large B-cell lymphoma (DLBCL) was the most common (68%). Primary NL, defined as neural involvement present at the time of diagnosis of lymphoma, was noted in 52% cases. Seventy percent of patients presented with sensorimotor weakness and neuropathic pain. Magnetic resonance imaging (MRI) was positive in 100% patients. Overall survival (OS) was significantly better for primary NL and NL associated with indolent lymphomas. Relapses were seen in 60% (24/40) of patients; 75% involved the peripheral or central nervous system at relapse. The use of rituximab in the frontline setting significantly impacted progression-free survival (PFS). Transplant consolidation was noted to be associated with improved OS. This study adds to the available literature on NL in the rituximab era. The overall outcomes have improved in recent years. In our experience, MRI and positron emission tomography/computed tomography may be required for accurate assessment of the extent of disease involvement and identification of an optimal biopsy site. The use of rituximab was associated with improvement in PFS, and autologous stem cell transplant was associated with OS.

Introduction

Neurolymphomatosis (NL) is an extremely rare clinical entity that is characterized by infiltration of the nerves by hematologic malignancies, such as non-Hodgkin lymphomas (NHLs) and acute lymphoblastic leukemia.^{1,2} NL refers to direct infiltration of endoneurium by neoplastic cells and must be distinguished from direct compression of nerves due to adjacent lymphadenopathy or extranodal lymphomatous masses, as well as paraneoplastic neuropathies.³ B-cell NHL constitutes the majority of cases, whereas T-cell lymphomas are rare.^{1,2,4,5} Clinically, NL can present as the initial and only manifestation of malignancy at the time of diagnosis or concomitant with nodal or other extranodal involvement (primary NL). It can also present as secondary NL that occurs as a site of progression or relapse of a previously

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diagnosed hematological malignancy.² These commonly manifest as painful neuropathy or polyradiculopathy, painless polyneuropathy, cranial neuropathy, and peripheral mononeuropathy.

The diagnosis of NL remains challenging, primarily as a result of the difficulty associated with obtaining a tissue biopsy from the affected site for histologic confirmation. However, in recent years, the increased use of magnetic resonance imaging (MRI) and ¹⁸F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) has resulted in better recognition of this disorder.^{2,6-12} Given the rarity of NL, limited data are available with regard to its clinical course, approach to diagnosis, treatment, and outcomes in the contemporary era. The most extensive case series of NL, reported by the International Primary Central Nervous System Lymphoma Collaborative Group, included 50 patients with NHL and leukemia; only 4 patients were exposed to rituximab.² Herein, we describe the clinical features, therapeutic interventions, and outcomes of a retrospective cohort of patients with NL in the rituximab era.

Methods

Clinical records of patients diagnosed with NL in association with NHL at the Mayo Clinic (Rochester, MN) between 1 January 2002 and 30 June 2018 were retrospectively reviewed. Eligibility criteria included primary or secondary NL cases histologically established by biopsy with ≥ 2 -year follow-up from the time of diagnosis of NL. Patients were identified using the electronic medical record from the Mayo Clinic Lymphoma Database at the Mayo Clinic. The study was conducted in accordance with the Declaration of Helsinki and was approved by Mayo Clinic Institutional Review Board.

Data collected included baseline characteristics, such as patient demographics, relevant disease, and clinical parameters. For diffuse large B-cell lymphoma (DLBCL), the cell of origin, assessed by Hans algorithm immunohistochemistry, was also obtained when available.¹³ Neurological function was evaluated according to the scale described by Talianky-Aronov et al (supplemental Table 1).¹⁴ Response to treatment was assessed by posttreatment radiologic studies and improvement in clinical symptoms. Complete response was defined as the complete disappearance of symptoms and radiologic abnormalities; patients achieving only partial resolution of either were classified as having a partial response. Repeat cerebral spinal fluid (CSF) studies were not required for response assessment. Progression-free survival (PFS) was defined as the interval between NL diagnosis and lymphoma relapse or death from any cause. Overall survival (OS) was defined as the time from NL diagnosis to death from any cause. The distributions of PFS and OS were estimated using Kaplan-Meier curves, and log-rank statistics were used to compare the outcomes between groups. A comparison between subgroups was investigated using Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables. Statistical analysis was performed using JMP software (JMP Pro, version 14.1.0; SAS Institute Inc.). *P* values were 2 sided, and the significance level was set at $<.05$.

Results

A total of 40 cases of biopsy-proven NL, in association with NHL, were identified between January of 2002 and June of 2018 at the Mayo Clinic. Baseline patient characteristics for the entire cohort are summarized in Table 1. B-cell NHL was associated with 97% (39/40) of NL cases. DLBCL was the most common type of NHL

(*n* = 27, 68%); 1 case of peripheral T-cell lymphoma not otherwise specified (PTCL, NOS) was identified. Among the DLBCL cases, cell-of-origin information based on the Hans algorithm was available in 10 cases, of which 5 were germinal-center B-cell phenotype. Primary NL was present in 21 (52%) cases, whereas secondary NL was present in 19 (48%) cases (Table 2). The median time from the initial diagnosis to secondary NL was 13.1 months (range, 1.4-164.6). Among those with secondary NL, in 97% of cases, the pathologic diagnosis remained unchanged with respect to the initial diagnosis, with the exception of 1 case with an initial diagnosis of DLBCL that was changed to low-grade B-cell lymphoma not otherwise specified (NOS). In more than half of the cases (*n* = 23, 57%), multiple neural sites were involved at presentation (Figure 1). Concomitant parenchymal brain involvement was seen in 10% (4/40) of cases. The most frequently affected neural structures were peripheral nerves (58%; 23/40). Most patients presented with sensorimotor weakness, whereas autonomic abnormalities were rarely seen. Neuropathic pain was encountered in $\sim 70\%$ (28/40) of patients. The neurologic function score, when graded based on the neurologic function scale described by Talianky-Aronov et al, ranged from 2-5 on the scale in the majority of cases (79%).¹⁴

Various diagnostic modalities included CSF cytology (29 patients), radiologic studies (MRI, *n* = 36 patients; PET/CT, *n* = 31 patients), and electromyography (*n* = 29 patients). At the time of NL diagnosis, CSF cytology was positive in 7 of 29 cases (24%), with positive flow cytometry in 4 of 9 (44%) cases. The MRI was positive in all 36 (100%) patients, and FDG PET/CT was positive in 23 of 31 (74%) patients. The MRI findings of NL were described as a diffuse or nodular neural thickening, with hyperintense T2-weighted signals, and postcontrast enhancement. Most patients (34/36) had findings of T2 hyperenhancement and postcontrast enhancement on the MRI, whereas the other 2 patients had only 1 of the findings. The peripheral nerve impairment was confirmed by electromyography in 28 of 29 (97%) patients. The peripheral nerves were the most common biopsy site, of which the sciatic nerve was the most frequent (Table 3).

Systemic therapy was administered to 37 of 40 (93%) patients. One patient with NL solely affecting the great auricular nerve was treated with surgery (parotidectomy). Seventy-two percent (29/40) of NL patients were treated with regimens containing high-dose methotrexate (HD-MTX; at least 2 methotrexate treatments dosed at ≥ 3.5 g/m²); 86% (25/29) were in the frontline setting. Various HD-MTX-containing regimens received by patients are summarized in Table 4. Sixty-seven percent (27/40) of patients were treated with rituximab, of whom 74% (20/27) were in the frontline setting. Among patients with a single site of neural infiltration, 3 of 17 received involved-site radiation therapy (RT) consolidation after the frontline therapy (trigeminal nerve, femoral nerve, and tibial nerve). One patient with marginal zone lymphoma underwent RT alone, with 25 Gy focused on the optic nerve sheath, and remained in remission at the last follow-up. High-dose chemotherapy followed by autologous stem cell transplant (HDC-ASCT) consolidation was performed in 43% (16/40) of patients. Of these, 56% (9/16) occurred in the frontline setting, and 1 patient with PTCL, NOS underwent an unrelated matched allogeneic transplant for an early diagnosis of therapy-related myelodysplasia.

The median neurologic function score after first-line treatment decreased from 2 to 1 based on the neurological function scale

Table 1. Baseline patient characteristics and clinical features of NL (entire cohort)

| Variable | Total, N = 40 |
|--|---------------|
| Demographics | |
| Age at diagnosis, median (IQR), y | 60.5 (37-83) |
| Male sex | 24/40 (60) |
| B-cell NHL | 39/40 (97) |
| WHO diagnosis | |
| DLBCL | 27/40 (68) |
| Others | 13/40 (32) |
| Follicular lymphoma, n | 2 |
| Mantle cell lymphoma, n | 1 |
| Marginal zone lymphoma, n | 2 |
| Lymphoplasmacytic lymphoma, n | 1 |
| Low-grade B-cell lymphoma NOS, n | 6 |
| Peripheral T-cell lymphoma NOS, n | 1 |
| Clinical characteristics | |
| Primary NL | 21/40 (52) |
| Bone marrow involvement | 11/37 (30) |
| B symptoms | 3/40 (7) |
| Elevated LDH | 14/40 (35) |
| Stage III/IV | 34/40 (85) |
| Parenchymal CNS involvement | 4/40 (10) |
| Patterns of involvement | |
| NL alone | 19/40 (48) |
| NL + CNS (cranial nerve, CSF, leptomeningeal, parenchymal brain) | 8/40 (20) |
| NL + systemic (nodal or extranodal other than NL) | 10/40 (25) |
| NL + CNS + systemic | 3/40 (7) |
| Affected nerve site | |
| Brachial plexus | 12/40 (30) |
| Lumbosacral plexus | 5/40 (12) |
| Cauda equina-nerve roots | 14/40 (35) |
| Other nerve roots | 3/40 (7) |
| Sciatic nerve | 12/40 (30) |
| Femoral nerve | 4/40 (10) |
| Other peripheral nerves* | 7/40 (17) |
| Cranial nerves† | 8/40 (20) |
| Multiple sites | 23/40 (57) |
| Neurological symptoms | |
| Motor weakness | 33/40 (82) |
| Sensory deficit | 32/40 (80) |
| Autonomic abnormalities | 3/40 (7) |
| Pain | 28/40 (70) |
| Neurologic Function scale (%) | |
| Grade 2-5 | 31/39 (79) |

Unless otherwise noted, data are n/N (%).

CNS, central nervous system; IQR, interquartile range; LDH, lactate dehydrogenase; WHO, World Health Organization.

*Peroneal nerve (2/40), great auricular nerve (1/40), finger digital nerve (1/40), sural nerve (1/40), tibial nerve (1/40), lateral antebrachial cutaneous nerve (1/40).

†Optic nerve (1/40), oculomotor nerve (1/40), trigeminal nerve (3/40), facial nerve (3/40), vestibulocochlear nerve (1/40).

Table 2. Baseline patient characteristics, clinical features, and management strategies of NL based on primary vs secondary NL

| | Primary NL, n = 20* | Secondary NL, n = 19 | P |
|---|---------------------|----------------------|-------------|
| Age at NL diagnosis, median (IQR), y | 57 (50.5-62) | 66 (59-76) | .014 |
| Aggressive lymphoma | 12 (60) | 16 (84) | .09 |
| Stage III/IV | 17 (85) | 16 (84) | .69 |
| IPI 3-5 | 7 (35) | 11 (58) | .15 |
| LDH > ULN | 5 (25) | 9 (47) | .10 |
| Systemic disease at time of NL diagnosis† | 8 (40) | 4 (21) | .17 |
| CNS involvement at NL diagnosis‡ | 8 (40) | 3 (16) | .09 |
| Single site of NL involvement | 7 (35) | 8 (42) | .64 |
| Treatment characteristics (frontline and relapsed setting) | | | |
| HD-MTX | 14 (70) | 15 (83) | .28 |
| Rituximab | 15 (75) | 12 (67) | .41 |
| ASCT consolidation | 10 (50) | 6 (32) | .24 |
| Number relapsed | 11 (55) | 12 (63) | .42 |
| Pattern of relapse | | | |
| Peripheral nerve/CNS | 8 (73) | 4 (33) | |
| Systemic alone | 0 | 2 (17) | |
| Systemic + peripheral nerve/CNS | 2 (18) | 4 (33) | |
| Missing data | 1 | 2 | |

Unless otherwise noted, data are n (%). Bold P value indicates significance.

ASCT, autologous stem cell transplant; IPI, International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper limit of normal.

*One case of PTCL, NOS was excluded from the analysis.

†Systemic involvement = nodal or extranodal involvement other than NL.

‡CNS involvement = cranial nerve, CSF, leptomeningeal enhancement, or parenchymal brain.

described above. The motor weakness was entirely and partially resolved in 6 of 33 patients (18%) and in 14 of 33 patients (42%), respectively. The sensory deficits disappeared in 10 of 32 (31%) patients and improved in 9 of 32 (28%) patients. Neuropathic pain resolved in 14 of 28 (50%) patients and partially decreased in 5 of 28 (18%) patients; the autonomic symptoms related to cauda equina involvement resolved in 2 of 3 (67%) cases. A complete resolution of all symptoms was achieved in 12 of 40 (30%) patients.

Response after frontline treatment by radiological testing was available in 31 (77%) patients. A complete resolution of the abnormalities previously detected on scans was seen in 12 (39%) cases. The overall response rate (ORR) based on the combination of clinical and radiologic improvement was 73% (27/37), with complete response achieved in 24% (9/37). With a median follow-up time of 127 months (interquartile range [IQR], 95-167) for those still alive, the median PFS and OS for the entire cohort were 14.2 months (95% confidence interval [CI], 10 months-not reached [NR]) and 72.6 months (95% CI, 30 months-NR), respectively (Figure 2). Although there were not any differences in the baseline characteristics, pattern of disease involvement, treatment strategies, or number of relapses, there was a significant difference in OS between those with primary vs secondary NL (138 months; 95% CI, 55 months-NR vs 25 months; 95% CI, 9.5-118; $P = .02$) (Figure 3; Table 2). B-cell NHL-associated NL ($n = 39$) was subdivided into indolent lymphomas (marginal zone, follicular lymphoma grade 1-2,

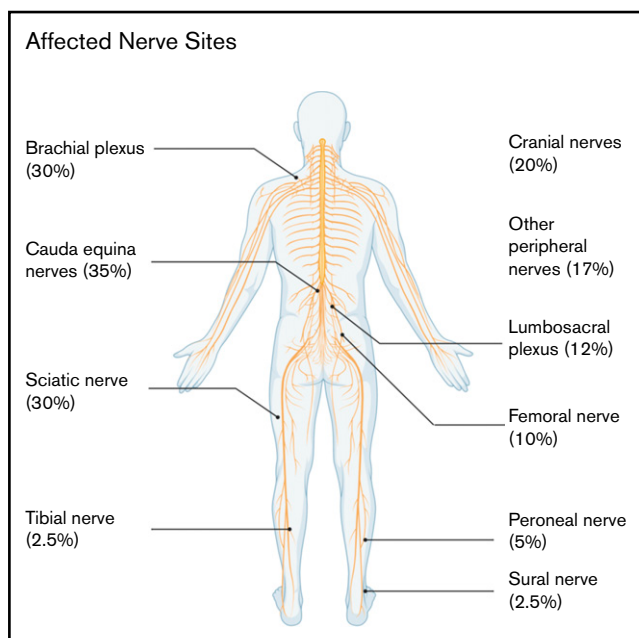


Figure 1. Nerve sites affected in the study cohort.

lymphoplasmacytic lymphoma, and low-grade B-cell lymphoma NOS) and aggressive lymphomas (DLBCL and leukemic mantle cell) (Table 5). Patients with aggressive lymphoma had a higher International Prognostic Index and received more HD-MTX-based treatment (89% vs 36%, $P < .0007$) and autologous stem cell transplant (ASCT) consolidation (frontline setting 58% vs 15%, $P = .01$; frontline and relapsed setting 50% vs 18%, $P = .07$). Despite these management differences, the median OS in NL associated with indolent lymphomas was NR (95% CI, 55.0 months-NR) vs 46.9 months (95% CI, 12.5-138.0) in aggressive type disease ($P = .023$) (Figure 3). The use of rituximab in the frontline setting significantly impacted PFS: NR with rituximab (95% CI, 11 months-NR) vs 11 months without rituximab (95% CI, 6.1-32.8) ($P = .05$) in the entire cohort. However, OS was not significantly different: NR with rituximab (95% CI, 21.7 months-NR) vs 64 months without rituximab (95% CI, 9.5-NR) ($P = .32$) (Figure 4). The use of HD-MTX in the frontline setting did not impact survival; OS and PFS were similar in the HD-MTX group (median PFS, 14.2 months; 95% CI, 9.2-NR) compared with groups who received other treatments (median PFS, 20.8 months; 95% CI, 6.2-NR) ($P = .68$) (Figure 5). Consolidation with HDC-ASCT in frontline or salvage setting was noted to be associated with an improved OS (median OS [with ASCT], 138 months; 95% CI, 55.7-NR vs 49.6 months; 95% CI, 10.2-NR [$P = .04$]) (Figure 6). A total of 24 of 40 patients had relapsed at median follow-up after frontline management. The pattern of relapse showed that 12 of 24 (50%) relapses were in the peripheral nerve/central nervous system (CNS) alone, 3 of 24 (12.5%) were in systemic (nodal or extranodal other than peripheral nerve/CNS) sites only, and 6 of 24 (25%) involved systemic and peripheral nerve/CNS sites. Data about the pattern of relapse were missing for 3 patients. Within primary NL patients, relapses more often involved peripheral nerve/CNS (73%) compared with secondary NL (33%) (Table 2). Patient characteristics and management strategies for those alive for >2 years after NL diagnosis are shown in supplemental Table 2.

Table 3. Site of biopsy for diagnosis of NL

| Biopsy site | n or n/N (%) |
|-----------------------------|--------------|
| Nerve roots | 11/40 (28) |
| Cervical | 2 |
| Thoracic | 1 |
| Lumbar | 3 |
| Sacral | 3 |
| Cauda equina | 2 |
| Peripheral nerves | 20/40 (50) |
| Sciatic nerve | 6 |
| Peroneal nerve | 3 |
| Femoral nerve | 2 |
| Median nerve | 2 |
| Other peripheral nerves* | 7 |
| Brachial plexus | 6/40 (15) |
| Cranial nerves [†] | 3/40 (7) |

*Lateral antebrachial cutaneous nerve (1/40), finger digital nerve (1/40), great auricular nerve (1/40), sural nerve (1/40), supraclavicular nerve (1/40), tibial nerve (1/40).

[†]Facial nerve (1/40), optic nerve (1/40), trigeminal nerve (1/40).

Discussion

To our knowledge, this is the largest single-center report describing the therapy and outcomes of biopsy-confirmed NL cases in the rituximab era. Two prior studies described clinical features and outcomes of NL.^{1,2} The rates of biopsy-confirmed diagnosis were

Table 4. Details of the various frontline systemic and non-systemic therapeutic interventions for the management of NL

| Treatment | n (%) |
|--|------------|
| HD-MTX-containing regimens, n/N (%) | 25/40 (62) |
| HD-MTX monotherapy | 15 |
| Methotrexate, temozolomide, rituximab | 6 |
| Methotrexate, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone | 3 |
| Rituximab, methotrexate, vincristine, procarbazine | 1 |
| Non-HD MTX-containing regimens, n/N (%) | 12/40 (30) |
| R-Bendamustine | 3 |
| R-CHOP | 3 |
| Rituximab, dexamethasone, cytarabine, cisplatin | 1 |
| Cyclophosphamide, vincristine, doxorubicin, dexamethasone | 1 |
| Cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, prednisone | 1 |
| Rituximab, ifosfamide, carboplatin, etoposide | 1 |
| Rituximab monotherapy | 1 |
| Melphalan-lenalidomide-dexamethasone | 1 |
| RT | 5 |
| IT chemotherapy | 5 |
| Consolidative ASCT | 16 |

ASCT, autologous stem cell transplant; IT, intrathecal; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

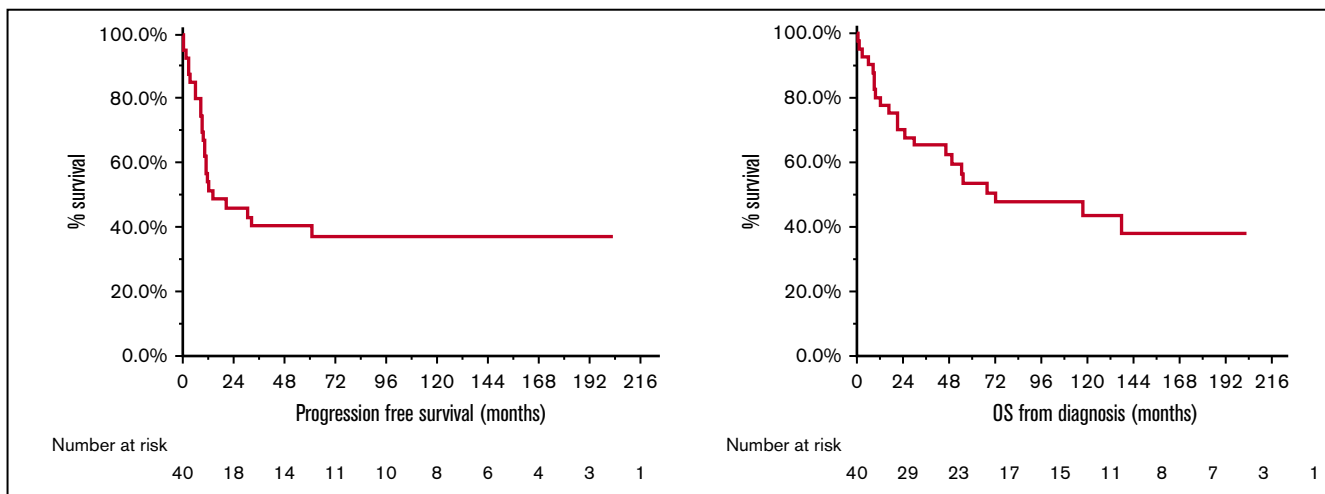


Figure 2. Kaplan-Meier curves. PFS with NL after frontline management: median PFS, 14.2 months; 95% CI, 10 months-NR (left panel). OS with NL: median OS, 72.6 months; 95% CI, 30-NR (right panel).

lower: 24 of 72 (33%) and 23 of 50 (46%), respectively.² Although the requirement for histologic diagnosis leads to a selection bias, several baseline characteristics of the present study were similar to the case series reported previously. Our study had a 60% male population, and the median age at diagnosis was 60.5 years; these data were similar to those described in the International Primary Central Nervous System Lymphoma Collaborative Group series (60% males; median age, 55.5 years). In our cohort, the rate of primary NL was higher (n = 21; 52%) compared with other studies (21-33%).^{2,7,15,16}

Because biopsy-proven NL was an inclusion criterion, our study provides accurate insights into the utility of radiologic modalities. The MRI and FDG-PET/CT positivity rate for detecting NL-related abnormalities was 100% and 74%, respectively. The high sensitivity of MRI to detect NL is in accordance with previous reports showing

positivity rates between 67% and 100%.^{2,6,8,10-12,17} The positivity rate of FDG-PET/CT in our study is slightly lower compared with earlier reports, ranging from 83% to 100%.¹⁸ In our study, of the 8 negative PET/CT cases, 2 were performed on patients with low-grade B-cell lymphoma NOS, and 1 was performed on a patient in whom the disease was resected before the scan for biopsy. Recently, DeVries et al. reported MRI and PET/CT findings of NL in 25 patients: the positivity rates were 95% and 88%, respectively. On the FDG PET/CT, NL appeared as linear or fusiform, and on MRI it appeared as a T2-weighted hyperintense enhancing mass in ~95% of cases.¹² Although the findings on MRI and FDG PET/CT are not independently diagnostic of NL, our study supports that they are highly suggestive in the context of a known diagnosis of NHL. In addition, in cases with low tumor burden or single-site disease, the FDG avidity on the PET/CT may not be as extensive as the signal on MRI as the result of decreased spatial resolution of PET.

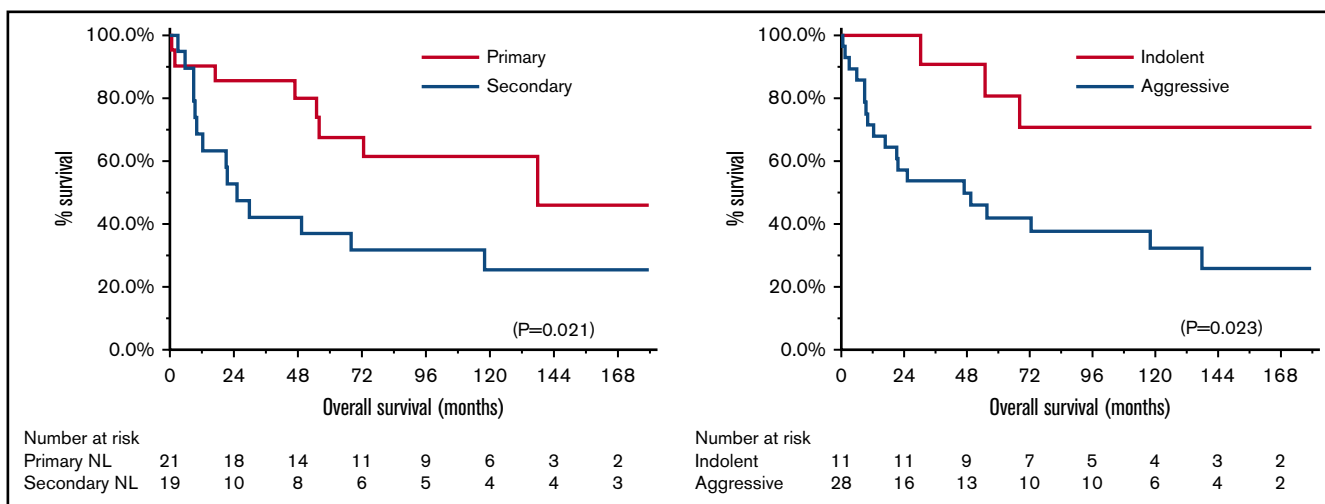


Figure 3. Kaplan-Meier curves. OS for primary NL vs secondary NL: median OS, 138.0 months; 95% CI, 55.0 months-NR vs median OS, 25.4 months; 95% CI, 9.5-118.2 (left panel). OS for NL associated with indolent vs aggressive lymphoma type: median OS, NR; 95% CI, 55.0 months-NR vs median OS, 46.9 months; 95% CI, 12.5-138.0 (right panel).

Table 5. Baseline patient characteristics, clinical features, and management strategies of NL based on indolent vs aggressive lymphoma type

| | Indolent, n = 11 | Aggressive, n = 28* | P |
|---|------------------|---------------------|--------------|
| Age at NL diagnosis, median (IQR), y | 59 (56-65) | 61.5 (51-69.5) | .70 |
| Primary NL | 3 (27) | 16 (57) | .09 |
| Stage III/IV | 9 (82) | 24 (86) | .55 |
| IPI 3-5 | 2 (18) | 16 (57) | .03 |
| LDH > ULN | 2 (18) | 12 (43) | .12 |
| Systemic disease at the time of NL diagnosis† | 6 (55) | 6 (21) | .05 |
| CNS involvement at NL diagnosis‡ | 3 (27) | 8 (29) | .67 |
| Single site of NL involvement | 3 (27) | 12 (43) | .30 |
| Treatment characteristics (frontline and relapsed setting) | | | |
| HD-MTX | 4 (36) | 25 (89) | .0007 |
| Rituximab | 8 (73) | 19 (70) | .69 |
| ASCT consolidation | 2 (18) | 14 (50) | .07 |
| Number relapsed | 5 (45) | 18 (64) | .23 |
| Pattern of relapse | | | |
| Peripheral nerve/CNS | 3 (60) | 9 (50) | |
| Systemic alone | 0 | 2 (11) | |
| Systemic + peripheral nerve/CNS | 2 (40) | 4 (22) | |
| Missing data | 0 | 3 | |

Unless otherwise noted, data are n (%). Bold P values indicate significance.

IPI, International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper limit of normal.

*One case of PTCL, NOS was excluded from the analysis.

†Systemic involvement = nodal or extranodal involvement other than NL

‡CNS involvement = cranial nerve, CSF, leptomeningeal enhancement, or parenchymal brain.

Thus, combining information obtained from MRI and PET/CT may help to identify a better site for fascicular biopsy.¹⁹

CSF cytology, performed at the time of NL diagnosis, detected malignant cells in only a small portion of cases analyzed (7/29). All but 1 CSF⁺ case in our study was associated with DLBCL. This was slightly lower than the previously reported number of 30% to 40%, which could be due to the biopsy requirement in this study.^{2,12,18} Patients with inconclusive imaging findings and negative CSF analysis are more likely to pursue a biopsy to confirm the diagnosis. Previous case series have reported the diagnostic yield of the biopsy to be ~85% to 90%.² Although these high numbers may be accurate in tumefactive cases, most patients have nonspecific radiologic findings, and the actual numbers may be lower. Despite a low positivity rate of CSF analysis for the detection of NL, we recommend that all patients diagnosed with or suspected of having NL have CSF analysis. This may reveal more extensive CNS involvement and impact management.

Optimal treatment of NL remains unknown. HD-MTX, with its ability to cross the blood-brain or blood-nerve barrier and its efficacy in primary CNS lymphoma, has been used more frequently in recent years for treating NL.²⁰ About two thirds of the patients in our series received treatment with HD-MTX as

monotherapy or in combination with other drugs. The benefit of HD-MTX in terms of survival or response remains unknown, because the data are inconsistent.^{2,17,21,22} Our entire patient cohort did not show a benefit with the use of HD-MTX; however, the number of patients is small and includes a heterogeneous cohort of indolent and aggressive lymphoma for which the use of HD-MTX differed. A recent study that also compared HD-MTX–based chemotherapy with other treatments in a cohort of 18 NL patients did not show any difference in outcomes between the 2 groups.¹⁶

The use of rituximab in NL has not been described extensively.^{4,10} In our series, 67% (27/40) of patients received rituximab, primarily in combination with other drugs. Rituximab use was associated with significant improvement in PFS compared with regimens not containing rituximab. The numbers are small to determine whether this effect occurs predominantly in patients with secondary NL or in those with systemic disease as part of the initial presentation. However, rituximab remains an essential component of the treatment of B-cell lymphomas, with or without CNS involvement, and it should be used for B-cell NHL–associated NL.^{23,24} Consolidative RT after frontline systemic therapy also is an area of debate. In our series, 4 patients underwent this strategy, of whom 3 had a single site of NL involvement. RT may have a limited role in patients with multiple sites of involvement that would require large radiation fields. Frontline consolidation with HDC-ASCT led to a significantly higher ORR in our cohort (100% vs 61%, $P = .03$). In addition, we noted an improvement in OS for patients who underwent HDC-ASCT (both initial and salvage setting). The treatment of NL varies, and some prefer to treat NL similarly to primary CNS lymphoma, with the use of HD-MTX and consolidation RT or HDC-ASCT.²⁵⁻²⁷ However, patients need to demonstrate chemosensitivity (better disease biology) and transplant eligibility from a comorbidities and general health standpoint to proceed with transplant, which may confer a selection bias leading to better survival in patients undergoing transplant. These approaches should be considered on an individual basis for the treatment of NL, especially for those associated with more aggressive types of NHL.

The long-term outcomes in our study, with a median OS of 72.6 months, are significantly better than the median OS of 10 months reported by Grisariu et al.² There are multiple reasons for this: antemortem diagnosis, selection bias due to the need for biopsy-proven disease, along with increased use of systemic treatment over RT or intrathecal therapy alone, and the use of rituximab and consolidative ASCT. Additionally, the use of newer therapies, such as ibrutinib, lenalidomide, and checkpoint inhibitors, as subsequent lines of treatment also could have impacted survival (supplemental Table 2). Our series is also more recent, and patients could have benefited from better supportive care. We compared outcomes of patients diagnosed before and after the year 2010 but did not find a significant difference (supplemental Figure 1). Our cohort also comprised higher proportion of patients with primary NL (52%) compared to the previous series. Primary NL has shown better survival than secondary NL, both in our cohort and the series described previously.² This could be explained, in part, by the chemorefractoriness of secondary NL, because the baseline disease characteristics, other than younger age at diagnosis in primary NL, as well as treatment strategies, such as HD-MTX, rituximab, and ASCT, were comparable between the 2 groups

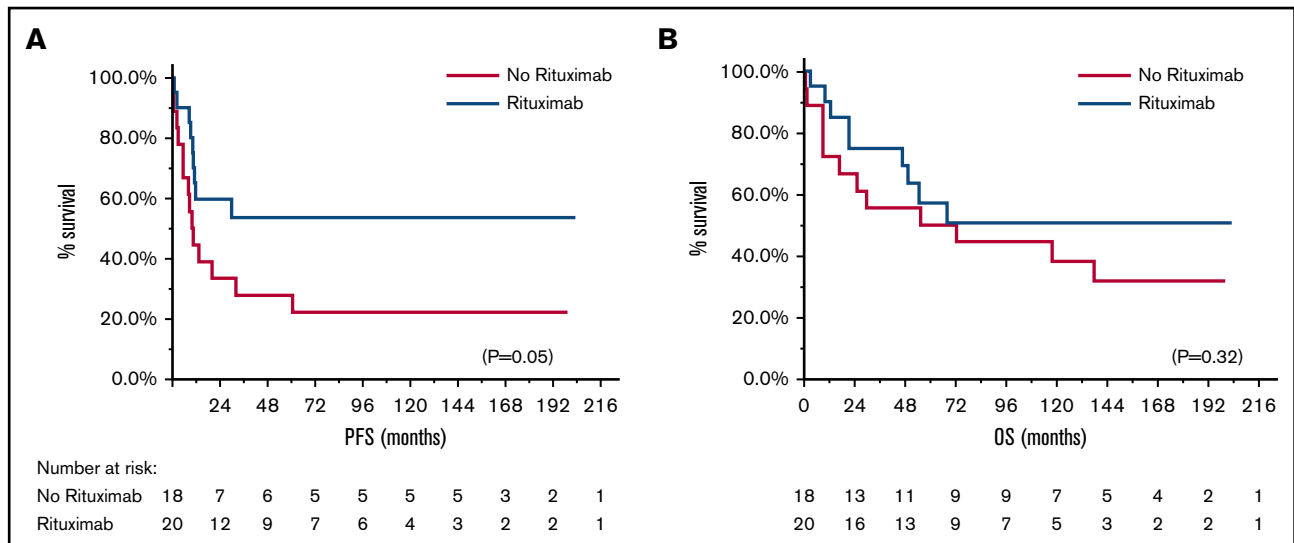


Figure 4. Kaplan-Meier curves. (A) PFS for cases receiving frontline rituximab-containing regimens vs treatments not containing rituximab: median PFS, NR; 95% CI, 11.0 months-NR vs median PFS, 11.0 months; 95% CI, 6.1-32.8 ($P = .05$). (B) OS for cases receiving frontline rituximab-containing regimens vs those not containing rituximab: median OS, NR; 95% CI, 21.7 months-NR vs median OS, 64 months; 95% CI, 9.5-NR ($P = .32$).

(Table 2). However, the data remain controversial with regard to the favorable outcomes associated with primary NL.^{7,8}

Our study is limited by the inherent bias associated with a retrospective study. The heterogeneous cohort is composed of different histologic NHL types and disease characteristics. In addition, the use of various therapeutic interventions, such as RT or HDC-ASCT, blurs the real impact of individual treatments, such as HD-MTX or ASCT. The numbers are small despite 16 years, owing to the rarity of the disease, which makes it difficult to derive conclusions related to treatments. However, our study represents the most extensive biopsy-proven series of this extremely rare disease that evaluated clinical features, diagnostic modalities, and treatment of NL in the

rituximab era. This study is also able to provide more reliable information about the accuracy of the imaging modalities. Additionally, we provide patterns of involvement of disease at the time of diagnosis and at relapse in primary/secondary NL and indolent/aggressive-associated NL.

Conclusions

A comprehensive diagnostic approach with a high index of suspicion is required for early diagnosis of NL. MRIs and FDG-PET/CT scans should be obtained to assess the extent of involvement and identify the best site for nerve biopsy when feasible. No standard-of-care treatment exists for NL, and it needs to be individualized. Rituximab-containing regimens and ASCT consolidation seem to

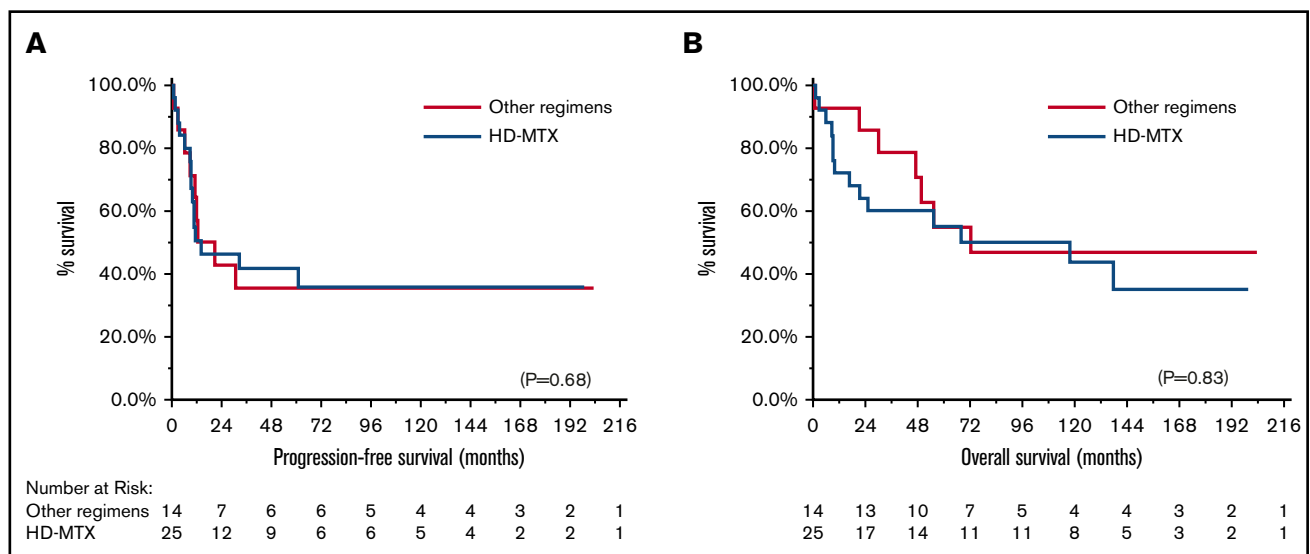


Figure 5. Kaplan-Meier curves. (A) PFS in patients receiving frontline HD-MTX-containing regimens vs patients receiving other systemic treatments: median PFS, 14.2 months; 95% CI, 9.2-NR vs median PFS, 20.8 months; 95% CI, 6.2-NR ($P = .68$). (B) OS in patients receiving frontline HD-MTX-containing regimens vs patients receiving other systemic treatments: median OS, 93.2 months; 95% CI, 17.0-NR vs median OS, 63.8 months; 95% CI, 21.3-NR ($P = .83$).

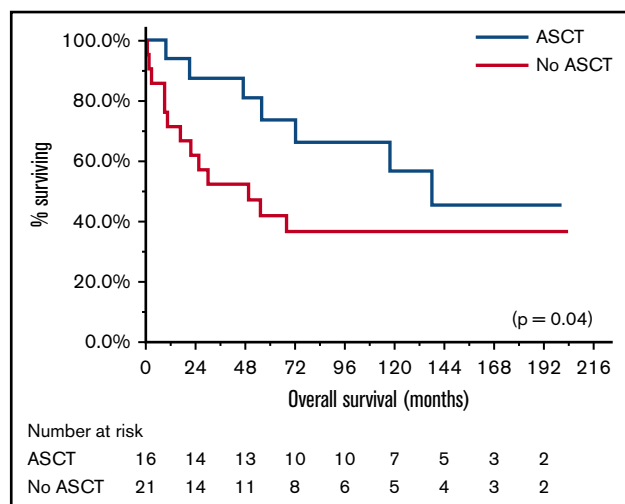


Figure 6. Kaplan-Meier curve comparing OS for cases receiving ASCT consolidation vs those who did not. Median OS, 138 months; 95% CI, 55.7-NR vs median OS, 49.6 months; 95% CI, 10.2-NR ($P = .04$).

impact survival. Long-term survival of NL appears to have improved in recent years.

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Authorship

Contribution: A.K., M.N., and P.B.J. conceived and designed the study; P.B.J., K.M.R., T.M.H., I.N.M., R.L.K., G.S.N., and C.H.H. provided study materials or patients; A.K., M.N., P.B.J., K.M.R., G.S.N., R.J.S., R.L.K., D.H.L., T.M.H., and I.N.M. collected and assembled data; A.K., M.N., P.B.J., T.M.H., I.N.M., R.J.S., and G.S.N. analyzed and interpreted data; R.L.K. reviewed the pathology of biopsy specimens; D.H.L. and C.H.H. reviewed radiologic data; and all authors wrote the manuscript, approved its final version, and agreed to be accountable for all aspects of this work.

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