The consequences of treatment and disease in patients with primary CNS non-Hodgkin's lymphoma: Cognitive function and performance status¹

Brian P. O'Neill,² Chiao-Hua Wang, Judith R. O'Fallon, Joseph P. Colgan, John D. Earle, Robert L. Krigel, Loren D. Brown, and William J. McGinnis

Coordinated by the North Central Cancer Treatment Group, Rochester, MN 55905

Per protocol, patients with primary CNS non-Hodgkin's lymphoma in an intergroup phase II trial conducted by the North Central Cancer Treatment Group and the Eastern Cooperative Oncology Group had their cognitive functions measured using the Folstein and Folstein Mini-Mental Status Examination (MMSE) and their physical functions measured using the Eastern Cooperative Oncology Group Performance Score (PS) at study entry, at each treatment evaluation, and at quarterly intervals thereafter until disease progression or death. Of the 53 eligible participants who began therapy, 46 (87%) had baseline MMSE scores recorded, 36 (68%) had at least one follow-up MMSE, and 32 (60%) had both, while 52 (98%) had baseline PS, 49 (92%) had at least one follow-up PS, and 48 (91%) had both. Patterns of MMSE and PS values over time were studied in each individual, in the group as a whole, in the 20 patients who completed the study regimen, in the 23 who survived more than a year, and in patients who were classified as nonprogressors at each key evaluation. For each patient, all recorded values were

plotted versus time, with dates of disease progression and death included, to look for signs of decline in cognitive or physical function preceding adverse events. Long-term declines in scores of both cognitive and physical function were observed in many treated patients with primary CNS non-Hodgkin's lymphoma. Nearly all patients who were alive more than 52 weeks after study entry had a demonstrable decline in cognitive and physical functionality. Such declines may occur before disease progression is documented; they may also occur in some patients who have long-term follow-up without evidence of disease progression. Declining MMSE and PS was a poor predictor of disease progression. There was no association of PS and toxicity. The data from this study demonstrated the considerable difficulties we encountered conducting an ancillary study such as this within a multicenter clinical trial. Firstly, the test instruments written into the protocol were unable to tell if the declines seen were due to disease, treatment, co-morbidity, or other factors. Secondly, the missing data created difficulties in interpreting outcome. *Neuro-Oncology* 1, 196–203, 1999 (Posted to *Neuro-Oncology* [serial online], Doc. 98-24, June 15, 1999. URL <neuro-oncology.mc.duke.edu>)

Received 9 October 1998, accepted 29 March 1999.

¹The work reported herein was supported in part by the Lindse-Bock Program in Neuro-Oncology of the Mayo Clinic Cancer Center and by NCCTG funds (NCI U10 CA 25225).

²Address correspondence and reprint requests to B.P. O'Neill, M.D., Department of Neurology, Mayo Clinic and Foundation, 200 SW First St., Rochester, MN 55905.

³Abbreviations used are as follows: ECOG, Eastern Cooperative Oncology Group; MMSE, Mini-Mental Status Examination; NCCTG, North Central Cancer Treatment Group; PCNSL, primary central nervous system non-Hodgkin's lymphoma; PS, performance score; WBRT, whole brain radiation therapy.

Primary CNS PCNSL³ is uncommon, present in only 0.5–2.0% of all primary brain tumors (O'Neill and Illig, 1989). Certain populations are at a heightened risk for developing this tumor, most notably patients with the acquired immune deficiency syndrome (Cote et al., 1996). However, recent reports suggest that, even in presumed immunocompetent persons, these tumors have increased in incidence and this increase is not simply because of the improvements in neuroimaging, neurosurgery, or neuropathology (Eby et al., 1988; O'Neill et al., 1993).

Nonacquired immune deficiency syndrome PCNSL occurs in older individuals. In most series, the median age at presentation is 60 years (Tomlinson et al., 1995). Thus, PCNSL occurs in patients at risk for neurocognitive decline. Such risk is a function of increased age and may be enhanced by co-morbid conditions such as head trauma, cerebrovascular disease, and Alzheimer's disease.

PCNSL is a treatable and potentially curable disease. However, current therapies have a known risk of neurotoxicity. Only recently have publications described neurobehavioral decline and the resultant decline in quality of life in treated PCNSL patients (Abrey et al., 1998; Blay et al., 1998; Crossen et al., 1995). Nevertheless, this group of patients has never been systematically assessed within a treatment trial for this disease. It seemed altogether reasonable to assess the consequences of survival in a recently completed phase II trial of combined modality therapy for PCNSL.

Materials and Methods

Patients

The study population consisted of all 53 eligible patients enrolled in an intergroup phase II trial conducted by NCCTG and ECOG and designed to assess the efficacy and toxicity of a multimodality regimen of PCNSL treatment. The regimen (two cycles of cyclophosphamide, vincristine, adriamycin, and prednisone, followed by WBRT, and then two cycles of high-dose cytosine arabinoside). Eligibility and therapeutic criteria and clinical results of this trial are described in detail elsewhere (O'Neill et al., 1995).

Protocol design called for cognitive and physical function to be measured by the Folstein and Folstein MMSE (Folstein et al., 1975) and the ECOG PS (Nesbitt et al., 1997), respectively, at study entry, at each treatment evaluation (weeks 3, 6, 16, 20, and 25), and at quarterly intervals thereafter until disease progression or death. The MMSE ranges from 0 to 30 (normal function), while the PS ranges from 0 (full and normal function) to 4 (bedridden). The PS was assigned by the examining physician and the MMSE by the physician, an oncology nurse, or a clinical assistant at the treatment venue. In some instances, disease progression was assigned when a patient failed to show for an appointment; in those instances, neither MMSE nor PS was recorded.

Fifty-three eligible patients (28 males, 25 females, median age of 60) received the first cycle of cyclophosphamide, vincristine, adriamycin, and prednisone; 33 of them terminated therapy prematurely for a variety of reasons, which are detailed in Fig. 1. Of these, seven stopped treatment early for reasons other than disease progression or death and were deemed "off study" and followed thereafter only for survival, new malignancies, and notable adverse events. Per study design, MMSE and PS assessments were not collected for these seven. Only the 20 (38%) who completed the entire treatment regimen were evaluated quarterly until disease progression or death.

	Number of Pt. Stopped				Total
	CHOP2	WBRT	HDAC1	HDAC2	
TREATMENT DEATH	2	1	0	0	3 (9%)
MEDICAL PROBLEM	3	2	2	0	7 (21%)
TOXICITY	0	1	0	0	1 (3%)
PROGRESSION	2	9	1	4	16 (48%)
VIOLATION	1	1	0	0	2 (6%)
REFUSED	2	0	2	0	4 (12%)

Fig. 1. Frequency count of reasons patients stop treatment. CHOP, cyclophosphamide, vincristine, adriamycin, and prednisone; WBRT, whole brain radiation therapy; HDAC, high-dose cytosine arabinoside.

Analysis Methods

Clinical and patient descriptors collected in the original clinical study (O'Neill et al., 1995) were also used in the analysis of the ancillary study. Information about co-morbid conditions at study entry was obtained from the flow sheets, as it was not recorded in the clinical trial files. Various graphical techniques (described more fully in the *Results* section) were applied to display all available MMSE, PS, objective response, and toxicity data to look for evidence of interesting associations that might be tested in future prospective trials. To quantify each patient's toxicity, a toxicity score was calculated at each evaluation by adding the grades of all toxicities recorded at that evaluation.

For some analyses, the evaluations performed at the following eight points in time were designated key evaluations: at baseline, after each of the five treatment cycles, and at the end of the third and fourth quarters of the first year (weeks 39 and 52). Changes in MMSE and PS values from baseline to each of the key evaluations were studied for all patients who were receiving protocol treatment, the 20 patients who completed the entire treatment regimen, and the subset of patients classified as nonprogressors at a specific key evaluation because their dates of disease progression and death occurred more than 30

Table 1. Summary information at each key evaluation for patients receiving protocol therapy

Treatment	Baseline		Week 3 after		Week 6 after		Week 16 after		Week 20 after		Week 25 after		1 Year after entry	
	(n = 53)		CHOP1 (n = 53)		CHOP2 (n = 43)		WBRT (n = 29)		HDAC1 (n = 24)		HDAC2 (n = 20)		(n = 12)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex														
Male	28	53	28	53	24	56	18	62	16	67	13	65	7	58
Female	25	47	25	47	19	44	11	38	8	33	7	35	5	42
Age														
Mean	59		59		59		60		58		59		58	
Median	60		60		60		63		60		60		60	
MMSE														
n	46		18		23		19		8		10		8	
Mean	24.0		26.0		24.4		25.7		26.4		26.1		26.6	
Median	26.0		27.5		26.0		27.0		26.0		27.0		27.0	
PS														
n	52		47		40		25		22		15		12	
Mean	1.6		1.7		1.7		1.4		1.3		1.3		1.0	
Median	2.0		2.0		1.5		1.0		1.0		1.0		1.0	
# Days after entry														
Min	0		3		32		66		110		158		343	
Mean	0		21		44		110		147		195		359	
Median	0		21		42		109		140		184		351	
Max	0		29		57		164		247		300		402	

CHOP, cyclophosphamide, vincristine, adriamycin, and prednisone; HDAC, high-dose cytosine arabinoside; WBRT, whole-brain radiation therapy.

days after that evaluation date. In addition, age-group comparisons (age ≤60 versus >60) were performed for each of these three patient sets.

Wilcoxon rank sum tests (Wilcoxon, 1945) were used to compare the distributions of patient characteristics and scores at each key evaluation. Distributions of time-to-progression and time-to-death were estimated with Kaplan-Meier curves (Kaplan and Meier, 1958) and compared with log rank tests (Mantel, 1966). Given the large number of tests that were performed, we reported unadjusted P values, but only those <0.01 indicate significant differences.

Results

Patients Receiving Protocol Treatment

The characteristics of the “on-study” patients and the availability of their MMSE and PS data at baseline and at each of the key evaluations are summarized in Table 1. The term on study refers to those patients still being followed according to protocol specifications. At study entry, the median age of the 53 eligible patients was 60, and nearly half (47%) were women. Their baseline PS and MMSE values were quite good, with median values of 2 and 26, respectively. By October 1997 disease progression had been recorded for 38 (72%), and 50 (94%) had died. Median time to progression was 29 weeks, and median survival was 42 weeks.

At each key evaluation, the median age of the patients who were still receiving study treatment (Table 1) was approximately 60 years, but the percentage of women decreased from 47 to 33% by week 20, when the last component of the study regimen was administered. Failure to obtain MMSE values was a major problem at every key evaluation due to procedural flaws, severe toxicity, disease progression, or acute medical problems. As shown in Table 1, the percentage of patients with missing MMSE values ranged from a low of 13% at baseline to highs of 66% after cyclophosphamide, vincristine, adriamycin, and prednisone-1 and high-dose cytosine arabinoside-1. Failure to obtain PS values occurred much less often; the percentage of patients with missing PS values ranged from a low of 0% after the first-year evaluation to a high of 25% after high-dose cytosine arabinoside-2.

Scatterplots of all MMSE and PS values recorded at each of the key evaluations are shown in Figs. 2 and 3, respectively. For interpretation purposes, in Fig. 2 the associated box-plots have been superimposed on the MMSE data, along with a line connecting the medians, and in Fig. 3, the range of PS values at each evaluation has been graphed along with a line connecting the means. These figures show remarkably little change in the condition of patients still on study during the 20-week treatment period and show slight improvements in the posttreatment period. To assess the impact of intermittently missing data values on these plots, we looked at the MMSE versus PS data for each of the 53 patients. It was

Fig. 2. Mini-mental status examination score versus treatment received. (See Fig. 1 for abbreviations.)

our impression that the shape of each patient curve was consistent even when data were missing. (These plots may be downloaded from the *Neuro-Oncology* web site at <http://neuro-oncology.mc.duke.edu>.) There was no evidence of consistent patterns of missing values for individual patients. MMSE values were recorded at one or more follow-up visits for 36 patients (68%) and at both baseline and a follow-up visit for 32 patients (60%), while PS values were recorded at one or more follow-up visits for 49 patients (92%) and at both baseline and a follow-up visit for 48 patients (91%).

To look for evidence that MMSE and PS values might be affected by toxicity or objective response to treatment, the more plentiful PS data were plotted against the toxicity score and the objective status at each of the key evaluations. The only evidence of such associations was the greater number of progressions seen at higher PS levels after whole-brain radiation therapy.

Interesting associations were sought among the patient functionality measures, especially whether changes in PS or MMSE predicted progression or death. Each participant's MMSE and PS at each recorded evaluation were plotted against time on study, along with the times at which the subject received each treatment, experienced disease progression, and/or died. Missing data rendered 27 (51%) of these patient plots noninformative about the comparative performance of MMSE and PS. However,

evaluation of the remaining 26 plots permitted a subjective grouping of 3 types of configurations: complementary MMSE and PS patterns with dramatic changes in both shortly before disease progression was diagnosed (23%); stable PS and MMSE patterns with no detectable change before disease progression was diagnosed (73%); and complementary PS and MMSE patterns with steady deterioration for many months before disease progression was diagnosed (4%). These plots may also be downloaded from the *Neuro-Oncology* web site.

Age Groups

Because the clinical trial in which these patients participated was designed to address the effect of age in this disease, the patient functionality data were also examined by age group (≤ 60 versus > 60). The notable findings were as follows: There was no major difference in the gender distributions of the two age groups at baseline; the dropout rates in the two groups were nearly identical until week 52, but the median age of the older group gradually decreased during the course of treatment; the older group had significantly higher (poorer) PS at baseline and tended to have substantially higher PS values at subsequent evaluations; and the older group had higher (better) MMSE values than the younger group at some key evaluations.

Fig. 3. Performance versus treatment received. (See Fig. 1 for abbreviations.)

Patients Who Completed the Study Regimen

The 20 patients who completed the entire study regimen constituted a particularly hardy subset of 13 men (median age, 60) and 7 women (median age, 60). In October 1997, when 18 of them (90%) had experienced disease progression and 19 (95%) had died, their median time to progression was 50 weeks and median survival was 90 weeks. The 11 (55%) who survived more than 52 weeks after study entry consisted of 6 men (median age, 57) and 5 women (median age, 63). Age-group comparisons of MMSE and PS values in this subset yielded results similar to those reported in the previous section, "Age Groups."

There were 23 patients who lived more than one year after study entry. Of these, only the 11 who completed the treatment regimen had MMSE and PS information available after week 52. One of them is still alive without disease progression; the remaining 10 have experienced disease progression, 2 of them during the first year. Plots of their MMSE and PS data showed a progressive decline of both cognitive and physical functional measures over time prior to disease progression. Fig. 4 is an example of scans from one such patient who completed the therapy regimen and whose deterioration was documented well after week 52 and worsened until tumor progression. This patient (age 55 at protocol entry) had serial imaging that displayed progressive diffuse white matter changes and cerebral atro-

phy beginning two years after diagnosis, a full 3½ years before tumor progression. Two additional patients had comorbid conditions that were sufficient to affect functionality: one patient (age 48) had sustained a head injury that required a craniotomy, while the other had a stroke syndrome (age 71) and required nursing home care.

Discussion

With or without a boosted treatment volume, WBRT has been the standard of care for PCNSL (Nelson et al., 1992). However, a dementing illness—often in conjunction with gait impairment—associated with diffuse white matter changes evidenced by imaging and neuropathologic criteria has been described in long-term survivors after WBRT (Abrey et al., 1998). These patients have been assumed to have brain tumor treatment toxicity compounded by the effects of age and age-related co-morbidity.

PCNSL resembles encephalitis with a diffuse infiltrative component and focal or multifocal areas of tumor concentration (Schiffer et al., 1987). Thus, unlike the situation in glioblastoma multiforme where involved field radiotherapy is the norm and the toxicity is loco-regional (Hochberg and Pruitt, 1980; Hochberg and Slotnick, 1980), it is not surprising then that PCNSL patients are at risk of developing widespread neurologic deficits from the very nature of the

Fig. 4. MRI scans from (A) 1994 and (B) 1996 showing progressive white matter hyperintensity and ventricular enlargement in a long-term survivor

disease and from the therapy. Since untreated PCNSL is a rapidly fatal disease (Henry et al., 1974), we have no information on the natural history of this disease.

More recently, chemotherapy has been combined with WBRT as initial therapy in PCNSL (Brada et al., 1990; DeAngelis et al., 1990; Shibamoto et al., 1990). Among the agents used, however, are drugs such as methotrexate, vincristine, and cytosine arabinoside, which have a clear neurotoxicity profile, particularly if used in conjunction with WBRT (Allen et al., 1980; Blay et al., 1998; Frick et al., 1986). The NCCTG/ECOG clinical trial of combined therapy, which enrolled patients from 1986 through 1994, was the first multi-institutional study of combined therapy in this disease to be completed and reported. At the time of study design, information was that the drugs chosen had a lower neurotoxicity profile than others in use or under consideration and that the risk of neurotoxicity could be reduced if the chemotherapy was given prior to WBRT (Poisson et al., 1979). However, this treatment program did not enhance the survival of patients with PCNSL, although there was a suggestion of a benefit to patients aged 60 years or less (O'Neill et al., 1995).

This study was also designed to assess the effects of treatment and/or disease on cognitive and physical function. We employed two easy-to-use and well-validated assessment measures available at the time of study design, the Folstein and Folstein MMSE examination and the ECOG performance score. Nevertheless, these two tools have a clear threshold effect. Furthermore, each is a unidi-

mensional measure of functional status, whereas quality of life is "a multidimensional construct with many more domains than physical well-being" (Weitzner et al., 1996). Unfortunately, scales such as the Functional Assessment of Cancer Treatment (FACT; Murray et al., 1995), the Quality Adjusted Survival (QAS; Trojanowski et al., 1989), and the National Life Quality Concept (NLQC; Weitzner et al., 1996), which have subsequently been validated and employed in patients with primary brain tumors, had not been published at the time of our study design. Also, since non-acquired immune deficiency syndrome PCNSL occurs in older persons, age may be a confounding factor in our PS data. A recent study (Murray et al., 1995) compared a newly constructed quality of life measure, quality-adjusted survival (QAS), to PS in a malignant glioma clinical trial and concluded that since PS is a measurement of daily activity and self-care skills, it is heavily influenced by patient age. In fact, our patients over the age of 60 years had higher PS and lower MMSE values in general.

We do not feel that we missed patients because PS was poor. Nearly all patients had PS data recorded at each evaluation, and the number of patients lacking MMSE data were similar at all PS levels and in the different age groups. Nevertheless, we did miss MMSE scores. Unlike trials done solely at tertiary care centers where personnel resources are more available, in our study design a health care provider at the treatment venue, which typically was a busy community-based oncology practice, determined the MMSE. Thus the tenacity of the personnel in collect-

ing data may have varied based on the flow of care at one of these institutions. A similar observation was made in another report from the NCCTG on MMSE and PS changes in glioma trials, but the impact of the missing data was less because of the substantially larger number of patients (Taylor et al., 1998).

Our data suggest that both cognitive and functional status decline in long-term PCNSL survivors. The MMSE and PS curves tended to mirror each other, generally showing improvement for 12–18 months, and then deterioration among the long-term participants. In some patients, changes in MMSE and/or PS clearly predated disease progression, suggesting that such changes could be based on the disease or treatment (or both). In other patients with clear declines in MMSE and PS, no recurrence of PCNSL could be documented by neuroimaging. However, neuroimaging in the latter patients, who were long-term survivors, suggested a diffuse white matter process accompanied by parenchymal volume loss and generalized ventricular dilatation similar to changes described after WBRT (DeAngelis et al., 1989; So et al., 1987). Surveillance scanning was performed sufficiently often to exclude recurrent tumor as the cause of observed imaging changes and functional declines. Thus, we feel confident that the observed functional decline truly reflected “consequences of survival.” Of course, infiltrative tumor below the detection level of the imaging modality could have occurred. Unfortunately, no post-mortem examinations were performed on any of these patients with late cognitive and performance decline, freedom from recurrent disease, and neuroimaging abnormalities. Several study patients died early from causes seemingly unrelated to PCNSL. In those, the absence of PCNSL on neuroimaging was corroborated by neuropathologic examination.

We feel that the study population reported herein reflects the usual situation encountered in clinical practice. All but bedridden (PS = 4) patients were eligible for treatment; their median age was 60; 19% were age 70 or older; and all had to be treated within 3 weeks of diagnosis. To date, only one other group has attempted to prospectively assess cognitive function in PCNSL patients (Crossen et al., 1994; Neuwelt et al., 1991). That group, however, assessed patients who were young and had a good performance status at the time of treatment. Furthermore, those patients likely survived their disease long

enough to be referred to a medical center for evaluation and treatment, a scenario shown to bias results in glioma trials (MacDonald et al., 1990). In other studies reporting on combined therapy, age has proven to be a powerful predictor of response, survival, and (by inference for young age) protection from neurocognitive decline. The participants in those other studies did not have careful and prospective neuropsychology studies (DeAngelis et al., 1990; Glass et al., 1994), however, and in at least one study, treatment did not require histologic confirmation (Freilich et al., 1996). Thus the clinician is left to wonder whether the results of these studies will be translatable to the typical PCNSL patient.

Developing better strategies for treating this disease is imperative. Since at least one-third and possibly as many as one-half of patients with systemic intermediate- and high-grade non-Hodgkin's lymphoma can be cured with current therapies (Fisher et al., 1993; Tondini et al., 1993), it seems reasonable to conclude that PCNSL is a potentially curable disease. Yet the special nature of the nervous system poses significant obstacles to effective treatment. This “high-priced real estate” leaves little room for an error that would produce toxicity from curative therapy. A particular irony of this disease is that the patients who are most in need of treatment are those that stand the most to lose from treatment complications.

It has been our intent to devise treatment schema and evaluation tools applicable to the typical patient in the community setting. We recognize this particular challenge and have learned important lessons from the data reported here. We plan to expand the assessment of neurocognitive function and quality of life within our new treatment approaches, employing newer validated measures into the study design and comparing them with measures employed in the present study. Furthermore, we will stress the need for data collection, especially in the community setting, ensuring that every patient is seen and assessed before a score of progression is assigned.

Acknowledgments

We are grateful for the expert technical support of Jill Burton and Debra Kvittum from NCCTG and the superb secretarial assistance of Leslie B. Ottjes of the Department of Neurology, Mayo Clinic.

References

- Abrey, L.E., DeAngelis, L.M., and Yahalom, J. (1998) Long-term survival in primary CNS lymphoma. *J. Clin. Oncol.* **16**, 859–863.
- Allen, J.C., Rosen, G., Mehta, B.M., and Horten, B. (1980) Leukoencephalopathy following high-dose IV methotrexate chemotherapy with leukovorin rescue. *Cancer Treat. Rep.* **64**, 1261–1273.
- Blay, J.Y., Conroy, T., Chevreau, C., Thyss, A., Quesnel, N., Eghbali, H., Bouabdallah, R., Coiffier, B., Wagner, J.P., Le Mevel, A., Dramais-Marcel, D., Baumelou, E., Chauvin, F., and Biron, P. (1998) High-dose methotrexate for the treatment of primary cerebral lymphomas: Analysis of survival and late neurologic toxicity in a retrospective series. *J. Clin. Oncol.* **16**, 864–871.
- Brada, M., Dearnaley, D., Horwich, A., and Bloom, H.J. (1990) Management of primary cerebral lymphoma with initial chemotherapy: Preliminary results and comparison with patients treated with radiotherapy alone. *Int. J. Radiat. Oncol. Biol. Phys.* **18**, 787–792.
- Cote, T.R., Manna, A., Hardy, C.R., Yellin, F.J., and Hartge, P. (1996) Epidemiology of brain lymphoma among people with or without acquired immunodeficiency syndrome. *J. Natl. Cancer. Inst.* **88**, 675–679.
- Crossen, J.R., Garwood, D., Glatstein, E., and Neuwelt, E.A. (1994) Neurobehavioral sequelae of cranial irradiation in adults: A review of radiation-induced encephalopathy. *J. Clin. Oncol.* **12**, 627–642.

- DeAngelis, L.M., Delattre, J.Y., and Posner, J.B. (1989) Radiation-induced dementia in patients cured of metastases. *Neurology* **39**, 789–796.
- DeAngelis, L.M., Yahalom, J., Heinemann, M.H., Cirincione, C., Thaler, H.T., and Krol, G. (1990) Primary CNS lymphoma: Combined treatment with chemotherapy and radiotherapy. *Neurology* **40**, 80–86.
- Eby, N.L., Grufferman, S., Flannelly, C.M., Schold, S.C., Jr., Vogel, F.S., and Burger, P.C. (1988) Increasing incidence of primary brain lymphoma in the U.S. *Cancer* **62**, 2461–2465.
- Fisher, R.I., Gaynor, E.R., Dahlborg, S., Oken, M.M., Grogan, T.M., Mize, E.M., Glick, J.H., Coltman, C.A., Jr., and Miller, T.P. (1993) Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N. Engl. J. Med.* **328**, 1002–1006.
- Folstein, M.F., Folstein, S.E., and McHugh, P.R. (1975) "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* **12**, 189–198.
- Freilich, R.J., Delattre, J.Y., Monjour, A., and DeAngelis, L.M. (1996) Chemotherapy without radiation therapy as initial treatment for primary CNS lymphoma in older patients. *Neurology* **46**, 435–439.
- Frick, J.C., Hansen, R.M., Anderson, T., and Ritch, P.S. (1986) Successful high-dose intravenous cytarabine treatment of parenchymal brain involvement from malignant lymphoma. *Arch. Intern. Med.* **146**, 791–792.
- Glass, J., Gruber, M.L., Cher, L., and Hochberg, F.H. (1994) Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: Long-term outcome. *J. Neurosurg.* **81**, 188–195.
- Henry, J.M., Heffner, R.R., Jr., Dillard, S.H., Earle, K.M., and Davis, R.L. (1974) Primary malignant lymphomas of the central nervous system. *Cancer* **34**, 1293–1302.
- Hochberg, F.H., and Pruitt, A. (1980) Assumptions in the radiotherapy of glioblastoma. *Neurology* **30**, 907–911.
- Hochberg, F.H., and Slotnick, B. (1980) Neuropsychologic impairment in astrocytoma survivors. *Neurology* **30**, 172–177.
- Kaplan, E.L., and Meier, P. (1958) Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457–481.
- MacDonald, D.R., Cascino, T.L., Schold, S.C., Jr., and Cairncross, J.G. (1990) Response criteria for phase II studies of supratentorial malignant glioma. *J. Clin. Oncol.* **8**, 1277–1280.
- Mantel, N. (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother. Rep. Pt. 1* **50**, 163–170.
- Murray, K.J., Nelson, D.F., Scott, C., Fischbach, A.J., Porter, A., Farnan, N., and Curran, W.J., Jr. (1995) Quality-adjusted survival analysis of malignant glioma. Patients treated with twice-daily radiation (RT) and carmustine: A report of Radiation Therapy Oncology Group (RTOG) 83–02. *Int. J. Radiat. Oncol. Biol. Phys.* **31**, 453–459.
- Nelson, D.F., Martz, K.L., Bonner, H., Nelson, J.S., Newall, J., Kerman, H.D., Thomson, J.W., and Murray, K.J. (1992) Non-Hodgkin's lymphoma of the brain: Can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. *Int. J. Radiat. Oncol. Biol. Phys.* **23**, 9–17.
- Nesbitt, J.C., Lee, J.S., Komaki, R., and Roth, J.A. (1997) Cancer of the lung. In: Holland, J.F., Bast, R.C., Jr., Morton, D.L., Frei, E., III, Kufe, D.W., Weichselbaum, R.R. (Eds.), *Cancer Medicine*. Fourth edition. Philadelphia: Williams and Wilkins. pp. 1723–1803.
- Neuwelt, E.A., Goldman, D.L., Dahlborg, S.A., Crossen, J., Ramsey, F., Roman-Goldstein, S., Brazier, R., and Dana, B. (1991) Primary CNS lymphoma treated with osmotic blood-brain barrier disruption: Prolonged survival and preservation of cognitive function. *J. Clin. Oncol.* **9**, 1580–1590.
- O'Neill, B.P., O'Fallon, J.R., Earle, J.D., Colgan, J.P., Brown, L.D., and Krigel, R.L. (1995) Primary central nervous system non-Hodgkin's lymphoma: Survival advantages with combined initial therapy? *Int. J. Radiat. Oncol. Biol. Phys.* **33**, 663–673.
- O'Neill, B.P., and Illig, J. (1989) Primary central nervous system lymphoma. *Mayo Clin. Proc.* **64**, 1005–1020.
- O'Neill, B.P., Tomlinson, F.H., O'Fallon, J.R., Scherthauer, B.W., Kurtin, P.J., and O'Neill, D.B. (1993) The continuing increase of primary central nervous system non-Hodgkin's lymphoma (PCNSL). *Ann. Neurol.* **34**, 313.
- Poisson, M., Hauw, J.J., Pouillart, P., Bataini, J.P., Mashaly, R., Pertuiset, B.F., and Metzger, J. (1979) Malignant gliomas treated after surgery by combination chemotherapy and delayed radiation therapy. Part II. Tolerance to irradiation after chemotherapy. *Acta. Neurochir. (Wien)* **51**, 27–42.
- Schiffer, D., Chio, A., Giordana, M.T., Novero, D., Palestro, G., Soffietti, R., and Vasario, E. (1987) Primary lymphomas of the brain: A clinicopathologic review of 37 cases. *Tumori* **73**, 585–592.
- Shibamoto Y., Tsutsui, K., Dodo, Y., Yamabe, H., Shima, N., and Abe, M. (1990) Improved survival rate in primary intracranial lymphoma treated by high-dose radiation and systemic vincristine-doxorubicin-cyclophosphamide-prednisolone chemotherapy. *Cancer* **65**, 1907–1912.
- So, N.K., O'Neill, B.P., Frytak, S., Eagan, R.T., Earnest, F., IV, and Lee, R.E. (1987) Delayed leukoencephalopathy in survivors with small cell lung cancer. *Neurology* **37**, 1198–1201.
- Taylor, B.V., Buckner, J.C., Cascino, T.L., O'Fallon, J.R., Schaefer, P.L., Dinapoli, R.P., and Schomberg, P. (1998) Effects of radiation and chemotherapy on cognitive function in patients with high-grade glioma. *J. Clin. Oncol.* **16**, 2195–2201.
- Tomlinson, F.H., Kurtin, P.J., Suman, V.J., Scheithauer, B.W., O'Fallon, J.R., Delly, P.J., Jack, C.R., Jr., and O'Neill, B.P. (1995) Primary intracerebral malignant lymphoma: A clinicopathological study of 89 patients. *J. Neurosurg.* **82**, 558–566.
- Tondini, C., Zanini, M., Lombardi, F., Bengala, C., Rocca, A., Giardini, R., Buzoni, R., Valagussa, P., and Bonadonna, G. (1993) Combined modality treatment with primary CHOP chemotherapy followed by locoregional irradiation in stage I or II histologically aggressive non-Hodgkin's lymphomas. *J. Clin. Oncol.* **11**, 720–725.
- Trojanowski, T., Peszynski, J., Turowski, K., Markiewicz, P., Goscinski, I., Bielawski, A., Bendarzewska, B., Szymona, J., Dabrowska, A., and Lopatkiewicz, J. (1989) Quality of survival of patients with brain gliomas treated with postoperative CCNU and radiation therapy. *J. Neurosurg.* **70**, 18–23.
- Weitzner, M.A., Meyers, C.A., and Byrne, K. (1996) Psychosocial functioning and quality of life in patients with primary brain tumors. *J. Neurosurg.* **84**, 29–34.
- Wilcoxon, F. (1945) Individual comparisons by ranking methods. *Biometrics* **1**, 80–83.