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● *Clinical Original Contribution*

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

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Between 1983 and 1987 the Radiation Therapy Oncology Group conducted a prospective phase II study to evaluate survival in primary non-Hodgkin's lymphoma of the brain treated with whole brain irradiation to 40 Gy and a 20 Gy boost to tumor plus a 2 cm margin. Forty-one patients are reported. Full follow-up is available on 35/41 who have died. Six are alive at 8.8–67.2 months from start of radiation therapy with a median followup of 53.9 months. Overall median survival was 11.6 months from start of radiation therapy and 12.2 months from diagnosis, with 48% surviving 1 year and 28% surviving 2 years. Karnofsky Performance Status and age were significant prognostic factors. Patients with a Karnofsky Performance Status of 70–100 had a median survival of 21.1 months compared to 5.6 months for patients with a status of 40–60 ($p < .001$). Fourteen patients < 60 years of age had a median survival of 23.1 months, while 27 patients ≥ 60 years of age had a median survival of 7.6 months (log-rank $p = .001$). Disease recurred in the brain in 25/41 (61%) of the patients, (21/41 in the brain only and 4/41 in the brain plus distant metastases). Despite high dose and large volume irradiation, primary Central Nervous System lymphoma still exhibits excessive mortality, especially in older patients. This paradox of the relative radioresistance of primary Central Nervous System lymphoma remains unresolved.

Primary non-Hodgkin's lymphoma of brain, CNS lymphoma, Reticulum cell carcinoma of brain, Microglioma.

INTRODUCTION

Non-Hodgkin's lymphoma outside of the central nervous system (CNS) is generally a highly radio-responsive disease with local control rates of over 90% achieved with doses of 25–35 Gy for non-histocytic histologies, and local control rates of 75–85% have been achieved with doses of 40–50 Gy for histocytic histologies (DHL & NHL) (2, 3, 10). Localized extranodal presentations (Stage I_E and II_E) outside of the CNS have higher local control rates and survival rates than do nodal presentations (4). When treated with radiation therapy to 40–50 Gy, local control is approximately 90%. However, approximately 50% of the patients relapse outside of the treated volume and only approximately 10% of the relapses are local failures. In early stage non-Hodgkin's lymphoma of the head and neck region, 30–65 Gy have produced local control rates of 91–100% and five year survival rates of 43–77% (7, 14, 15, 23, 31–33).

In contrast, when primary CNS lymphoma (which constitutes only 1.6% of all cases of extranodal non-Hodgkin's lymphoma) (16) has been treated with doses of 40–50 Gy, approximately 90% of the patients who have died from their disease have died from local recurrence and only approximately 10% died of disseminated disease. As of 1975 when Littman and Wang (19) reviewed the literature, only six out of 150 patients (4%) with primary CNS lymphoma had survived 5 years. In 1982 when the Radiation Therapy Oncology Group (RTOG) undertook the task of trying to determine why the local failure rate

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was so high in primary CNS lymphoma, radiation doses of 20–55 Gy, (median dose of 40 Gy) were reported to produce median survivals of 24 months (18) and 42 months (19). The radiation portals used ranged from local field to whole brain, with many patients having received only local field irradiation. Three questions remained to be answered: (1) Was local failure due to geographic or marginal miss because of the less-than-optimal methods available to define tumor volume in the pre-CT scan era, that is before 1975? (2) Was local failure due to the multicentric and diffusely infiltrating nature of the disease (8, 13)? With multifocal disease identified in up to 44% of cases, and with gross disease frequently infiltrating the leptomeninges (6, 13), the usual whole brain fields used to treat primary and metastatic brain tumors would not have encompassed all of the meninges. (3) Could local control and survival be improved by increasing the tumor dose to 60 Gy and treating all areas at risk for microscopic disease to 40 Gy, (a dose that should produce sterilization of at least 80–90+% of non-CNS non-Hodgkin's lymphoma)? These were the questions that Radiation Therapy Oncology Group protocol 8315 (RTOG 8315) sought to answer. This paper reports on the outcome of that study.

METHODS AND MATERIALS

Case material

Between May 1983 and November 1987, the Radiation Therapy Oncology Group (RTOG) conducted a Phase II protocol to evaluate the efficacy of whole brain and meningeal irradiation to 40 Gy, plus a 20 Gy boost to gross disease, in the treatment of primary non-Hodgkin's lymphoma* of the brain. To be eligible patients had to be 18 years of age or older, have a Karnofsky performance status (KPS) of at least 40, and have biopsy-proven non-Hodgkin's lymphoma involving the parenchyma of the brain without involvement of the spinal cord by myelogram or of the cerebral spinal fluid (CSF) by cytology. Patients had to have no evidence of disseminated disease by physical exam, chest X ray, CT of abdomen and/or lymphangiogram and bone marrow biopsy. Patients had no AIDS or AIDS-related symptoms. Patients were excluded if they had lymphomatous meningitis without a parenchymal lesion, prior radiotherapy and/or chemotherapy, or a prior malignancy excepting basal cell cancer of the skin not involving the head and neck region or carcinoma *in situ* of the uterine cervix. Skin testing was done with [(Tuberculin) Purified Protein Derivative] (PPD), mumps and DNCB (dinitrochlorobenzene) in 51% of the cases. T and B cell lymphomas were characterized in 44% of the patients by using immunohistochemical methods for immunoglobulins and selected T cell markers.

Table 1. Pretreatment characteristics (N = 41)

		N	%
KPS	70–100	21	51
	40–60	20	49
Age	<60	14	34
	≥60	27	66
NFC	Work (I)	11	27
	Home (II)	20	49
	Hospital (II)	10	24
Sex	Male	24	59
	Female	17	41
Surgery	Biopsy	17	42
	Resection	23	56
	Unknown (Craniotomy)	1	2
Lesion	Single	33	81
	Multiple	8	19

KPS = Karnofsky Performance Status; NFC = Neurological Function Classification.

A total of 51 cases were entered by 22 institutions (see Appendix I). Ten cases were ineligible because of disseminated disease (three patients), changes in pathologic diagnosis upon central review (three patients), insufficient histologic material to confirm diagnosis (three patients), and incomplete data (one patient). This left 41 properly entered and eligible cases that constitute this report. Distribution of patients by KPS, age, NFC (neurological function classification), sex, extent of surgery, and multiplicity of lesions is given in Table 1.

Radiation therapy

Radiation therapy was delivered by 4–10 MV linear accelerator or by Co^{60}, with a minimum SAD (source axis distance) of 80 cm. Initially the whole brain and meninges down to the bottom of C_2 (See Figure 1) were irradiated by parallel opposed portals to 40.00 Gy in 1.8 Gy fractions. A 20.00 Gy boost was then delivered by two or three field technique to the contrast enhancing lesion(s) plus a 2 cm border. During radiation therapy all but three patients were maintained on dexamethasone. The daily dose of dexamethasone ranged between 0–44 mg/d with a median dose of 8 mg/d.

Chemotherapy

No chemotherapy was given until disease progression, with two exceptions. One case received methotrexate (MTX) via an Ommaya reservoir immediately after radiation therapy. The patient then developed distant metastases involving the testis and received additional chemotherapy. The second case had M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone) started on day 2 of radiation

* Primary non-Hodgkin's lymphoma of the brain has been historically referred to as reticulum cell sarcoma, microgliomatosis, perivascular sarcoma, periadventitial sarcoma, adventitial sarcoma, perithelial sarcoma, reticuloendothlial sarcoma, malignant reticulosis, malignant lymphoma, malignant reticuloendotheliosis, reticulohistiocytic encephalitis and atypical granulomatous encephalitis (28).

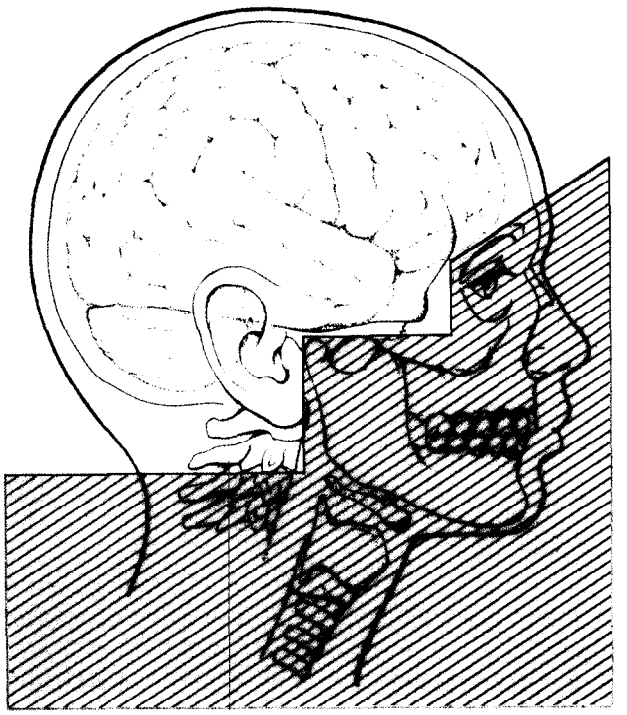

Fig. 1. Treatment portal for whole brain and meninges. Note, inferior border includes C2, as well as the entire frontal lobe, the cribriform plate and the middle fossa.

therapy and the radiation dose was consequently reduced to 54.00 Gy. After completion of radiation, MTX with leucovorin rescue was started.

Chemotherapy was given to seven patients for disease progression. Intravenous cytoxan and i. t. MTX were given to one patient when disease spread to the spinal cord. Vincristine, Adriamycin and Cytoxan were given to the patient who developed metastasis to the testis. Vincristine, Adriamycin, [1,3-bis(2-chloroethyl)-1-nitrasurea] (BCNU) and procarbazine were given to one patient for a new brain lesion. MTX was given to two patients for local recurrence. BCNU was given to one patient for local recurrence and bone marrow dissemination. ProMACE-MOPP (doxorubicin, cyclophosphamide, etoposide, nitrogen mustard, vincristine, procarbazine, prednisone) without methotrexate and local radiation therapy to the eyes was given to one patient for orbital metastasis. Following salvage chemotherapy, all patients died of progressive disease with a median survival of 7 months from start of radiation therapy.

Study parameters/disease evaluation

Neurological examinations were performed, and steroid dosage recorded, at the following times: prior to therapy, weekly during radiotherapy, then every 3 months for 2 years, then every 4 months for 1 year, then every 6 months until 5 years, and then yearly thereafter. CT scans were performed pre-operatively, post-operatively prior to radiotherapy, four months after the start of radiotherapy and at least at the time of neurologic deterioration. Most of the patients had serial CT scans along with routine neurologic follow-up. Chest X rays were done prior to therapy, every 6 months and at the time of suspected recurrence or dissemination. CT scans of the abdomen, or lymphangiograms, were done prior to therapy, at 2 years and at time of suspected dissemination. The quality of survival was measured by KPS and neurological function classification (NFC): (I) able to work, minor or absent neurological findings; (II) able to be at home with or without nursing care, neurological findings present but not serious; (III) hospitalized with major neurological findings; (IV) hospitalized with serious neurological findings including coma.

Statistical analysis

Survival and progression-free survival were calculated from the date radiation therapy started. Progression was scored when disease recurred either locally or distantly as determined clinically and/or by CT scan. All time related curves were estimated by Kaplan-Meier (17) method and were compared using the log-rank statistic (21). Multivariate analyses using the Cox Model were used to identify important prognostic factors relating to survival (5).

RESULTS

Analysis of this study 3.3 years after its completion reveals that a total of 27 out of 41 patients (66%) died of their lymphoma. Six out of 41 patients (15%) survived without evidence of disease at last follow-up visit with a median survival of 53.9 months (range of 8.8–67.2 months) from start of radiation therapy, and 54.5 months (range of 9.0–68.0 months) from diagnosis. Eight out of 41 patients (20%) have died without evidence of lymphoma from intercurrent disease: infection (4), cardiac problems (1), stroke (1), subdural hematoma (1) (see discussion below under possible toxicity).

The overall survival for the 41 patients from first day of radiation therapy is given in Figure 2. The median survival was 11.6 months from start of treatment and

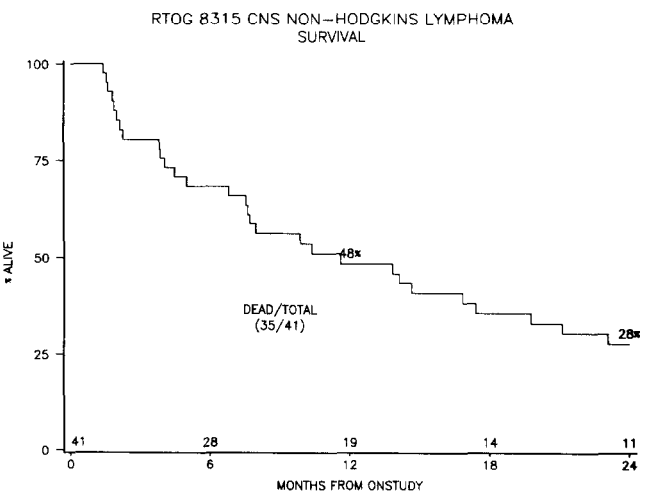

Fig. 2. Overall survival of primary Non-Hodgkin's lymphoma of the brain. One year survival is 48% and 2 year survival is 28%.

Table 2. Survival* by prognostic variables

	N	Median (mos.)	1 Yr. (%)	2 Yr. (%)	P
All cases	41	11.6	48	28	
KPS 70–100	21	21.1	71	46	
KPS 40–60	20	5.6	25	10	<.001
Age <60	14	23.1	70	47	
Age ≥60	27	7.6	37	19	.004
NFC work	11	19.8	73	36	
NFC home	20	13.8	55	33	
NFC hospital	10	5.6	10	10	.005
Female	17	6.8	29	6	
Male	24	19.8	62	44	.005
Biopsy	17	6.8	34	34	
Resection	23	14.7	61	26	ns
Single lesion	33	14.7	54	32	
Multiple lesions	8	8.6	25	13	ns

* Survival is measured from the first day of radiation therapy.
KPS = Karnofsky Performance Status; NFC = Neurological Function Classification.

12.2 months from diagnosis. This includes four patients who died during radiation therapy due to disease progression (3) and Herpes encephelitis (1); plus one patient who did not receive the last radiation treatment due to deterioration, and one who died 2.5 months later.

Median survival from start of radiation therapy and percent survival at 1 and 2 years are summarized in Table 2 by prognostic variables. Cox regression analysis (Table 3) indicated that KPS was the most significant prognostic variable ($p < .01$). Survival by KPS is given in Figure 3. Survival by age is given in Figure 4. Survival by sex was also statistically significant ($p = .005$) with the median survival for men being 19.8 months compared to a median survival of 6.8 months for women. Although Cox regression analysis (Table 3) indicated that sex was the second most important prognostic factor ($p < .05$), closer inspection showed that women were older (88% with age > 60 vs. 50% of males with age > 60) and tended to have worse KPS. Therefore, the selection of sex in the model may have masked the true prognostic significance of age. In fact, when sex was not included in the regression model, age became significant ($p < .05$). Neurological function classification was strongly correlated with KPS and was found not to be significant in the model already containing KPS.

CT scan response

Twenty-six patients had post treatment CT scans done 4 months after the start of radiotherapy that were available for central review. Patients with disease progression during radiotherapy were not included. Patients with CT scans outstanding (that were not received by RTOG headquarters) were not included. Sixteen patients had a complete response (CR) of disease by CT scan. At the time of the CT scan they were off of Decadron (15 patients) or on a reduced dosage (1 patient). Median survival was 19.8 months. Five patients were scored as almost a CR based upon CT scan changes of residual low density regions in 3 scans done without contrast and 2 scans that showed minimal hyperdensity along the wall of a lateral ventricle while off of Decadron. Their median survival was 24.2 months, therefore they have been included in the CR group in Figure 5. It is probable that if a repeat CT scan had been obtained with contrast and/or done several weeks later it would have demonstrated a CR. Five patients had serial CT scans showing decreased tumor volume, but with significant gross residual disease. These were scored as a partial response (PR): (1) One patient with two lesions demonstrated a mixed response with complete disappearance of one lesion but pesistance of a second lesion that may have been at the edge of the boost field. (2) The other patient demonstrated marked decrease in CT tumor volume. It is possible that the increase in Decadron dose may have been due to a delayed acute radiation reaction, although it is also possible that it was related to disease progression. The median survival of the PR group was 9.9 months (see Figure 5).

Among the 16 CR (complete respondees), two were

Table 3. Cox model

Covariates	Increased survival	Decreased survival	Relative risk	Statistical significance
KPS	70–100	40–60	3.55	.002
Sex	Male	Female	2.43	.032
Age	<60	≥60	2.04	.111
Prior surgery	Resection	Biopsy	2.02	.045
Lesions	Single	Multiple	2.42	.083

Note: Using the step-down procedure to identify independent pre-treatment factors related to survival.

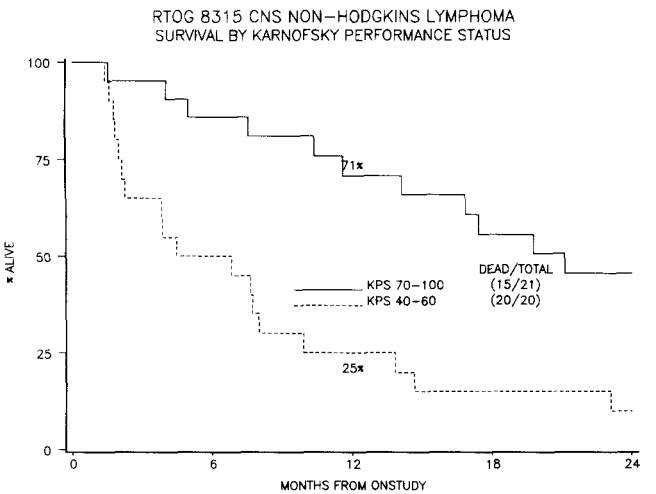

Fig. 3. Survival by Karnofsky Performance Status (KPS). For KPS of 70–100 (ambulatory patients) survival at one year is approximately 3 times the survival for KPS of 40–60 (non-ambulatory patients).

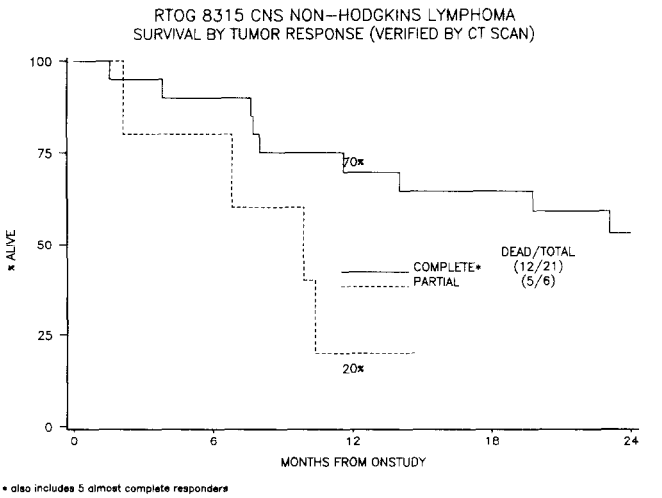

Fig. 5. Survival by CT scan tumor response. There is a dramatic difference in survival at one year for complete responders compared with partial responders, i.e., 70% versus 20%. Complete tumor response is measured by CT scan response and zero or decreased Decadron dose.

disease free for over 5 years (at 61.5 months and 65.8 months) and one at 8.8 months before being lost to follow-up. Three additional patients were disease free when they died of intercurrent disease at 1.5, 3.8 and 19.8 months, and two patients had local control in the brain but died of distant disease at 7.7 and 22 months. Five out of 16 CR experienced in field recurrences (including one associated with distant metastases and one associated with a simultaneous marginal recurrence). An additional patient had a marginal recurrence where the 80% isodose cut across gross tumor. Only one patient developed new contralateral disease that happened to occur in the volume that received 60 Gy.

Histology

Based upon central pathology review, the distribution of cases by the Rappaport classification, Working Formulation, and Luke's classification is given in Table 4. Plasmacytoid differentiation appeared to be associated with a worse survival. In the Rappaport classification patients with histiocytic lymphoma with plasmacytoid differentiation had a median survival of 7.6 months com-

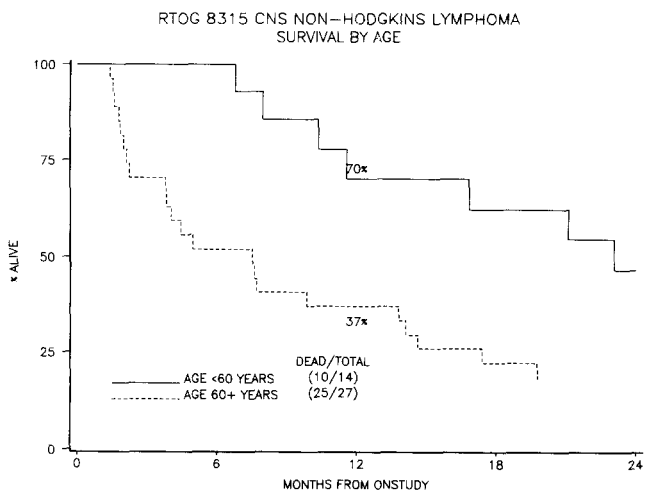

Fig. 4. Survival by age. Survival of patients under 60 years is approximately twice the survival of patients 60 years or older.

Table 4. Distribution of cases by pathologic classification

	No. pts.	Percent
(A) Rappaport classification		
Histiocytic	37	90
Without plasmacytoid differentiation	26	63
With plasmacytoid differentiation	11	27
Poorly differentiated lymphocytic	2	5
Undifferentiated large cell	1	2
Lymphoblastic	1	2
(B) Lukes classification		
Small cell cleaved	2	5
Large cell cleaved & non-cleaved	23	56
Without plasmacytoid differentiation	18	44
With plasmacytoid differentiation	5	12
Large cell cleaved	4	10
Large cell non-cleaved	9	22
Without plasmacytoid differentiation	5	12
With plasmacytoid differentiation	4	10
Undifferentiated	1	2
Immunoblastic	2	5
(C) Working formulation		
Intermediate grade:		
Small cell cleaved	2	5
Large cell cleaved & non-cleaved	23	56
Without plasmacytoid differentiation	19	46
With plasmacytoid differentiation	4	10
Large cell cleaved	3	7
Large cell non-cleaved	10	24
Without plasmacytoid differentiation	5	12
With plasmacytoid differentiation	5	12
High grade:		
Undifferentiated	1	3
Large cell immunoblastic	2	5

pared to 11.0 months for patients without plasmacytoid differentiation. This difference was not statistically significant because of small patient numbers. The trend of shorter survival with plasmacytoid differentiation also was observed in the Working Formulation, but again the numbers were too small to be significant. The preponderance of intermediate grade types, the presence of only two cases (5%) of immunoblastic histology, and only one case (3%) of undifferentiated histology confirm the absence of AIDS cases.

Eighteen patients had B and T cell immunophenotyping on paraffin embedded sections performed at the referring institutions. Four out of 18 (22%) were B cell positive: three large cell cleaved and noncleaved, and one large cell. All were aged 74–79 years, and all died of persistent/progressive disease within 2–5 months of diagnosis. Two out of 18 (11%) were T cell: one large cell cleaved and non-cleaved and one large cell non-cleaved. They were 67 and 79 years old. One died of intercurrent disease at 2 months and one is alive at 29 months. Twelve patients who tested negative for both B and T cell antigens survived 11.9 months (range of 1.8–30.5 months).

Skin testing with PPD, mumps and DNCB was done in 20 patients. Four patients (20%) had at least one skin test positive and were therefore not anergic. Although these patients had a more prolonged survival of 6.8–97.2 months (median of 20.5 months), they all recurred in the brain and two also recurred distantly. All patients tested, except for one anergic patient, were on Decadron (or some other steroid) at the time of skin testing.

Site of failure

Local failure at the site of original disease remains the predominant site of failure (see last series in Table 5). Twenty-one out of 41 (51%) of the patients failed in the brain alone, plus 4/41 (10%) failed in the brain with distant metastases (two spinal cord, one testes, one bone marrow) for a total of 25/41 (61%) failure rate in the brain. Only 3/41 (7%) failed with distant metastases alone (one spinal cord, one liver and abdominal nodes, one eye). The total number of spinal cord failures was three (7%). Two out of three failed with intramedullary disease instead of epidural disease. Brain failures occurred solely within the original tumor volume within the treatment field with four exceptions: (1) new disease developed in the contralateral hemisphere within the treatment portal, (2) a mar-

Table 5. Patterns of failure in primary CNS lymphoma

Author	No. pts.	Number of failures				CSF/Sp. cord alone
		Total	Local	Non-CNS:	Location	
Henry *et al.* (12)	83	83	83	6	Adrenal, kidney, bowel, testicle, lymph nodes	—
Mendenhall *et al.* (22)	11*	6	6	0		—
Berry and Simpson (1)	21	16	≤16	2	Multiple organs + spinal cord; testicle, kidney + lung	—
Gonzalez *et al.* (11)	15	12	11	1	Outside CNS	CSF[†] 1
Letendre *et al.* (18)	16[‡]	7	≤7	0		Presumed sp. cd. 1
Littman and Wang (19)	18[§]	15	≤14	2	Lung, heart + spinal cord, (-brain); breast	
Freeman *et al.* (9)	19	17	17	0		3 CSF or meninges
Murray *et al.* (24)	10**	6	3	1	Bone	2 CSF
Sagerman *et al.* (29)	12	11	11	2	Hepatic; C_2 by direct extension + vitreous involvement	0
Rampen *et al.* (27)	8[††]	8	8	0		1 sp. cd.
This series	41	28	25	4	Testes; liver + abdominal nodes; eye; bone marrow	3 sp. cd.
Totals	254	209	201	18 (7%)	+	11 (4%)
						= 11% total distant failure rate

* Excluded 1 pt. who presented with meningineal involvement only without a parenchymal lesion identified on CT scan who failed with involvement of meninges, spinal roots, organs and brain.

† 3 pts. had a positive CSF cytology on study and 3 developed positive cytology but these were not reported as sites of relapse except in 1 case.

‡ Excluded 1 pt. who presented with lymphomatous meningitis.

§ Excluded 1 pt. who had an orchiectomy for lymphoma at time of brain surgery.

** Excluded 1 pt. who developed positive CSF during treatment.

†† Excludes 4 pts. with positive CNS on study, none of whom developed dissemination outside of the CNS and only one who failed in the spinal cord, and 3 of whom failed in the brain.

ginal miss occurred simultaneously with an infield recurrence, and (3) two cases of a marginal miss, that is recurrent disease at the edge of the treatment field in the region of low dose. Local control remains the challenge in non-Hodgkin's lymphoma of the brain.

Toxicity

There were three cases of severe toxicity: (1) A grade 4 skin toxicity, a wound infection with a subsequent ulceration that required debridement and skin grafting; (2) A CNS toxicity after methotrexate delivered by an Ommaya reservoir: CT scans demonstrated an absence of tumor yet presence of bilateral encephalomalacia around the catheter and in the region of the primary tumor surgery; (3) A probable toxicity in a 56-year-old woman with necrosis that may have been related to underlying brain pathology and/or lymphoma. She had had a "brain abscess" in the right frontal lobe 3 years prior to entry onto study. This "brain abscess" might have been a focus of lymphoma that could not be diagnosed. After treatment for lymphoma she deteriorated neurologically despite a stable CT scan and was in coma during her last 13.8 months. Autopsy revealed radiation effect in the corpus callosum, necrosis, and recurrent lymphoma.

There are three possible CNS toxicities that may have simply been independent events: (1) A subdural hematoma and diffuse leukoencephalopathy with an MRI scan negative for tumor seven months after radiation therapy in a 67-year-old man. A possible contributing factor to the leukoencephalopathy was that he was not on Decadron during radiation therapy until near the end of radiation therapy when he developed symptoms requiring initiation of Decadron. (2) A TIA and organic brain syndrome with dementia 3 years after radiation therapy in a 70-year-old man. (3) A stroke one and a half years after radiation therapy, with a CT scan negative for tumor 6 weeks prior, in a 71-year-old man. There were four (10%) elderly patients (ages 60–79, median 74) who died of infection without evidence of lymphoma: herpes encephalitis, cholestatic hepatitis and sepsis, sepsis, and pneumococcal pneumonia. None of them had received chemotherapy.

DISCUSSION

Survival after radiation therapy

Aggressive irradiation that treated the whole brain and meninges plus a boost to gross disease to 60 Gy only resulted in a median survival of 11.6 months from start of radiotherapy and 12.2 months from diagnosis. This is no different than that reported in the literature (see Table 6), where the median survival from diagnosis ranges between 11.5 and 42 months with a median of 17 months, with doses of 40–55 Gy to the whole brain and/or tumor, with some patients receiving tumor boosts to total doses of 55–60 Gy. The median age of most series (19, 20, 22, 24, 27, 29, 30) was about 10 or 11 years younger than the median age of our population of 66 years, with the exception of the Freeman and Gonzales series (9, 28) where it was 5–7 years younger. Two-thirds of our patients were over the age of 60. Although the older age, with its associated worse prognosis, may have masked a modest increase in survival, the use of larger fields that encompassed all gross disease plus the use of 60 Gy should have improved survival or at least local control to 80–90% or better based upon local control rates and dose response data from non-Hodgkin's lymphoma outside of the CNS (2, 3, 10). Unfortunately the survival of patients with primary non-Hodgkin's lymphoma of the brain is no better than the survival of patients with malignant glioma (25, 26).

Local control

Despite a total tumor dose of 60 Gy, local control still remains the challenge of non-Hodgkin's lymphoma. The

Table 6. Literature review of survival rates and associated ages

Author	Year	No. pts.	(No.) 60+ yrs.	Age in years Range (median)	Survival in mos.* Range (Median)
Littman *et al.* (19)	1975	19	(8)	43–68 (55)	2–120 (42)
Rampen *et al.* (27)	1980	12	(3)	31–71 (55)	3–41 (14)
With 4 CSF + patients eliminated		8	(3)	37–71 (55)	3–41 (11.5)
Letendre (18)	1982	17	—	—	2–91 (24)
Mendenhall *et al.* (22)	1983	9	(3)	17–70 (55)	0.5–48 (12)
Gonzalez *et al.* (11)	1983	15	(7)	46–74 (59)	3–54 (21)
Sagerman *et al.* (29)	1983	12	(5)	15–81 (55)	0–188 (18)
Loeffler *et al.* (20)	1985	10	(3)	10–71 (50)	2–97 (15)
Freeman *et al.* (9)	1986	11	(3)	38–77 (61)	3–56 (20)
Murray *et al.* (24)	1986	10	(2)	34–65 (49)	5–120 (18)
Shibamato *et al.* (30)	1990	30	(13)	11–78 (57)	1–188 (14)
This series		41	(27)	20–79 (66)	1–67 (11.6)†

* Survival in most series is from date of diagnosis whereas survival in the present series is from the start of radiation therapy. The interval between date of diagnosis and start of radiation therapy ranged from 7 to 41 days with a median of 19.4 days (.64 months).

† 11.6 months from start of radiotherapy and 12.2 months from date of diagnosis.

total distant failure rate outside of the brain was only 17% which compares to 10% for other series reported in the literature (see Table 6). To put it in a different perspective, out of 28 failures, 25 (89%) failed locally and 21 (74%) had only local failure. A total of seven (25%) had distant metastases, although only three (11%) of the failures were due only to distant metastases. Thus, local control is clearly the major factor that needs to be improved. In our study, 22 out of the 25 local recurrences (88%) occurred within the 60 Gy region. There was marginal miss by the conedown field in three out of 25 local recurrences (12%). Unfortunately, doses higher than 60 Gy, when delivered by conventional fractionation, carry an unacceptable risk of brain necrosis.

Radiation response by CT scan

The dramatic CT scan response of a CR in 62% and almost a CR in 19% is in marked contrast to the minimal, if any, response demonstrated by malignant gliomas where complete response to radiation therapy is a very rare occurrence (personal observation based on over 500 cases reviewed by DFN). Unfortunately, the dramatically improved CT scan response does not translate into improved long term control or survival. Even when the CT scan showed total clearance of tumor, or almost complete tumor clearance with only a small focus of contrast enhancement remaining (that might have totally disappeared in 4–6 weeks had a CT scan been repeated at that short interval), the median survival was only 19.8 and 24.2 months respectively. Autopsies have demonstrated the presence of CNS lymphoma not demonstrated by CT scan.

Apparent radiation resistance

The important question remains, "Why is non-Hodgkin's lymphoma in the brain so resistant to radiation therapy, when non-Hodgkin's lymphoma in other locations is locally controlled 80–90% of the time by 30–40 Gy?" Even with diffuse histiocytic lymphoma outside of the brain, 40 Gy affords an 80% local control rate (2, 3, 10). Does the micro-environment of the brain alter the radiosensitivity? Or does the blood brain barrier and lack of lymphatic access prevent the body's immune system from destroying the remaining lymphoma cells after irradiation?, as lymphoma cells remaining after radiotherapy in non-CNS parts of the body are presumably destroyed by the body's immune system. Or, is the immune system of patients with CNS lymphoma simply less effective in mounting an immune response than the immune system of other lymphoma patients? Or does the irradiated brain produce growth factors that stimulate CNS lymphoma regrowth?

A more answerable question is whether survival and local control of primary CNS non-Hodgkin's lymphoma can be increased by combining chemotherapy with high dose radiation therapy or by using hyperfractionation (treatment twice daily with smaller individual doses) to increase the total radiation dose. Prospective studies will be needed as it is impossible to draw conclusions about therapy from the non-randomized small series that exist in the literature. This is because the prognostic variables of age and KPS to date have affected outcome more than therapy. There is a small series by Shibamoto *et al.* (30) that raises some hope. In this study, 30–42 Gy (median 31 Gy) whole brain irradiation plus a 18–30 Gy boost to a total tumor dose of 49–61 Gy (median 52.5 Gy), was followed by 4–6 courses of vincristine, doxorubicin, cyclophosphamide and prednisone (VEPA). Eight out of 10 patients completing therapy survived 16–100 months with three out of ten alive and free of disease (NED) at 64+, 70+ and 100+ months. There was, however, significant mortality [brain necrosis (1) and pneumonia (1)] and morbidity [brain necrosis requiring surgery (1) and severe neurological deterioration (2)].

The high toxicity reported by Shibamoto is probably in part due to the sequencing of high dose radiation therapy and multiagent chemotherapy. Radiation therapy does alter the blood brain barrier. The most documented drug x-ray interaction in the brain is with methotrexate. Methotrexate given intravenously or by Ommaya reservoir after radiation therapy has greater toxicity than when it is given before radiotherapy. If one includes those patients entered on protocol but who were ineligible or not evaluable on central pathology review, then there is another case of leukoencephalopathy in a 28-year-old man who received intrathecal methotrexate without evidence of progression. Thus, two out of three patients given methotrexate soon after, or with, radiation developed leukoencephalopathy, and the patient who did not develop leukoencephalopathy had had his total radiation dose modified down to 54 Gy.

Presently the RTOG is conducting a prospective phase II trial (RTOG 8806) to evaluate pre-irradiation CHOD chemotherapy for three cycles (Cyclophosphamide 750 mg/m^2 i.v. day 1, Adriamycin 50 mg/m^2 i.v. day 1, Vincristine 1.4 mg/m^2 i.v. day 1 and dexamethasone 6 mg/m^2 po days 1–5, repeated every 21 days. The total radiation dose is unchanged at 59.40 Gy. Ultimately a phase III randomized intergroup study is needed to answer the question of how best to combine chemotherapy and radiotherapy.

REFERENCES

1. Berry, M. P.; Simpson, W. J. Radiation therapy in the management of primary malignant lymphoma of the brain. Int. J. Radiat. Oncol. Biol. Phys. 7: 755–759; 1981.

2. Bush, R. S.; Gospodarowicz, M. The place of radiation therapy in the management of patients with localized non-Hodgkin's lymphoma. Rosen, S. A., Kaplan, H. S., eds. In:

Malignant lymphomas. Orlando: Academic Press; 1982: 485–502.
3. Bush, R. S.; Gospodarowicz, M.; Sturgeon, J.; Alison, R. Radiation therapy of localized non-Hodgkin's lymphoma. Cancer Treat. Rep. 61: 1129–1136; 1977.
4. Chen, M. G.; Proznitz, L. R.; Gonzalez-Serva, A.; Fischer, D. B. Results of radiotherapy in control of stage I and II non-Hodgkin's lymphoma. Cancer 43: 1245–1254; 1979.
5. Cox, D. R. Regression models and life tables. J. Royal Stat. Soc. 30: 187–220; 1972.
6. Edgar, R.; Dutcher, T. F. Histopathology of the Bing-Neel syndrome. Neurology 11: 239–245; 1961.
7. Fraser, R. W.; Chism, S. E.; Stern, R.; Fu, K. K.; Buschke, F. Clinical course of early extranodal non-Hodgkin's lymphomas. Int. J. Radiat. Oncol. Biol. Phys. 11: 177–183; 1985.
8. Freeman, C.; Berry, J. W.; Cutler, S. J. Occurrence and prognosis of extranodal lymphomas. Cancer 29: 252–260; 1972.
9. Freeman, C. R.; Shustik, C.; Brisson, M. Primary lymphomas of the central nervous system. Cancer 58: 1106–1111; 1986.
10. Fuks, Z.; Kaplan, H. S. Recurrence rates following radiation therapy of nodular and diffuse malignant lymphomas. Radiology 108: 675–684; 1973.
11. Gonzalez, D. G.; Schuster-Utterhoeve, L. J. Primary non-Hodgkin's lymphoma of the central nervous system. Cancer 51: 2048–2052; 1983.
12. Henry, J. M.; Heffner, R. R.; Dillard, S. H.; Earle, R. M.; Davis, R. L. Primary malignant lymphomas of the central nervous system. Cancer 34: 1293–1302; 1974.
13. Hoover, R.; Fraumeni, J. F. Risk of cancer in renal-transplant recipients. Lancet 2: 55–57; 1973.
14. Horiuchi, J.; Okuyama, T.; Matsubara, S.; Shibuya, H.; Suzuki, S.; Kamiyama, R. Extranodal non-Hodgkin's lymphoma in the head and neck. Irradiation and clinical course. Acta Radiol. Oncol. 21: 393–399; 1982.
15. Jacobs, C.; Hoppe, R. T. Non-Hodgkin's lymphomas of head and neck extranodal sites. Int. J. Radiat. Oncol. Biol. Phys. 11: 357–364; 1985.
16. Jellinger, K.; Radaskiewicz, R. H.; Slowik, F. Primary malignant lymphomas of the central nervous system in man. Acta Neuropathol. (Berlin) 6(Suppl.): 95–102; 1975.
17. Kaplan, E. L.; Meier, P. Non-parametric estimations from incomplete observations. J. Am. Stat. Assoc. 53: 457–481; 1958.
18. Letendre, L.; Banks, P. M.; Reese, D. F.; Miller, R. H.; Scanlon, P. W.; Kiely, J. M. Primary lymphoma of the central nervous system. Cancer 49: 939–943, 1982.
19. Littman, P.; Wang, C. C. Reticulum cell sarcoma of the brain. A review of the literature and a study of 19 cases. Cancer 35: 1412–1420; 1975.
20. Loeffler, J. S.; Ervin, T. J.; Mauch, P. Primary lymphomas of the central nervous system: Patterns of failure and factors that influence survival. J. Clin. Oncol. 3: 490–494; 1985.
21. Mantel, N. Evaluation of survival data and two new rank order statistics arising in its considerations. Cancer Chemother. Rep. 50: 187–220; 1972.
22. Mendenhall, N. P.; Thar, T. L.; Agrr, O. F. Primary lymphoma of the central nervous system. Cancer 52: 1993–2000; 1983.
23. Mill, W. B.; Lee, F. A.; Franssila, K. O. Radiation therapy treatment of stage I and II extranodal non-Hodgkin's lymphoma of the head and neck. Cancer 45: 653–661; 1980.
24. Murray, K.; Kun, L.; Cox, J. Primary malignant lymphoma of the central nervous system. J. Neurosurg. 65: 600–607; 1986.
25. Nelson, D. F.; Diener-West, M.; Horton, J.; Chang, C. H.; Shoenfeld, D.; Nelson, J. S. Combined modality approach to treatment of malignant gliomas. Reevaluation of RTOG 7401/ECOG 1374 with long-term follow-up: A joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study. NCI Monog. 6: 279–284; 1988.
26. Nelson, D. F.; Diener-West, M.; Weinstein, A. S.; Schoenfeld, D.; Nelson, J. S.; Sause, W. T.; Chang, C. H.; Goodman, R.; Carabell, S. A randomized comparison of misonidazole sensitized radiotherapy plus BCNU and radiotherapy plus BCNU for treatment of malignant glioma after surgery: Final report of an RTOG study. Int. J. Radiat. Oncol. Biol. Phys. 12: 1793–1800; 1986.
27. Rampen, F. H. J.; van Andel, J. G.; Sizoo, W.; van Unnik, J. A. M. Radiation therapy in primary non-Hodgkin's lymphomas of the CNS. Eur. J. Cancer 16: 177–184; 1980.
28. Rubinstein, L. J. Tumors of the central nervous system. Atlas of tumor pathology, 2nd series, okate 6. Washington, DC: Armed Forces Institute of Pathology; 1972.
29. Sagerman, R. H.; Collier, C. H.; King, G. A. Radiation therapy of microgliomas. Radiology 149: 567–570; 1983.
30. Shibamoto, Y.; Tsutsui, K.; Dodo, Y.; Yamabe, H.; Shima, N.; Abe, M. Improved survival rate of primary intracranial lymphoma treated by high dose radiation and systemic vincrstine-doxorubicin-syclophosphamide-prednisolone chemotherapy. Cancer 65: 1907–1912; 1990.
31. Shirato, H.; Tsujii, H.; Arimoto, T.; Miiyamoto, M.; Azumi, N.; Nojima, T.; Watanabe, S.; Ilie, G. Early stage head and neck non-Hodgkin's lymphoma. The effect of tumor burden on prognosis. Cancer 58: 2312–2319; 1986.
32. Teshima, T.; Chatani, M.; Hata, K.; Inoue, T.; Miyahara, H.; Sato, T.; Shibata, H.; Kusakabe, H.; Tateishi, R.; Suzuki, T. Radiation therapy for primary non-Hodgkin's lymphoma of the head and neck in stage I-II. Strahlenther. Onkol. 162: 478–483; 1986.
33. Wulfrank, D.; Speelman, T.; Pauwels, C.; Roels, H.; DeSchryver, A. Extranodal non-Hodgkin's lymphoma of the head and neck. Radiother. Oncol. 8: 199–207; 1987.

APPENDIX

RTOG 8315 participating institutions

New York University, Halifax Hospital Medical Center, LDS Hospital, Medical College of Wisconsin, Tom Baker Cancer Center, University of Alberta, Allegheny General Hospital, SUNY Health Science Center at Brooklyn, Thomas Jefferson University Hospital, Lutheran Medical Center, Marshfield Clinic, Washington University School of Medicine, Rhode Island Hospital, Baptist Hospital of Miami, University of California/San Francisco, Columbia Presbyterian Medical Center, Dartmouth Hitchcock Medical Center, Hahnemann University, Kansas City Clinical Oncology Center, Montefiore Medical Center, and Sutter Community Hospital.