INT 0143

RADIATION THERAPY ONCOLOGY GROUP

RTOG 93-10

AN INTERGROUP PHASE II COMBINED MODALITY TREATMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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SCHEMA

R All patients will receive Methotrexate, Procarbazine, Vincristine and intra-Ommaya **E**
Methotrexate, over 10 weeks followed by whole brain irradiation *(Section 6.1.2)*

G *a) Patients with residual tumor will receive 1.8 Gy once a day, five days a week for*
I *25 fractions over five weeks to 45 Gy commencing week 11).*
S
T *b) Patients with **no** residual tumor will receive 1.2 Gy b.i.d., at least 6 hours apart,*
E *five days a week for 30 fractions over 3 weeks to 36 Gy.*
R

Within three weeks after the completion of RT, patients will receive two courses of ara-C, separated by 3-4 weeks *(each course is two doses separated by 24 hours).*

TREATMENT FLOW SHEET *(refer to Section 7.0 for details)*

Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Methotrexate i.v. 2.5 gm/m^2	X		X		X		X		X										
Vincristine i.v. 1.4 mg/m^2	X		X		X		X		X										
Procarbazine p.o. 100 mg/m^2,d x 7	X				X				X										
Methotrexate IO 12 mg		X		X		X		X		X									
Leucovorin 20 mg p.o. q 6 hr x 12 doses	X		X		X		X		X										
Leucovorin 10 mg p.o. b.i.d x 8 doses		X		X		X		X		X									
Decadron --mg/d x 7	16	12	8	6	4	2													
Bactrim ^{DS} 1 tablet b.i.d x 3 days	X	X	X	X	X	X	X	X	X	X									
Clotrimazole troche 1 tablet 5 x day	X	X	X	X	X	X	X	X	X	X									
Radiation therapy											X	X	X	X	X				
Ara-C 3 gm/m^2/d																X			X

Eligibility: *(See Section 3.0 for details)*

- Histologic proof of non-Hodgkin's lymphoma by brain biopsy
- HIV-1 negative
- Bone marrow function defined as absolute neutrophil count ≥ 2000 cells/mm^3 and platelet count ≥ 100,000 cells/mm^3, liver function *(bilirubin £ 2.0 and SGOT £ 2 times upper limit of normal),*
- Adequate renal function *(creatinine clearance ³ 50)* and normal serum electrolytes
- Life expectancy of at least 8 weeks
- Karnofsky Performance Status *(KPS)* ≥ 50
- No active malignancies except basal cell carcinoma of the skin or cervical carcinoma *in situ*
- Signed study-specific informed consent form
- No prior chemotherapy or cranial irradiation
- Registration must take place within 4 weeks of histologic diagnosis.

Required Sample Size: 28 + 40 (revision #3) **6/30/95, 10/1/96**

RTOG Institution # _____

RTOG 93-10 (SWOG 9310) **ELIGIBILITY CHECK**

RTOG Case # _____

SWOG Case # _____

_____(Y/N) 1. Histologic proof of non-Hodgkin's lymphoma by brain biopsy? *(If yes, skip to Q3)*

_____(Y) 2. Has leptomeningeal nonparenchymal lymphoma been ruled out as specified in Section 3.1.1 of the protocol?

_____(Y) 3. Has it been 4 weeks or less since histologic diagnosis?

_____(Y) 4. Has the patient had a negative pre-treatment systemic evaluation as specified in the protocol to exclude an extra-cerebral source of lymphoma?

_____(N) 5. Any prior chemotherapy or cranial irradiation?

_____(≥ 2) 6. Report absolute neutrophil count *(x 1000)*.

_____(≥100) 7. Report the platelets *(x 1000)*.

_____(≤ 2) 8. Report the bilirubin *(mg %)*.

_____(Y) 9. Is the SGOT ≤ 2 times the upper limit of normal?

_____(Y) 10. Is the creatinine clearance at least 50 cc/min/ 1.73 m^2?

_____(Y) 11. Are serum electrolytes normal?

_____(≥ 50) 12. Report the KPS.

_____(Y) 13. Is the patient HIV-1 negative?

_____(N) 14. Any pre-existing immunodeficency such as renal transplant recipient?

_____(Y) 15. Life expectancy at least 8 weeks?

_____(N) 16. Is there a concurrent malignancy other than basal cell carcinoma *in situ*?

_____(Y) 17. Has the patient signed a study-specific informed consent form?

_____	Patient's Name	_____	Sex
_____	Verifying Physician	_____	Race
_____	Patient ID #	_____	Social Security Number
_____	Referring Institution	_____	Zip Code *(9-digit if available)*
_____	Medical Oncologist	_____	Method of Payment
_____	Birthdate	_____	Treatment Start Date
		_____	Treatment Assignment

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Primary central nervous system lymphoma *(PCNSL)* is a rare neoplasm but one that is being seen with increasing frequency even in immunocompetent patients.[1] Retrospective studies establish that conventional treatment utilizing corticosteroids to control neurologic symptoms and cranial radiotherapy gives a median survival of 10-18 months with a 3-4% 5-year survival.[2-5] These data were confirmed by a prospective study completed by the Radiation Therapy Oncology Group *(RTOG)*.[6] Although most patients experience a complete response with radiation, the majority of patients relapse in the brain and/or leptomeninges, usually within the first 1-2 years after treatment. Once relapse has occurred, palliation with chemotherapy is short-lived.[7]

1.2 Several years ago, 32 non-AIDS patients with PCNSL were prospectively staged and treated at Memorial Sloan-Kettering Cancer Center *(MSKCC)*. At the time of diagnosis, no patient was found to have evidence of systemic lymphoma; however, five *(19%)* had evidence of ocular lymphoma, a frequent association with PCNSL, presumably as a direct extension of the disease from the brain or as another site of this multicentric neoplasm. 69% had definite *(defined as a positive CSF cytology)* or probable *(defined as a suspicious cytology)* leptomeningeal infiltration at diagnosis, and all patients had tumors abutting a ventricular surface.[8]

1.3 Autopsy reveals leptomeningeal tumor in all cases at the time of parenchymal brain relapse; the leptomeningeal involvement may be widespread *(disseminated throughout the CSF)* or localized *(focal involvement of the meninges overlying a site of parenchymal brain* lymphoma)[9]. Because cranial RT is only palliative for the vast majority of patients and chemotherapy appears to be useful in some patients with recurrent PCNSL, chemotherapy was added to cranial RT as initial therapy for non-AIDS PCNSL to see if prolonged remission and enhanced survival could be achieved. At MSKCC, patients were treated with pre-RT intravenous methotrexate *(MTX 1 gm/*m^2) combined with intra-Ommaya *(IO)* MTX. All MTX was completed prior to the initiation of RT and followed by whole brain RT *(WBRT) (40 Gy)* with a 14.4 Gy boost. RT was followed by two courses of high-dose ARA-C with each course consisting of two doses of 3 gm/m^2/dose separated by 24 hours. This regimen was completed by 31 patients and their response was compared to 16 additional patients treated simultaneously WBRT alone. Although this was not a randomized study, patients who received combined modality therapy had a median time to recurrence of 41 months compared to a median of 10 months for those treated with RT alone *(p=0.003)*. Subsequent data analysis with longer follow-up reveals the median time to recurrence of patients treated with chemotherapy plus RT is 52 months. Although median survival was doubled from 21 to 42 months, this was not statistically significant in part because of small patient numbers and the additional treatment administered at the time of recurrence. These data demonstrate the chemosensitivity of PCNSL to systemic agents and strongly suggest that combined modality therapy improves survival over conventional RT alone.[10]

1.4 Alternative approaches have included the use of blood-brain barrier disruption followed by intra-arterial MTX, cyclophosphamide, procarbazine and dexamethasone.[11] The goal was to treat patients using chemotherapy alone, and to reserve cranial RT for progressive or unresponsive disease. Sixteeen patients received this regimen as initial therapy and were evaluable. The median survival was 44.5 months, clearly superior to RT alone; however, ten patients relapsed and nine received cranial RT. The time to relapse was not reported.

1.5 Additional chemotherapy regimens have also demonstrated improved survival; however the adoption of standard combination chemotherapy regimens successfully used in the treatment of comparable systemic non-Hodgkin's lymphomas have not proved effective.[12-15] The inability to sustain a response from these regimens can be attributed to their inability to penetrate the intact blood-brain barrier, an important factor in this disease. While the blood-brain barrier is abnormally permeable in regions of bulk disease, it is intact in areas of microscopic tumors which may not even be evident on MR scan and is responsible for relapses which occur in areas remote from the original site of tumor, the typical pattern of PCNSL recurrence.[16]

1.6 Despite the addition of chemotherapy to RT, relapses continued to be observed in the brain, eyes and meninges. Sustained remissions from systemic non-Hodgkin's lymphoma can be attributed to vigorous combination chemotherapy regimens which are employed in disseminated lymphoma and often added to

focal RT in Stage I and II disease.[17-18] Although confined to a single extranodal site at presentation *(Stage I^E)*, PCNSL is usually disseminated within the nervous system at diagnosis, necessitating a similar vigorous approach to initial treatment for eradication of all disease. For this reason, we have designed a pre-radiotherapy combination chemotherapy regimen to further identify potentially useful systemic agents in the treatment of this brain tumor, and to incorporate the successful practices established in the therapy of systemic lymphoma. Furthermore, this will be the first attempt to replicate promising single institutional experiences across multiple institutions. Our preliminary experience using a comparable regimen in nine patients treated at Memorial Sloan-Kettering demonstrate that it is safe to administer. Two patients had toxic MTX levels at 72 hours and required hydration, leucovorin and bicarbonate for an additional few days. Neither developed clinical toxicity and both were successfully re-treated with MTX. All nine patients have had a complete response to treatment, eight achieving CR after chemotherapy prior to beginning cranial irradiation. All are alive for a median survival of seven months *(range: 4-16 months)* and none have relapsed. Two patients had developed delayed cognitive impairment. These initial data are promising and suggest the regimen is reasonably well tolerated and easy to administer.

1.7 After treatment with chemotherapy and RT, most PCNSL patients have a complete radiographic response with disappearance of all enhancing lesions on CT/MR scan. However, some patients have tiny persistent foci of enhancement with a > 90% reduction in their tumor mass. These foci may persist for many months, even years, occasionally resolving over time and never effecting neurologic symptoms *(unpublished observations)*. The significance of these radiographic abnormalities is unclear and they likely do not represent persistent active disease. This situation may be analogous to patients with systemic lymphoma who have persistent adenopathy *(particularly in the mediastinum)* after treatment which represents fibrosis but not residual disease. To distinguish these "incomplete responses" from those patients with a true partial response *(ie: persistent disease but a 50% reduction in the size of their tumor mass)*, we will classify them into two separate categories: major partial response and minor partial response. This will afford the opportunity to analyze whether or not this is an important or accurate distinction, and enable an understanding of the significance of these punctate residual enhancing areas.

2.0 OBJECTIVES

2.1 To assess the rate of tumor response to combination chemotherapy prior to the start of radiation.

2.2 To compare survival using a combined modality approach to historical controls using radiotherapy alone.

2.3 To assess the long-term toxicity of this regimen.

2.4 Based upon the response rate and survival of patients enrolled in this study, to consider a randomized trial to compare chemotherapy alone versus chemotherapy plus radiation in an effort to reduce the morbidity of cranial irradiation.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologic proof of non-Hodgkin's lymphoma by brain biopsy. Those rare patients who have an inconclusive biopsy or who are not candidates for biopsy may be eligible provided they have a typical cranial CT or MR scan to ensure that leptomeningeal nonparenchymal lymphomas are not included *(and meet at least one of the following two criteria)*:
Radiographic criteria are defined as the presence of hypo,-iso,-or hyperdense parenchymal contrast-enhancing *(usually homogeneously)* mass lesions(s).

3.1.1.1 A positive CSF cytology for lymphoma or a monoclonal lymphocyte population as defined by cell surface markers or gene rearrangement.

3.1.1.2 Biopsy of the vitreous or uvea demonstrating non-Hodgkin's lymphoma if ophthalmological examination reveals cells in the posterior chamber or vitreous.

3.1.2 Patients must be registered within 4 weeks of histologic diagnosis.

3.1.3 Bone marrow: defined as absolute neutrophil count ≥ 2000 cells/mm^3 and platelet count ≥ 100,000 cells/mm^3.

3.1.4 Liver: bilirubin ≤ 2.0mg% and SGOT ≤ 2 times upper limit of normal.

3.1.5 Renal: creatinine clearance ≥ 50cc/min/1.73 m^2 and normal serum electrolytes.

3.1.6 Patients must have a life expectancy of at least 8 weeks.

3.1.7 KPS ≥ 50.

3.1.8 Patient must be HIV-1 negative.

3.1.9 Patient must sign a study-specific informed consent form.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior cranial irradiation.

3.2.2 Concurrent malignancies excluding basal cell carcinoma of the skin or cervical carcinoma *in situ*. Patients with a remote *(³ 5 years)* history of a malignancy are eligible provided they meet all other eligibility requirements.

3.2.3 Pre-existing immunodeficiency such as renal transplant recipient.

3.2.4 Prior treatment with chemotherapy.

3.2.5 KPS < 50.

3.2.6 Absolute neutrophil count < 2000 cells/mm^3, platelet count < 100,000 cells/mm^3, bilirubin > 2.0 mg% SGOT > 2 times upper limit of normal, creatinine clearance < 50 cc/min/1.73 m^2 and abnormal serum electrolytes.

3.2.7 Pregnant or nursing women.

4.0 PRETREATMENT EVALUATION

4.1 Pre-registration

4.1.1 A complete history and physical, including a neurological examination and Karnofsky Performance Status will be performed.

4.1.2 Hematopoietic: HGB, WBC, differential and platelet count.

4.1.3 Biochemical: Liver function tests including bilirubin, SGOT, alkaline phosphatase, LDH, BUN, electrolytes, creatinine, creatinine clearance, serum glucose.

4.1.4 Chest x-ray, PA and lateral.

4.1.5 Pregnancy test for women in the childbearing years.

4.1.6 Cranial MR or CT scan without and with intravenous contrast.

4.1.7 HIV-I serology will be required of all patients.

4.1.8 Prior to entry histologic confirmation of the diagnosis is necessary.

4.1.9 If a cerebral biopsy can not be performed or pathologic material is inconclusive and the patient has evidence of uveitis or vitreal inflammation on slit-lamp examination, then a vitreous or uveal biopsy will be performed.

4.2 Pre-treatment

4.2.1 Lumbar puncture with CSF examination for glucose, protein, cells, cytology by cytopsin prep, gamma-globulins, oligoclonal bands, immunoelectrophoresis, and lymphocyte markers. At the time of the first intra-Ommaya MTX administration, CSF should be sent for the same analysis listed above. CSF from the Ommaya will not substitute for a spinal tap; however, in patients with a large posterior fossa mass, a lumbar puncture may not be safe and would not be required.

4.2.2 Complete ophthalmologic examination, including a slit-lamp examination.

4.2.3 A mini-mental status examination will be performed.

4.2.4 *All patients will have an Ommaya reservoir*. The reservoir can be placed during the same operative procedure as the diagnostic biopsy if confirmation of lymphoma is possible on a frozen section. If this cannot be accomplished, the reservoir will be placed during a second procedure.

5.0 REGISTRATION PROCEDURES

5.1 RTOG Institutions

5.1.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Demographic Data
- Treatment Start Date

5.2 SWOG Institutions

5.2.1 Investigators will call the Southwest Oncology Group Statistical Center at 206/667-4623 between the hours of 6:30 a.m. and 1:30 p.m. *(PT)* Monday through Friday, excluding holidays. This must be done in order for the Southwest Oncology Group Statistical Center to complete the registration with RTOG prior to the close of business. The Statistical Center will obtain and confirm all eligibility criteria and information as per Section 5.1, RTOG Registration. In addition, the Statistical Center will request the date informed consent was obtained and the date of IRB approval for each entry. The Statistical Center will then contact RTOG to register the patient after which the Statistical Center will contact the institution to confirm registration and relay the treatment assignment and case number for that patient. RTOG will forward a confirmation of treatment assignment to the Statistical Center for routing to the participating institution.

5.2.2 Patients must be registered prior to the initiation of treatment ***(no more than three working days prior to the planned start of treatment)***. The information listed on the RTOG Eligibility Check must be provided at the time of registration. The caller must also be prepared to provide the date of Institutional Review Board approval for this study. Patients will not be registered if the IRB date is not provided or is > 1 year prior to the registration date.

6.0 RADIATION THERAPY

6.1 Treatment Regimen (10/1/96)

6.1.1 Patients will start radiation therapy after completion of 10 weeks of chemotherapy *(approximately week 11)* provided hematologic values are adequate. If a patient experiences neurologic deterioration that can be attributed to progressive disease on CT/MRI scan during chemotherapy, the patient will proceed immediately to cranial irradiation.

6.1.2 ***a) For patients with residual tumor*** on post-chemotherapy CT/MRI scan or slit-lamp examination, daily treatments of 1.8 Gy shall be delivered five days per week. All portals shall be treated each day. Total dose to the whole brain and meninges shall be 45 Gy in 25 fractions over five weeks. Dose distribution should be performed through the central axis and at C2. A compensator may be required to limit cervical cord dose to 45 Gy.

b) For patients with no residual tumor *(i.e., complete response to chemotherapy)* on post chemotherapy CT/MRI scan or slit-lamp examination, daily treatments of 2.4 Gy *(1.2 Gy b.i.d., a minimum of 6 hours apart)* shall be delivered five days a week. All portals will be treated at each treatment. Total dose to brain and meninges will be 36 Gy in 30 fractions over 3 weeks. Dose distributions will be performed through the central axis and at C2. A compensator may be required to limit cervical cord dose to 36 Gy.

6.1.3 Doses are specified as the target dose which shall be representative of the dose in the center of the target volume. For two opposed coaxial equally weighted beams, the target dose shall be specified on the central ray at mid-separation of beams.

6.1.4 The whole brain treatment will be delivered by opposed lateral fields. The inferior border will be at the bottom of C2 shielding the anterior portion of the eye *(anterior to the bony canthi).*

If ocular lymphoma is evident on slit-lamp examination, both eyes will be included in the whole brain field until a dose of 36 Gy has been reached. The anterior portion of the stepwise block *(as discussed above)* will be inserted at this dose level.

6.1.5 Spinal RT is not permitted in this protocol. Any patient eligible for the study who is thought to need spinal RT *(i.e., symptomatic leptomeningeal tumor)* should be discussed with the protocol chairman.

6.2 Physical Factors

Treatment shall be delivered with megavoltage machines of energy ranging from Cobalt 60 up and include 10 MeV photons. Source to skin distance for SAD techniques must be at least 80 cm. Source sizes shall be no more than 2 cm in isotope machines. For Cobalt 60 machines, secondary collimation is suggested. Electron, particle or implant boost is not permissible.

6.3 Localization, Simulation and Immobolization

The patient shall be treated in the appropriate position for location of the lesion. A head holding device that is transparent to x-rays must ensure adequate immobilization during therapy. The initial treatment volume shall include the entire brain and meninges down to the bottom of C2.

6.4 Treatment Planning (10/1/96)

6.4.1 The whole brain treatment shall be delivered by opposed lateral fields. The anterior, superior and posterior borders of the treatment portal shall include 1 cm of "fall off" except on treatment units with larger penumbras such as cobalt where the "fall off" should be 2 cm. The inferior border shall be the

inferior aspect of C2 with custom-made cerroband block shielding the lens *(without blocking the posterior one third of the globe, or inferior-most section of the frontal lobe overlying the cribiform plate).* The block should also cover the nasopharynx-pharynx *(Appendix VI).* Simulation/localization films and portal verification films of all initial fields shall be submitted to RTOG along with isodose distribution, complete treatment record and all relevant calculation data.

6.4.2 If ocular lymphoma is evident on initial slit-lamp examination, repeat slit-lamp examination will be done pre-radiotherapy. If ocular lymphoma is still present, both eyes will be included in the whole brain radiation field until a dose of 36 Gy over 20 fractions has been reached. A cerroband block as described in Section 6.4.1 will be inserted at 36 Gy and treatment will be continued to 45 Gy.

If no residual ocular lymphoma is present on slit-lamp examination pre-radiotherapy, a cerroband block *(as described in Section 6.4.1)* would be inserted throughout the radiation.

6.5 Interruption of Treatment for RT Toxicity

6.5.1 RT is to be interrupted if total WBC ≤ 1500 cells/mm^3 or granulocyte ≤ 500 cells/mm^3 or if platelets ≤ 75,000 cells/mm^3 until counts return to those levels.

6.5.2 Unpublished toxicities or unusual toxicities involving RT administered as outlined above should be reported to RTOG study chairman and to RTOG Headquarters.

6.5.3 Radiation to the brain can cause scalp dermatitis, alopecia, nausea vomiting, somnolence, and, infrequently, myelosuppression. Radiation to the eyes can cause cataract, retinal changes and optic neuropathy.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 **Schedule**: All patients will receive MTX, Procarbazine, Vincristine and intra-Ommaya MTX *(see Section 4.2.4)* over 10 weeks followed by whole brain irradiation. **(10/1/96)**

- *MTX (2.5 gm/m^2 i.v)* on weeks 1,3,5,7 and 9 followed by leucovorin rescue *(20 mg p.o. q 6 hours)* 24 hours after the MTX infusion begins and daily MTX levels for three days. Dose capped at 5 gm *(2 m^2).*

- *Vincristine* 1.4 mg/m^2 bolus on weeks 1,3,5,7 and 9. Dose capped at 2.8 mg *(2 m^2).*

- *Procarbazine* 100 mg/m^2/day for one week on weeks 1,5, and 9.

- *Intra-Ommaya MTX (12 mg/dose)* x five doses *(weeks 2, 4, 6, 8, and 10)* followed by low-dose leucovorin

- *High-Dose ARA-C* at 3 gm/m^2 x 2 separated by 24 hours at the end of RT and again 3-4 weeks later. Dose capped at 6 gm *(2 m^2).*

- *Dexamethasone* 16 mg/day; taper as outlined in text

- *Bactrim DS* 1 tablet p.o. b.i.d. for three consecutive days each week while on dexamethasone and for one month after steroid discontinuation.

- *Clotrimazole* 1 tablet p.o. 5x/day during pre-RT chemotherapy and while on dexamethasasone.

TREATMENT FLOW SHEET (6/30/95, 10/1/96)

Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Methotrexate i.v. 2.5 gm/m^2	X		X		X		X		X										
Vincristine i.v. 1.4 mg/m^2	X		X		X		X		X										
Procarbazine p.o. 100 mg/m^2, d x 7	X				X				X										

Methotrexate IO 12 mg		X		X		X		X		X									
Leucovorin 20 mg p.o. q 6 hrx 12 doses	X		X		X		X		X										
Leucovorin 10 mg p.o. b.i.d x 8 doses		X		X		X		X		X									
Decadron --mg/d x 7	16	12	8	6	4	2													
Bactrim DS 1 tablet b.i.d x 3 days	X	X	X	X	X	X	X	X	X	X									
Clotrimazole troche 1 tablet 5 x day	X	X	X	X	X	X	X	X	X	X									
Radiation therapy											X	X	X	X	X				
Ara-C 3 gm/m^2/d																X			X

7.2 **Methotrexate *(MTX)***:

High-dose MTX has been shown to be effective in both the initial treatment of PCNSL, even without RT, and at relapse.[7,10,19-21] Doses exceeding 500 mg/m^2 can also penetrate into the CSF although CSF levels are not reliably therapeutic or sustained for an adequate duration when the dose is < 1 gm/m^2. [23]Because of its documented efficacy and the ability to deliver MTX into the CSF with higher doses, we will use intravenous MTX, at 2.5 gm/m^2; five doses of intra-Ommaya MTX *(12 mg/dose)* will be interspersed throughout the treatment regimen to provide continued chemotherapeutic coverage of the CSF. Using systemic plus intrathecal MTX affords adequate penetration into both the brain parenchyma and the CSF while minimizing the total dose of MTX delivered, a known risk factor for delayed MTX-RT induced neurotoxicity.[23] When used for intra-Ommaya administration, 12mg will be dissolved into preservative-free normal saline. When used for high-dose intravenous administration, 2.5gm/m^2 will be diluted into 500 cc D5W plus 25 meq $NaHCO_3$ which will be infused over two hours. Intra-Ommaya MTX must be used immediately after reconstitution, but i.v. MTX will remain stable for 24 hours if kept refrigerated. Methotrexate is commercially available in 20mg, 50mg and 1gm vials as a lyophilized preservative-free powder.

7.3 **Vincristine *(VCR)***:

VCR is an essential agent in all combination chemotherapy regimens designed to treat disseminated systemic non-Hodgkin's lymphoma.[16] It is considered one of the most important and active drugs in the treatment of these tumors. Although it does not penetrate an intact BBB, it will reach the areas of gross disease identified by contrast-enhanced CT and MR scan. Vincristine is commercially available *(Oncovin)* in 1, 2 and 5mg vials which must be kept refrigerated until use. It is stable in the refrigerator until the expiration date noted by the manufacturer.

7.4 **Procarbazine *(PCB)***:

PCB is a lipophilic alkylating agent with known activity against malignant non-Hodgkin's lymphomas; it has been used successfully in several combination regimens *(COP-BLAM, CAP-BOP)* to treat disseminated systemic lymphoma.[16] Of pharmacologic importance, PCB penetrates the normal blood-brain barrier *(BBB)* with ease. Although areas of bulky parenchymal tumor have an impaired BBB, as evidenced by dense contrast enhancement on CT/MR scans, microscopic infiltration by malignant lymphocytes in remote regions of the brain is seen in all autopsied cases. Eradication of tumor in these areas of relatively preserved or normal BBB will require lipophilic agents. There are no data on the use of PCB in the treatment of PCNSL. Procarbazine is commercially available *(Matulane)* as 50 mg capsules which can be stored at room temperature.

7.5 **Cytosine arabinoside *(ara-C)***:

Ara-C is an anti-metabolite which can penetrate into the CNS after high-dose administration.[24-25] It has established utility in the treatment of meningeal leukemia, and as a single agent, has been shown to produce regression of parenchymal brain metastases from systemic non-Hodgkin's lymphoma.[26-27] Ara-C is commercially available *(Cytosar)* as a powder in 100 mg, 500 mg, 1gm and 2gm vials. It is reconstituted as directed in the package insert and further diluted in 500cc D5W. The reconstituted product remains stable for 48 hours if refrigerated.

7.6 **Dexamethasone**:

Corticosteroids are an integral feature of combination regimens for systemic lymphoma. Corticosteroids alone can produce complete or partial regression of PCNSL lesions in at least 40% of patients although these responses are usually short-lived.[8] Dexamethasone is commercially available as 0.5, 1.5, 2.0 and 4.0mg tablets which can be stored at room temperature.

7.7 **Trimethoprim sulfamethoxazole *(Bactrim DS - double strength)***:

Bactrim is used prophylactically against the development of Pneumonocystis carinii pneumonia. It is commercially available containing 160 mg trimethoprim and 800 mg sulfamethoxazole and can be stored at room temperature. Patients with sulfa allergies can receive aerosolized pentamidine 300 mg monthly throughout their course of corticosteroids and for one month after steroid discontinuation.

7.8 **Clotrimazole *(Mycelex troche)*:**

Clotrimazole is used prophylactically against the development of oral candidiasis. It is commercially available in 10 mg tablets and can be stored at room temperature.

7.9 **Treatment Plan**:

Patients will receive pre-radiation systemic MTX, PCB, VCR and intra- Ommaya MTX followed by cranial radiotherapy.

7.9.1 Intravenous MTX, 2.5 g/m^2, diluted in 500cc D5W containing 25 meq $NaHCO_3$, will be infused over 2 hrs on weeks 1, 3, 5, 7 and 9. MTX will be capped at 2 m^2 or not to exceed 5 gm. Prior to systemic MTX administration, 1meq/kg of $NaHCO_3$ in 50 cc D5W will be given.

7.9.2 Intravenous VCR 1.4mg/m^2 will be given as a bolus on weeks 1, 3, 5, 7 and 9. The maximal VCR dose will be reached at 2 m^2 or not to exceed 2.8 mg.

7.9.3 PCB *(100 mg/m^2/day)* will be given orally for one week beginning weeks 1,5 and 9. Patients will be on tyramine-free diets during PCB administration. The total dose is added for the seven day period and given in the best approximation with 50 mg capsules*(e.g. 200 mg x 5 days and 150 mg x 2 days).* The whole dose is given once at bedtime with an anti-emetic given 1/2 hour prior to the procarbazine. It can be administered via feeding tube if the patient cannot swallow.

7.9.4 Intra-Ommaya MTX, 12 mg dissolved in preservative-free normal saline, will be administered on weeks 2, 4, 6, 8, and 10. Leucovorin, 10 mg po bid, will be administered for 8 doses after each dose of intrathecal MTX.

7.9.5 Leucovorin, 20 mg po q 6h for 12 doses, will begin 24 hours after systemic MTX infusion starts. For the first 24 hours after MTX administration, total fluid intake delivered primarily by i.v. hydration should be 1500-1800 cc/m^2 and increased to 2000 cc/m^2 for the following 48 hours. Hydration should be admistered using D5W + 75 meq $NaHCO_3$/L to maintain urine pH = 7.0. Every urine determination of pH < 7.0 requires additional $NaHCO_3$ using two tablets *(10 gr)* or an i.v. bolus of 15 meq $NaHCO_3$ in 50cc D5W for patients unable to take pills. If a patient is unable to take oral leucovorin, it will be administered i.v. at 20 mg q6hr, beginning 24 hrs after systemic MTX infusion and continued until the 72 hr MTX level has returned. Daily CBC, electrolytes, BUN/creatinine and MTX levels will be obtained for the three days following i.v. MTX administration. If MTX levels are toxic at 24 or 48 hours *(> 1x10^{-5} M or 1x10^{-6} M respectively)*, leucovorin will be increased to 40 mg p.o. or i.v. q6 hours and total fluid intake will increase to 3000cc/m^2. MTX levels > 1x10^{-7} M at 72 hr will dictate continued leucovorin *(40 mg p.o. i.v. q6h)*, hydration at 3000 cc/m^2/day and $NaHCO_3$ until MTX level is 1x10^{-8} or less. Patients will be instructed to refrain from eating citrus fruit or drinking citrus fruit juices or vitamin C-fortified drinks *(e.g. Hawaiian Punch)* during MTX administration and for the duration of post-MTX hydration to avoid acidification of the urine. Aspirin and non-steroidal anti-inflammatory drugs are also avoided during treatment with MTX.

Leucovorin Rescue After Each Dose of High-Dose Methotrexate (6/30/95, 10/1/96)

Day of MTX	24 hr Post MTX	48 hr Post MTX	72 hr Post MTX
Prior to MTX: $NaHCO_3$ 1 meq/kg in 50 cc D5W	Total Fluid Intake = 1500-1800 cc/M^2 of D5W + 75 meq/$NaHCO_3$/L	Total Fluid Intake = 2000 cc/M^2 of D5W + 75 meq $NaHCO_3$/L	Total Fluid Intake = 2000 cc/M^2 of D5W + 75 meq $NaHCO_3$/L

MTX 2.5 gm/M^2 in 500 cc D5W + 25 meq $NaHCO_3$ infused over 2 hr.	To begin 24 hr after the start of i.v. MTX: Leucovorin 20 mg p.o. q 6 hr or i.v. Leucovorin	Leucovorin 20 mg p.o. q 6 hr or i.v. Leucovorin	Leucovorin 20 mg p.o. q 6 hr or i.v. Leucovorin
Immediately after MTX infusion start i.v. hydration using D5W + 75 meq $NaHCO_3$/L	Labs: CBC, BUN/Cr, electrolytes + MTX level	Labs: CBC, BUN/Cr, electrolytes + MTX level	Labs: CBC, BUN/Cr, electrolytes + MTX level
	MTX level should be < 10^{-5} M at 24 hr	MTX level should be < 10^{-6} M at 48 hr	MTX level should be < 10^{-7} M at 72 hr

7.9.6 At the start of chemotherapy, patients will receive dexamethasone 16 mg/day for the first week. The dose will be reduced to 12 mg/day during the second week, to 8 mg/day the third week, 6 mg/day the fourth week, 4 mg/day the fifth week and 2 mg/day the sixth week. Beginning the seventh week *(the fourth dose of i.v. MTX and VCR)* dexamethasone will be discontinued, and the patient will remain off corticosteroid until the start of RT. At the beginning of cranial irradiation, patients can be restarted on 6mg/day dexamethasone, but the dose will be gradually reduced such that corticosteroid is no longer administered by the completion of RT. If the patient has no or minimal evidence of disease on the MR scan obtained after pre-RT chemotherapy and the patient is neurologically well, dexamethasone need not be re-started to initiate WBRT. No dexamethasone is given during treatment with ara-C. At any time during the course of therapy, if patients require an increased dose of corticosteroid because of their neurological status, the dose can be adjusted as necessary, but any change will be recorded.

7.9.7 Within three weeks after the completion of radiotherapy, patients will receive the first of two cycles of high-dose ara-C. Each cycle will consist of two doses of 3g/m^2 ara-C delivered as a 3-hour infusion. The doses will be separated by 24 hours. The cycles will be separated by 3-4 weeks. The ara-C dose will be capped at 2 m^2 or a total of 6 gms.

7.10 Dose Alterations (10/1/96)

7.10.1 *Pre-radiation chemotherapy*: IV MTX, vincristine and procarbazine should be administered on schedule unless the absolute neutrophil count *(ANC)* is < 1000/mm^3 or the platelet count is < 70,000/mm^3. If either condition applies, the drugs should be withheld for 1 week, or less if the counts improve sooner. MTX, vincristine and procarbazine can then be administered at full-dose. If the ANC is persistently below 1000/mm^3 or the platelet count persistently below 70,000/mm^3 for 2 weeks, then the dose of PCB will be reduced to 75/mg/m^2 for the subsequent course; however, the doses of MTX and vincristine will not be altered.

7.10.2 If a rash develops while a patient is taking procarbazine, the drug will be discontinued during that cycle. If the patient has subsequent procarbazine-containing cycles of therapy, the drug can be re-introduced as scheduled, but it will be permanently discontinued if the rash reappears. VCR will be discontinued for grade 3 or 4 sensory, motor or autonomic disturbance. If a patient experiences grade 2 or higher nephrotoxicity from MTX, a repeat creatinine clearance must be obtained prior to the next dose of MTX. The creatinine clearance must be ≥ 50cc/min/1.73 m^2 to receive further MTX otherwise MTX must be discontinued.

7.10.3 G-CSF can be administered at the disretion of the individual investigator for chemotherapy-induced neutropenia *(ANC < 1000/mm^3)* at any time during the protocol. Its use will be recorded but is not required.

7.10.4 At the time of Ommaya puncture, the platelet count should be ≥ 50,000. If the platelet count is < 50,000, IO MTX should be witheld until the count recovers to ≥ 50,000; however, this postponed dose of IT MTX should not be administered within 48 hours of either a dose of i.v. MTX or another scheduled dose of IO MTX.

7.10.5 If a patient experiences neurologic deterioration that can be attributed to progressive disease during chemotherapy, the patient will proceed immediately to cranial irradiation. Progression must be documented on MR scan before chemotherapy is discontinued and RT begun. Patients with ocular involvement who have progression of their ocular disease during chemotherapy can proceed to RT even if the CNS disease is responding.

7.10.6 *Post-radiation chemotherapy*: The second cycle of high-dose ara-C can be delayed for as long as 2 weeks if the ANC is < 1000/mm^3 or the platelet count is < 70,000/mm^3. If the ANC or platelet count does not recover within these 2 additional weeks, the second cycle of ara-C should not be administered at all.

7.11 Toxicity

7.11.1 Systemic MTX can produce myelosuppression, GI toxicity, particularly mucositis, liver dysfunction, renal failure and rarely interstitial pneumonitis.

7.11.2 IT MTX can produce headache, fever, vomiting, and seizures acutely. Delayed toxicities include seizures, arachnoiditis, and leukoencephalopathy manifested by somnolence, confusion, ataxia, dementia and occasionally convulsions and coma. IT MTX can also produce systemic toxicity as outlined above.

7.11.3 Procarbazine can produce myelosupression, and nausea and vomiting. Hypertension can occur when foods containing tyramine are ingested due to inhibition of mono-amine oxidase, and Antabuse-like reactions may occur when alcohol is taken with PCB. Cutaneous and pulmonary hypersensitivity reactions are rare complications.

7.11.4 Vincristine can cause a peripheral neuropathy including cranial neuropathy or autonomic dysfunction such as constipation. It can also cause alopecia and can result in local necrosis after extravasation.

7.11.5 ara-C can produce nausea and vomiting, and myelosuppression. Conjunctivitis is an unusual complication. Cerebellar dysfunction is a rare complication of high-dose ara-C, particularly at this dose.

7.11.6 An increased frequency and severity of CNS toxicity with the concomitant or sequential use of cranial radiation, systemic MTX and/or IT MTX has been reported. This amplified toxicity occurs less frequently when systemic MTX is administered prior to the initiation of whole brain radiation.

7.11.7 It is not known whether procarbazine, vincristine and/or ara-C combined with cranial RT can enhance the potential for delayed CNS toxicity.

7.11.8 Dexamethasone can cause psychosis, diabetes, myopathy, hypertension and osteoporosis when taken for a prolonged period.

7.12 Adverse Drug Reaction Reporting/RTOG Members (2/14/95)

7.12.1 The following guidelines for reporting adverse drug reactions *(ADRs)* apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, Study Chair, and RTOG Data Management within 10 working days:

7.12.1.1 Any ADR which is both serious *(life threatening, fatal)* and unexpected.

7.12.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.12.1.3 Any death on study if clearly related to the commercial agent(s).

7.12.2 The ADR report should be documented on FDA Form 3500 *(Appendix IV)* and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
(301) 230-2330, available 24 hours
fax # 301/230-0159

7.13 Adverse Drug Reaction Reporting/SWOG Members (2/14/95)

7.13.1 All Southwest Oncology Group *(SWOG)* investigators are responsible for reporting of adverse drug reactions according to the NCI and Southwest Oncology Group Guidelines. SWOG investigators must:

Call the SWOG Operations Office 210/677-8808 within 24 hours of any suspected adverse event deemed either drug-related, or possibly drug-related.

Instructions will be given as to the necessary steps to take depending on whether the reaction was previously reported, the grade *(severity)* of the reaction, study phase, and whether the reaction was caused by investigational and/or commercial agent(s). The SWOG Operations Office will immediately notify the RTOG Headquarters Data Management Staff as listed in the RTOG reporting guidelines.

7.13.2 **Within 10 days the investigator must send the completed (original)** DCT form *(for regimens using investigational agents)* or the FDA 3500 form *(for regimens using only commercial agents)* to the NCI:

Investigational Drug Branch

P.O. Box 30012
Bethesda, Maryland 20824

7.13.3 In addition, within 10 days the investigator must send:
- a copy of the above report,
- all data records for the period covering prestudy through the adverse event, and
- documentation of IRB notification to the following address:

ADR Program
SWOG Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3218

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY (10/1/96)

10.1 Central pathology review will be performed by Dr. James Nelson for every case to confirm eligibility. The histology must be that of the primary CNS lymphoma. The tissue should be fixed in 10% neutral buffered formalin.

10.2 The following material must be submitted to the Pathology Coordinator at RTOG Headquarters *(using a Pathology Submission Form)* within four weeks of study entry. SWOG members will send slides, blocks, pathology reports, and submission forms to the SWOG Statistical Center *(see Section 12.2)* for forwarding to RTOG.

10.2.1 A copy of the surgical pathology report*(s)*.

10.2.2 At least one hematoxylin and eosin stained section and twenty *(see Section 10.6)* coated, unstained sections from all available paraffin blocks of malignant lymphoma. All sections should be cut at a thickness of six microns.

10.2.3 Forward central review materials to:

RTOG Pathology Coordinator
1101 Market Street, 14th Floor
Philadelphia, PA 19107
***(215)* 574-3192**

10.2.4 Autopsy is strongly encouraged. Autopsy reports should be sent to RTOG Headquarters for evaluation of effects of this therapy on malignant and normal brain tissue. Samples may be requested for central pathology review.

10.3 CNS lymphomas will be classified according to the modified Rappaport classification.[28,29] In addition, tumors will be classified according to the Lukes-Collins classification and according to the NCI Working Formulation.[30] Correlations between subtypes in each of the three classifications and therapeutic response will be determined. Further studies including chromosomal analysis and immunohistochemistry will be performed to further classify the tumor whenever possible.

10.4 CSF or vitreous specimens obtained which document initial involvement or recurrence *(any possible specimen)* will also have a central pathology review. In addition, any negative CSF cytology which is the basis for objective response *(i.e., conversion from positive to negative)* must be submitted for central review.

10.5 Specimens will be retained until the study is closed.

10.6 Fixed Tumor Bank

10.6.1 Eight of the twenty slides will be retained by RTOG for the RTOG Fixed Tumor Bank for use in future translational studies.

10.6.2 The pathology report must document that the submitted specimens include tumor.

10.6.3 Pathology identification numbers must agree with the pathology report.

10.7 Tumor Repository

10.7.1 In addition, patients may have fresh tissue prepared and submitted to the RTOG Tumor Repository. Refer to protocol RTOG 93-08.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (6/30/95, 10/1/96)

	Pre Tx	Week 1 24 hrs	Day 3 48 hrs	Day 4 72 hrs	Wks 2,4 6,8 & 10	Week 3 Day 1	Week 11	Week 16	Week 24
H&P; KPS	X					X	X	X	X
CXR	X								
	Pre Tx	Week 1 24 hrs	Day 3 48 hrs	Day 4 72 hrs	Wks 2,4 6,8 & 10	Week 3 Day 1	Week 11	Week 16	Week 24
Pregnancy test	X								
CranialMRI/CT	X						X	X	X
HIV Test	X								
CSF	X				X[a]				X
Ophth.	X						X	Xd	X[d]
Mini-MS	X						X	X	X
CBC, platelets[f]	X	X	X	X	X	X	X	X[e]	X
CR/BUN[f]	X	X	X	X		X		X	X
Lytes[f]	X	X	X	X		X		X	X
MTX Level[f]		X	X	X		Xb			
LFTS	X				X	X		X	X
CrCl	X				X[g]				

a. CSF obtained at the time of intra-Ommaya MTX administration.
b. Repeated only if there was nephrotoxicity from prior MTX dose.
c. Follow week 1 schedule for weeks 3,5,7, and 9.
d. If initial ocular exam is positive.
e. Twice weekly in weeks 17-23.
f. Prior to each dose of i.v. chemotherapy. These tests as well as an MTX level will be obtained daily for the 3 days following high dose MTX administration.
g. Repeat creatinine clearance *(> 50cc/min)* to be obtained if the patient experiences renal insufficiency or MTX-induced renal toxicity during high-dose chemotherapy.

11.2 Evaluation During Study

11.2.1 Patients will be evaluated regularly by means of general and neurological examinations, and KPS. An evaluation will be performed at the time of entry, and at least every four weeks during the course of treatment. After completion of therapy, patients will be evaluated every 2 months for one year then as per Section 12.1.

11.2.2 A CBC, platelet count, electrolytes, renal and liver function as well as appropriate blood chemistries will be performed prior to each dose of intravenous chemotherapy. CBC, platelets, electrolytes, BUN, creatinine and a MTX level will be obtained daily for the three days following high-dose i.v. MTX administration. After high-dose ara-C, a CBC and platelet count should be done twice a week until the WBC and platelets have recovered.

11.2.3 If a patient experiences renal insufficiency or MTX-induced renal toxicity during high-dose chemotherapy, a repeat creatinine clearance must be obtained before the next dose of systemic MTX. The creatinine clearance must be >50 cc/min/1.73m^2.

11.2.4 CT or MR scans without and with contrast will be obtained in patients pre- and post-operatively *(pre-entry)*. Scans will be done: *(a)* Post-chemotherapy and pre-radiotherapy *(b)* Post-radiotherapy and immediately pre-ara-C administration. *(c)* 4 weeks after completion of ara-C. *(d)* Every two months for the first year. *(e)* Every 4 months for the second year *(f)* Every 6 months thereafter.

11.2.4.1 CT/MRI required for <u>submission</u>:

a. pretreatment evaluation
b. post-chemotherapy *(preRT)*
c. post completion of all therapy
d. at progression during therapy and at the time of recurrence during follow-up period.

11.2.5 CSF will be obtained at the time of each administration of IO MTX, and every 4-6 months for the first year for routine follow-up or more often if clinically indicated. CSF will be analyzed for glucose, protein, cell count and cytology by cytospin prep. CSF will be obtained from the Ommaya reservoir and a repeat lumbar puncture at the time of any recurrence.

11.2.6 An ophthalmological examination with slit-lamp will be performed pre-radiotherapy and whenever a patient develops visual symptoms or develops any relapse **(10/1/96)**.

11.2.7 Mini-mental status examinations will be performed at the completion of pre-RT chemotherapy, after RT, after all treatment, and at each follow-up until relapse. This will help assess the long-term cognitive status of the patients. See Section 11.4.

11.3 Criteria for Response

11.3.1 Therapeutic response will be measured by the following:

a. Response *(Sections 11.3.2-7)*
b. Disease-free survival, as determined by enhanced MR scan, and lumbar puncture and ophthalmological examination, if indicated.
c. Survival

11.3.2 *Response*: All tumor measurements must be recorded in centimeters and must have the longest diameter and its perpendicular applied at the widest portion of the tumor recorded. For those with multifocal disease, the sum of the products of the two greatest diameters of all measurable lesions will be used to determine response. Cranial MR scans will be the primary means of assessing tumor size.

11.3.3 *Complete Response*: Disappearance of all enhancing tumor. The patients must be off steroid therapy and neurologically stable or improved. For those with a positive cytology, a response will constitute the disappearance of malignant cells from the CSF on both ventricular and lumbar specimens.

11.3.4 *Major Partial Response* **(PR-1)**: Greater than or equal to 90% reduction in enhancing tumor, stable or reduced steroid dose, and the patient must be neurologically stable or improved.

11.3.5 *Partial Response* **(PR-2)**: 50% or greater decrease *(less than 90%)* in enhancing tumor. No simultaneous increase in size of any lesion or the appearance of new lesions may occur. Patients must be on a stable or decreasing dose of steroids, and neurologically stable or improved.

11.3.6 *Progressive Disease*: Greater than 25% increase in enhancing tumor or the appearance of new lesions in the brain, eye or the appearance of a new positive CSF cytology. The patient may be neurologically stable or worse and on stable or increasing doses of corticosteroid.

11.3.7 *Stable Disease:* All other situations.

11.3.8 The duration of the response and the time to progression will be recorded.

11.4 Instructions For Administration of Mini-Mental Status Examination (MMSE)

The Mini-Mental Status Exam could be administered by the physician, a nurse or an assistant trained in the administration of such tools. The person administering the Mini-Mental Status Exam needs to be sensitive to when the patient shows embarrassment of their inability to answer these questions. Patients should be assured by telling them that this is another way of telling how the treatment is affecting their brain tumor. It also needs to be made clear to the patient that it is very important to get this type of information directly from them. The person administering the test needs to understand that either the correct answer is given or not. There should be no partial credit for answers short of the mark.

11.4.1 *Orientation*

1. Ask for the year, season, date, day, month: Then ask specifically for parts omitted, e.g., "Can you also tell me what season it is?" One point for each correct.
2. Ask in turn, "Can you tell me the name of this department?" *(state, county, town, hospital, floor).* One point for each correct.

11.4.2 *Registration*

Ask the patient if you may test his memory. Then say the names of 3 unrelated objects, clearly and slowly, about one second for each. After you have said all 3, ask him to repeat them. This first repetition determines his score *(0-3)* but keep saying them until he can repeat all 3, up to 6 trials. If he does not eventually learn all 3, recall cannot be meaningfully tested.

11.4.3 *Attention and Calculation*

Ask the patient to begin with 100 and count backward by 7. Stop after 5 subtractions *(93, 86, 79, 72, 65).* Score the total number of correct answers. If the patient cannot or will not perform this task, ask him to spell the word "world" backward. The score is the number of letters in correct order, e.g., dlrow=5, dlorw=3.

11.4.4 *Recall*

Ask the patient if he can recall the 3 words you previously asked him to remember in the registration

section. Score 0-3.

11.4.5 *Language*

NAMING: Show the patient a wrist watch and ask him what it is. Repeat for pencil. Score 0-2.

REPETITION: Ask the patient to repeat the sentence after you. Allow only one trial. Score 0-1.

11.4.5.1 Follow a 3-Stage Command

Give the patient a piece of plain blank paper and ask him to follow your instructions: "Take a paper in your right hand, fold it in half and put it on the floor." Score 1 point for each part correctly executed.

11.4..5.2 Reading

On a blank piece of paper, print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask him to read it and do what it says. Score 1 point only if he actually closes his eyes.

11.4.5.3 Writing

Give the patient a blank piece of paper and ask him to write a sentence for you. Do not dictate a sentence. It is to be written spontaneously. It must contain a subject and a verb and be sensible. Correct grammar and punctuation are not necessary.

11.4..5.4 Copying

On a clean piece of paper, draw two intersecting pentagons, each side about 1 inch, and ask him to copy it exactly as it is. All 10 angles must be present and 2 must intersect to score 1 point. Tremor and rotation are ignored.

11.5 Criteria for Discontinuing Study Treatment

11.5.1 Patients will be followed until death.

11.5.2 Progressive CNS disease or the development of systemic lymphoma.

11.5.3 The development of unacceptable systemic or CNS toxicity.

11.5.4 Patients can be removed from study treatment at their request.

11.6 Patient Status Definitions

11.6.1 Patients who refuse all Procarbazine, Vincristine, ara-C, and Methotrexate will be considered *canceled* and will be removed from the trial. No patient followup will be required.

11.6.2 Patients found to be *ineligible* after study entry will be removed from the study. No patient followup will be required.

12.0 DATA COLLECTION

12.1 Summary of Data Submission (10/1/96, 3/7/97)

Item	Due
Demographic Form **(A5)**	Within 1 week of study entry
Medical Oncology Treatment Planning Form**(M2)**	
Initial Mini-Mental Status Evaluation **(MS)**	
PreRx CT/MRI scan **(C1)** and Report **(C3)**	
Initial Evaluation Form **(I1)**	Within 2 wks of study entry
Diagnostic Pathology Report **(P1)**	Within 4 wks of study entry
Pathology Slides/Blocks **(P2)**	
Mini-Mental Status Evaluation **(MS)**	Within 1 week of end of initial chemo
Interim Report **(F9)**	
Chemotherapy Flowsheet **(M1)**	
Mini-Mental Status Evaluation **(MS)**	
CT/MRI Scan **(C2)** and Report **(C3)**	
Mini-Mental Status Evaluation **(MS)**	Within 1 week of RT end
Interim Report **(F9)**	
Radiotherapy Form **(T1)**	
Final Dosimetry Information:	
Daily Treatment Record **(T5)**	
Isodose Distribution **(T6)**	

Calculation Data **(TL)** Portal and Sim Films **(TP)**	
Chemotherapy Flowsheet **(M1)**	Within 1 week after each post RT chemo cycle.
CT/MRI Scan **(C2)** and Report **(C3)**	Post completion of all therapy
Follow-up Form **(F1)** Mini-Mental Status Evaluation **(MS)**	At end of all treatment, then q 2 months through year 1 year; q 4 months x 1 year, q 6 months x 3 years, then annually. Also at progression/relapse. And at death *(F1 only).*
Autopsy Report **(D3)**	As applicable

12.2 SWOG DATA SUBMISSION (2/14/95)

12.2.1 Two copies of all forms as listed in Section 12.1 should be submitted at the required intervals. Include the RTOG protocol number and patient case number as well as the Southwest Oncology Group study number and patient number. Send to:

Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA 98104-2092

12.2.2 **Rapid Review Items:** The Medical Oncology Treatment Planning Form requires rapid submission and must be faxed *directly* to RTOG: **Fax # 215/928-0153**.

12.2.3 All dosimetry and required MR/CT scans *(see Section 11.2.4.1)* will be sent *directly* to:

Radiation Therapy Oncology Group (RTOG)
1101 Market Street
Philadelphia, PA 19107
ATT: Dosimetry

12.2.4 **BOTH SWOG and RTOG assigned case and study numbers must be recorded on all items submitted.** *Unidentified data will be returned*

12.2.5 **Request for Study Information and Forms Request:**
Requests for additional information or clarification of data will be routed through SWOG for distribution to the individual institution. The RTOG memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response. Periodically *(generally three times per year)* computer generated lists identifying delinquent material are prepared and are routed through SWOG for distribution.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Two-year overall survival rates.

13.1.2 Tumor response rates prior to the start of radiotherapy.

13.1.3 The frequency and severity of treatment morbidity.

13.2 Sample Size (10/1/96)

This trial is building upon the experience of the MSKCC phase I trial. The MSKCC study indicated a median survival time of 42 months and two-year survival of 76% measured from the time of diagnosis in patients treated with a similar regimen[8]. Patients treated with radiotherapy alone and chemotherapy after progression in RTOG trial 83-15 had a median survival time of 12 months and two-year survival of 28%[6]. Therefore, two-year survival is expected to be in the range from 28% to 76%. The largest standard of error is associated with a two year rate of 50% *(assuming a binomial distribution).* In order to provide a

maximum standard error of 10% for the two-year survival estimate, then a maximum of 25 evaluable patients will be required. Assuming a 5% inevaluability rate *(ineligible and canceled patients, see Section 11.6 for definition),* **the total required sample size is 28 patients.**

This sample size will permit estimation of the tumor response rates prior to the start of radiotherapy with a standard error of at most 10%.

(added: 8/30/96) The estimate of tumor response based upon the first 13 patients is 46%. Patients achieving a complete response after induction therapy will receive a reduced total dose of radiation therapy *(36 Gy)*. The hypothesis is that the reduced radiation therapy dose will result in less CNS morbidity. The change in mini-mental status exams *(MMSE)* from baseline to one-year will be used to assess CNS morbidity. A change of 5 points on the MMSE is related to clinically significant differences in cognitive functioning in patients with brain tumors. Assuming the standard deviation of the change score is 4.7, then 15 patients with a complete response after induction chemotherapy will need to be evaluated at one-year to determine if this reduced dose results in less CNS morbidity. In order to have 15 patients with baseline and one-year MMSE's, then 19 patients will be required; therefore, **a total of 40 patients will be required** after the revision in order to accrue 19 patients with a complete response.

13.3 Patient Accrual (10/1/96)

The patient accrual was projected to be three cases per month. At that rate, it will take 10 months to reach the required 28 cases. From November 1, 1994 to April 1, 1996 the average accrual was 1.6 patients per month; from February to July of 1996 the average accrual was 2.2 patients per month. Assuming 2 patients per month then the revision will take 20 months to complete. If the average monthly accrual rate is less than 1 patient, the study will be re-evaluated with respect to feasibility.

13.4 Analyses Plans

13.4.1 *Interim Analyses*

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

a) the patient accrual rate with a projected completion date for the accrual phase;
b) compliance rate of treatment delivery with respect to protocol prescription;
c) the frequency and severity of the toxicities.

Through examining the above items, the RTOG Data Monitoring Committee and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for this study and, if necessary, the Executive Committee, so that corrective action can be taken.

13.4.2 *Analysis for Reporting the Initial Treatment Results*

This analysis will be undertaken when each patient has been potentially followed for a minimum of two years. The usual components of this analysis are:

a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
b) reporting institutional accrual;
c) distribution of important prognostic baseline variables by treatment arm;
d) observed results with respect to the endpoints described in Section 13.1.

The analysis will done on the intent-to-treat basis. This is defined as all patients who at least start chemotherapy. Subgroup analyses will be undertaken depending upon the size of the subsamples.

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APPENDIX I
INT 0143

RTOG 93-10
SWOG 9310

AN INTERGROUP PHASE II COMBINED MODALITY TREATMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have lymphoma of the brain. My doctor feels that my participation in this study may be helpful. The purpose of this study is to determine whether chemotherapy in addition to radiotherapy is a beneficial treatment for primary central nervous system lymphoma. Primary lymphoma of the brain is a rare tumor which is usually treated with whole-brain radiotherapy. In most patients, radiation causes substantial shrinkage or disappearance of the tumor; however, in the vast majority of patients, the tumor comes back. Chemotherapy combined with radiation has been used successfully in the treatment of identical lymphomas which occur in other areas of the body outside of the brain. For this reason, I have been asked to join a study using both chemotherapy and brain radiation for the treatment of lymphomas restricted to the brain. Pregnant or nursing patients are excluded from participation. Sexually active male and female patients must avoid pregnancy during therapy.

DESCRIPTION OF PROCEDURES (10/1/96)

The treatment to be given to me is as follows: I will be examined by a physician involved in this study and have several tests before treatment begins including a spinal tap and an examination by the ophthalmologist *(eye doctor)*. In addition, I will have a blood test to check for exposure to HIV, the virus which causes AIDS since primary nervous system lymphoma may be associated with AIDS which would change my treatment. Unless done during the brain biopsy procedure, a reservoir for the administration of chemotherapy into my spinal fluid must be inserted; this is called an Ommaya reservoir. The Ommaya reservoir is a small plastic device under the skin on my head, about the size of a quarter, which allows for easy sampling and delivery of drug into the spinal fluid; it is inserted under local or general anesthesia by my neurosurgeon. It is permanent although it can be removed if necessary.

Most of the chemotherapy will be given before brain radiation begins and will require four days of hospitalization for each dose of chemotherapy. Three different drugs will be used before the radiation begins. One drug, Methotrexate, will be given by vein *(2 hr intravenous infusion)* and also into my spinal fluid by repeated *(5)* taps of the Ommaya reservoir. Vincristine will be given by vein *(administration takes a few minutes)* and procarbazine will be given by mouth. Dexamethasone will be given orally for the first six weeks during chemotherapy and may again be given during radiation. The full course of chemotherapy will take about 10 weeks to complete, and my blood counts will be closely followed during this time.

Brain radiation will begin after the chemotherapy; I will have a CT or MR scan and eye examination after chemotherapy and before radiation is started.

If tumor is still present on this CT or MR scan, or an eye examination I will receive radiation treatments once a day every day, Monday through Friday. If eye examination shows tumor in my eye*(s)*, radiation will also be given to my eye*(s)*. The course of radiation will take about five weeks to complete. If no tumor is visible on this CT or MR scan, I will receive radiation treatments twice a day, 6 hours apart, every day, Monday through Friday. This course of radiation will take three

weeks to complete.

A CT or MR scan will then be obtained after radiation is over. After completion of radiation I will receive 2 courses of the last chemotherapy drug, cytosine arabinoside or ara-C. This drug is given by vein *(3 hour infusion)* and usually requires 2 days in the hospital. The entire course of treatment takes approximately 4 months to complete. At the end of all therapy a CT or MR scan or eye examination will be obtained every 2 months for 1 year, every 4 months for the second year and with my followup visits after that. Depending upon my response to the treatment, additional scans may be necessary. At each follow-up visit, my memory will be tested with a series of questions *(mini-mental status examination)* to help follow my progress.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Methotrexate may cause a drop in my blood counts although I will be given an antidote *(leucovorin)* to guard against this. Methotrexate may cause mouth sores, diarrhea, seizures, uncoordination, and lethargy. Rarely, serious kidney difficulties, liver or lung problems can result from MTX therefore i.v. fluids are given for three days after each dose to prevent damage from occuring to any of these organs. Most of these problems will resolve if further doses of the drug are withheld but improvement may take weeks to months. Methotrexate delivered into my spinal fluid may cause fever, headache, vomiting or confusion which usually resolves without any treatment. Leucovorin is also administered orally for four days following each dose of intra-Ommaya methotrexate.

Procarbazine can cause nausea and vomiting although drugs to try to prevent or minimize this side effect will be given. It also causes a drop in blood counts leading to an increased susceptibility to infection *(low white blood cell number)* or bleeding *(low platelet count)*. It may cause fatigue, sleepiness, or rash. I will also be required to avoid certain foods such as alcohol and particular cheeses, which can cause high blood pressure or nausea and vomiting when combined with procarbazine. I will be given a sheet containing diet instructions.

Vincristine may cause damage to the nerve endings in my fingers and toes. This may result in numbness, tingling and weakness particularly in my feet. It can also cause lightheadedness when standing, jaw pain, constipation, and rarely, facial weakness or double vision.

Cytarabine (ara-C) can cause a drop in blood counts which may increase my vulnerability to infection or bleeding. It may also cause nausea and vomiting and lead to irritation of my eyes. Occasionally it can cause tremor and problems with balance although this is unlikely at the dose I will be receiving.

Dexamethasone may cause stomach ulcers, diabetes, high blood pressure, insomnia, depression or euphoria, enhanced appetite with weight gain and muscle weakness. Use of dexamethasone may increase my vulnerability to a specific type of pneumonia called PCP for Pneumocystis Carinii Pneumonia which my doctor will try to prevent with oral Bactrim, an antibiotic. Chemotherapy and dexamethasone can cause a fungal infection in my mouth; I will receive oral clotrimazole, an anti-fungal medication, to prevent this.

Radiation therapy to the brain may produce reddening and peeling of my scalp, tiredness, headache and possible nausea. It causes loss of scalp hair, but the hair usually may grow back 2-4 months after treatment stops although it may be less full than prior to radiotherapy. Radiation to my eyes may cause cataracts and damage to vision. Long term side effects of radiation may include memory difficulties which can range from mild to severe which may be progressive. There is a small risk of damage to normal brain tissue *(called brain necrosis)* which may cause symptoms similar to a stroke occuring in that area of the brain. It is possible that combining chemotherapy with brain radiation may enhance the possibility and severity of these problems, but the true incidence of delayed side effects is unknown.

Ommaya Reservoir will require a separate consent.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped though some may

be permanent. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr._____ _____ the investigator in charge at _____ _____. In addition, I may contact _____at _____ _____ for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include radiation therapy alone, chemotherapy alone, other chemotherapy with radiation therapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group *(RTOG)*. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration *(FDA)*, the National Cancer Institute *(NCI)* , qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue, blocks, and/or slides, may be sent to a central office for review and research investigation associated with this

protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_____ _____

Patient Signature *(or Legal Representative)* Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX IV

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting Guidelines

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff *(215/574-3150)*.

2. The Principal Investigator will also report to the Study Chairman by telephone the details of the significant reaction.

3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures.

5. For those incidents requiring telephone reporting to the National Cancer Institute *(NCI)*, Investigational Drug Branch *(IDB)* or Food and Drug Administration *(FDA)*, when feasible, the Principal Investigator should first call RTOG *(as outlined above)* unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence *(Adverse Reaction Reports or Drug Experience Reports)* submitted to NCI, IDB, FDA, or to another Cooperative Group *(in the case of RTOG sponsored intergroup studies)* must also be submitted to RTOG Headquarters when written documentation is required.

6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.

7. See the specific protocol for criteria utilized to grade the severity of the reaction.

8. The Principal Investigator when participating in RTOG sponsored intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.

9. Institutions must also meet their individual Institutional Review Board *(IRB)* policy with regard to their toxicity reporting procedure.

10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

Adverse Drug Reactions - Drug and Biologics

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had not previously been identified as

a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal *(grade 5)* or life threatening *(grade 4)* adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions *(≥ grade 2)* resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. Form 1639 is to be used in reporting details *(see attached).* All relevant data forms must accompany the RTOG copy of Form 1639.

iii. All neurotoxicities *(> grade 3)* from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting and a special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is only a reasonable suspicion.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch *(IDB)*
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent.	Report by phone within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent.	As above
- All life threatening *(grade 4)* events which may be due to agent.	As above
- First occurrence of any toxicity *(regardless of grade).*	Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal *(grade 5)* and life threatening *(grade 4)* known adverse reactions due to investigational agent.	Report by **phone** to RTOG Headquarters and the Study Chairman <u>within 24 hours</u> **A written report must be sent to RTOG within working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)
- All fatal (grade 5) and life threatening (grade 4) <u>unknown</u> adverse reactions resulting from or suspected to be related to investigational agent.	Report by **phone** to RTOG Headquarters, the Study Chairman and <u>IDB</u> within **<u>24 hours</u>**. **A <u>written report</u> to follow within 10 working days.
- All grade 2, 3 <u>unknown</u> adverse reactions resulting from or suspected to be related to investigational agent.	**Report **<u>in writing</u>** to RTOG Headquarters and <u>IDB</u> within 10 working days.

****** See attached NCI Adverse Drug Reaction Reporting Form

APPENDIX V

INTERGROUP PARTICIPATION IN RTOG STUDIES

GENERAL GUIDELINES

I. REGISTRATION: RTOG will be responsible for all registration/ randomizations. The procedure is:
-Each institution affiliated with a Cooperative Group will phone their group and supply the eligibility check information.
-The participating Cooperative Group will then telephone RTOG 215/574-3191 between 8:30 a.m. and 5:00 p.m. ET and supply the necessary eligibility and stratification information. RTOG will then assign a case number and treatment assignment. The participating Cooperative Group will then inform its member institution.
-RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group forward a copy of the calendar to the participating institution.

II. PROTOCOL DISTRIBUTION: Each participating cooperative group is responsible for distribution of the protocol to its members. All protocol amendments will be sent by RTOG to each participating Group office for distribution to member institutions. All communication with NCI regarding this protocol will be routed through the RTOG.

III. INSTITUTIONAL PARTICIPATION: It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases.

IV. CONFIRMATION/CALENDARS: A Confirmation of Registration notice and a Data Collection Calendar is produced for each case registered and/or randomized. These will be distributed by RTOG to the appropriate cooperative group office for distribution to their members, if appropriate.

The form identification code which appears on the Calendars in the "key" columns is found on the form in the lower right corner.

You are expected to respond to each of the items listed either by submitting the item, by notifying us in writing that the item is not available or that the assessment was not done. The calendar may also list items which are not forms (CAT Scan reports, pathology reports) but are specific source documents. These items will be noted in the data collection section of the protocol but will not be listed on the Forms Package Index.

Additional items/forms may be required depending on events that occur e.g. if surgery was done a surgical report may be required. See the protocol for conditional requirements.

Unless specified otherwise, all patients are followed until death or termination of the study.

V. FORMS: Forms packages may be obtained from the participating Cooperative Group office. Attached is a list *(Forms Package Index)* of all data collection forms used in the study, the toxicity criteria for this study, if applicable and a sample of the data collection forms.

The RTOG assigned case and study number must be recorded on all data items submitted. Except for material which requires rapid review *(see below)*, data should be routed according to the mechanism set up by the participating Group. Generally the participating group will require forms to be routed through their office and they will send the forms to

American College of Radiology
Radiation Therapy Oncology Group - 14th Floor

1101 Market Street
Philadelphia, PA 19107

VI. LABELS: Preprinted labels are available for source document data items (radiographic reports, etc.) Supplied white labels are to be used for film identification.

The blank labels will be supplied to the participating Group for distribution to the individual institutions as patients are registered at RTOG.

When completing the labels, be specific when describing films, e.g.: "Pre op CT Brain Scan, "Large Photon Localization Film", "Follow-up Bone Scan", etc.

Data managers are advised to consult technical staff for assistance when labeling radiotherapy films. Correct film identification is the responsibility of the institutions and is essential to maintain efficient data flow.

VII. CANCELLATION/INELIGIBILITY: Patients who are found to be ineligible subsequent to registration are to be followed according to plan unless you receive written instructions to the contrary.

Patients who receive no treatment whatsoever may be cancelled, however, written notification and an explanation must be received at RTOG Headquarters as soon as this has been determined. We must receive this notification not later than two weeks after registration. We will notify you of the determination made regarding the status of the case and instructions regarding subsequent data submission.

VI. RAPID REVIEW ITEMS: Time critical data which requires rapid submission must be sent directly to RTOG *(See Section V)*. These items are:

M2 - Medical Oncology Treatment Planning Form *(if required by the Protocol)*
T2 - Protocol Treatment Form
T3 - Photon Localization film *(for all fields treated initially)*
T4 - Photon dose calculations *(for all fields treated initially)*

IX. REQUEST FOR STUDY INFORMATION AND FORMS REQUEST: Requests for additional information or clarification of data will be routed through the participating Cooperative Group office for distribution to the individual institution.

The memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response.

Periodically (generally three times per year) computer generated lists identifying delinquent material are prepared. These are routed by RTOG through the participating group for distribution.

X. QUESTIONS REGARDING:

Randomization/Registration	Registration Secretary (215) 574-3191
Pathology	Pathology Coordinator (215) 574-3161
Data/Eligibility/Treatment/ Adverse Reactions	Data Manager (215)574-3214

Data Management Procedures	Data Manager (215)574-3214
Protocols/Amendments	Protocol Administrator (215) 574-3195
Radiotherapy data items *(films, radiographs, isodose summations, treatment records, scans, reports and calculations)*	Dosimetry Clerk (215) 574-3219

If you are unable to reach the person noted, and your call is urgent, ask to speak to any data manager.

XI. ADVERSE REACTIONS/AND TOXICITY

From Radiotherapy: Unusual toxicities, and all grade 4-5 toxicities are to be reported by telephone to RTOG Headquarters, the Group Chairman Dr. James Cox and to the Study Chairman. If the Chairman is unavailable, ask to speak to the Data Manager for this study.

From Investigational Agents: Are to be reported according to NCI guidelines. In addition, RTOG Headquarters and the Study Chairman are to receive notification as outlined by the NCI procedures, i.e. if telephone notification is necessary, RTOG and the Study Chairman must also be called.

Copies of all toxicity reports and forms submitted to NCI must be sent to RTOG Headquarters also.

From Commercial Drugs: Are to be reported according to NCI/FDA guidelines. A copy of the reports and forms submitted to FDA must be sent to RTOG.

APPENDIX VI

TYPICAL TREATMENT FIELD