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RADIATION THERAPY ONCOLOGY GROUP

RTOG 95-07

PHASE I STUDY OF TOPOTECAN PLUS CRANIAL RADIATION FOR GLIOBLASTOMA MULTIFORME

SCHEMA

R Topotecan 0.5 mg/m² per day i.v. given five times per week
E q3 weeks x maximum 3 courses* (*first ten patients*), opened: 10/13/95; closed: 1/4/96

then escalate to 1.0 mg/m² per day x 5 days q3 weeks x maximum 3 courses*
G (*second ten patients*), opened: 5/1/96; closed: 6/14/96
I

then escalate to 1.5 mg/m² per day x 5 days q3 weeks x maximum 3 courses*, opened: 10/25/96
S
T Cycle 1 radiation treatment days 1-5 (*protocol days 1-5*)
E Cycle 2 radiation treatment days 16-20 (*protocol days 22-26*)
R Cycle 3 protocol days 43-47

Radiation Therapy Treatment Volume 60 Gy/30 fractions/6 weeks
(2 Gy fractions once a day five days a week)

Total RT	60 Gy
Initial Field**	46 Gy
Boost Field ***	14 Gy
Fraction Size	2 Gy

* Unless there is disease progression

** For the first 46 Gy/23 fractions, the treatment volume should include the volume of contrast-enhancing lesion and surrounding edema on preoperative CT/MRI scan plus a 2.0 cm margin.

*** After 46 Gy, the tumor volume should include the contrast-enhancing lesion (*without edema*) on the presurgery CT/MRI scan plus a 2.5 cm margin.

Eligibility: (See Section 3.0 for details)

- Histology-confirmed glioblastoma multiforme
- Tumor supratentorial in location
- Therapy begins within five weeks of surgery (*but within one week after registration*)
- No prior chemotherapy, radiotherapy to the head and neck, or radiosensitizer
- Age ≥ 18 years
- Karnofsky Performance Status ≥ 50%
- Neurologic functional status 0, 1, or 2
- Hemoglobin ≥ 10 g/dL, absolute neutrophil count ≥ 1500/mm³, platelets ≥ 100,000/mm³
- BUN ≤ 25 mg/dL and creatinine ≤ 1.5 mg/dL
- Bilirubin ≤ 1.5 mg/dL and SGPT or SGOT ≤ twice normal range
- Normal chest x-ray
- Signed study-specific informed consent

Required Sample Size: maximum 45

6/3/96
10/25/96

Institution # _____

RTOG 95-07

ELIGIBILITY CHECK (1/31/96)

Case # _____

(page 1 of 2)

- _____(Y) 1. Histologically confirmed glioblastoma multiforme or gliosarcoma?
- _____(Y) 2. Diagnosis made by surgical biopsy or excision?
- _____(Y) 3. Is tumor supratentorial in location?
- _____(Y) 4. Will therapy begin within 5 weeks of surgery?
- _____(N) 5. Has patient received prior radiotherapy to head and neck, chemotherapy or radiosensitizer?
- _____(≥ 18) 6. What is the age of the patient?
- _____(≥ 50) 7. What is the Karnofsky Performance Status?
- _____(0-2) 8. What is the Neurological Function Status?
- _____(≥ 10) 9. What is the hemoglobin?
- _____(≥ 1.5) 10. What is the absolute neutrophil count (*x 1000*)?
- _____(≥ 100) 11. What is the platelet count?
- _____(≤ 25) 12. What is the BUN?
- _____(≤ 1.5) 13. What is the creatinine?
- _____(≤ 1.5) 14. What is the bilirubin?
- _____(Y) 15. Is the SGOT or SGPT ≤ twice your institution's normal range?
- _____(Y) 16. Has a diagnostic CT or MRI with and without contrast been performed pre-operatively?
- _____(Y/N) 17. Has the same scan with and without contrast been performed post operatively?
- _____(Y) If no, did the patient have only a stereotactic needle biopsy?
- _____(Y) 18. Has a study-specific consent been signed?
- _____(Y) 19. Has the patient's steroid dose been stable for the past seven days?
- _____(M/F) 20. What is the patient's gender? (*if male, skip to Q23*)
- _____(N/Y) 21. Does she have child-bearing potential? (*if no, skip to Q23*)
- _____(Y) 22. Has she tested negative for pregnancy?

Institution # _____

Case # _____

(page 2 of 2)

_____(Y/N) 23. Is the patient sexually active?

_____(Y) If yes, has patient been counseled about practicing contraception while undergoing treatment and for 3 months after completing treatment?

_____(N) 24. Is the tumor multifocal?

_____(N) 25. Is the tumor recurrent?

_____(N) 26. Does the patient have AIDS?

Patient's Name

Verifying Physician

Patient ID #

Referring Institution # if different

Birthdate

Sex

Race

Social Security Number

Zip Code (9 digit if available)

Method of Payment

Treatment Start Date (must be after registration)

Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Chemotherapy of Brain Tumors

Presently the nitrosoureas are the main chemotherapy for malignant astrocytomas. Most often they have been used in a "pseudo-adjuvant" setting in conjunction with or immediately following radiation treatment. Although it is generally believed that they can effectively increase the duration of survival, these effects tend to be quite modest.¹⁻³ Other agents that may have some activity include procarbazine, vincristine, 5-fluorouracil, VP-16, VM-26, dianhydrogalactitol, cisplatin, and AZQ.³⁻⁵ However, these drugs rarely produce significant numbers of complete or durable responses.

A second problem in the chemotherapy of brain tumors is that although the nitrosoureas are the mainstay of therapy, because of their ability to cause delayed and cumulative myelosuppression, they can be delivered only at infrequent intervals (*ie. every 6-8 weeks*). In theory this may limit the degree of primary tumor control if long drug-free periods occur. Agents producing less myelosuppression which can be given more frequently may help to alleviate this problem.

A third major problem is that of tumor heterogeneity. Malignant gliomas have great heterogeneity with respect to various morphologic features⁶ and with respect to sensitivity to chemotherapeutic agents.^{7,8} Therefore single drug treatment is likely to be relatively ineffective for producing long-term tumor control. However, identification of more active agents may make effective combination chemotherapy of brain tumors a more realistic goal.

A final problem with chemotherapy of brain tumors is adequate delivery of active drugs to the tumor. This is important if a significant dose-response relationship is present. Although many investigators feel that drugs that cross the blood-brain barrier are most effective against intracranial tumors, there is some controversy about its importance in the treatment of primary brain tumors.^{9,10} Several studies utilizing intracarotid artery mannitol infusions followed by drugs have shown some promise in allowing drugs to pass through the blood-brain barrier.¹¹⁻¹² Intracarotid artery infusion of drugs alone has also been attempted to increase the local concentration of drug in the blood infusing the tumor region with some success.^{13,14} Interstitial delivery of chemotherapy directly within brain tumors and high-dose systemic chemotherapy with autologous bone marrow or peripheral progenitor cell rescue have also been proposed to overcome the drug delivery issue.^{15,16} However, these techniques are technically difficult to perform, have potentially significant morbidities attached to them, and have not yet demonstrated superiority over conventional treatment.

1.2 Topotecan: Mechanism of Action

Camptothecin and its analogues, including topotecan, are believed to exert cytotoxic effects through the inhibition of topoisomerase I.^{17,18} This is the only known class of drugs which exhibits this mechanism of action. However, inhibition of topoisomerase activity is not an unknown mechanism of action since many classes of drugs (*eg. epipodophyllotoxins*) operate through inhibition of topoisomerase II (*topo II*).

Topoisomerases are enzymes which break strands of DNA so that the strands can be rotated around each other and then the break resealed. They can be divided into two classes according to the nature of the mechanisms of action they employ.¹⁹

Type I topoisomerase is a monomeric protein of about 100 Kilodaltons (*KDa*). It is capable of making a transient break in a single strand of the DNA helix. This reduces the torsional strain on the DNA and allows the DNA to unwind ahead of the replication fork. This enzyme is capable of relaxing highly negatively supercoiled DNA. In the eukaryotic version of this enzyme, a phosphotyrosyl bond is formed between the enzyme and the 3' end of the DNA break. In this process there is a transfer of a phosphodiester bond in the DNA to the protein. The structure of the DNA is manipulated and the DNA is rejoined. Since the reaction requires only the transfer of bonds, not irreversible hydrolysis, no input of energy is required. Topo I is believed to function in DNA replication, RNA transcription, genetic recombination, chromosomal condensation/decondensation and in viral encapsulation. Its presence is not cell-cycle dependent and it is found in quiescent as well as proliferating cells. It appears, however, that this enzyme is not required for the viability of cells. Topo II seems to fulfil the functions of topo I when it is absent. Double mutants, which lack both topo I and II have defects of replication and transcription.¹⁹

Cells lacking the topo I enzyme are resistant to camptothecin, while cells containing higher topo I levels are hypersensitive to these drugs. The camptothecins seem to block the rejoining step of the breakage-reunion reaction of the enzyme, leaving the enzyme covalently bound to DNA.^{19,20} This results in protein associated single strand

breaks in the DNA.

1.3 Experimental Antitumor Activity

Topotecan demonstrated good antitumor activity (*increased life spans (ILS) > 95%*) in several intraperitoneally (IP) and intravenously (IV) implanted murine tumor systems, including P388 leukemia, L1210 leukemia, B16 melanoma, Lewis lung carcinoma and M5076 reticulum cell sarcoma.¹⁸⁻²¹ Topotecan was equally effective when administered IP or IV against IP or IV implanted tumors. Subcutaneous administration did not result in any local tissue damage. This drug was also equally effective when administered enterally or parenterally in some tumors, suggesting that, in mice, the bioavailability is high.

The antitumor activity of topotecan in tumor-bearing mice can be enhanced by using an intermittent dosing regimen. Results were dependent upon how sensitive the tumor model was to bolus treatment with topotecan. In studies in which topotecan was administered every three hours for 4 doses, a broader therapeutic dose range was noted in tumors that were quite sensitive to bolus therapy, including IV-implanted L1210 leukemia, IP M5076 reticulum sarcoma, SC colon 51, and SC B16 melanoma. In tumor types that were less sensitive to bolus therapy, such as SC implanted colon 26 and Madison 109 lung carcinomas, the divided dose resulted in a greater degree of inhibition at the MTD.¹⁸

The activity of topotecan has also been investigated using a human tumor clonogenic assay.²² Fifty-five human tumor specimens were exposed to topotecan for one hour at a concentration of either 1 or 10 µg/ml or as a continuous exposure (0.1 or 1.0 µg/ml). At a concentration of 0.1 µg/ml of continuous exposure, response rates of 29, 27, and 37% were seen against breast, nonsmall cell lung, and ovarian cancers, respectively. Activity was also seen against stomach, colon, and renal cancer, and mesothelioma. Incomplete cross-resistance was noted with doxorubicin, 5-FU and cyclophosphamide.

1.4 Animal Toxicity

Preclinical toxicology testing has been performed in BDF1 mice, Sprague-Dawley rats and beagle dogs.¹⁸ The single dose LD₁₀ in mice was 75 mg/m². This compound demonstrates strong cumulative toxicity since the five daily dose LD₁₀ in mice was 14 mg/m²/d. In a single dose toxicity study, rats given 147.5 mg/m² experienced dose-related toxicity to proliferating tissues of the gastrointestinal tract, bone marrow, and lymphoid tissues. Toxicity was reversible in surviving rats. Lethality occurred in 3/12 rats on days 5-6 of the study. Toxicity at 7.49 mg/m² (0.1 x MELD₁₀) was mild and reversible. Rats administered 13.8 mg/m² daily for five days experienced dose-related toxicity to the same proliferating tissues as mice who received 147.5 mg/m² on the single dose study. The testis and liver were also affected. Death occurred in 5/12 rats on days 7-8 of the study.

Single and five daily dose toxicity studies were also performed in beagle dogs. Lethality was seen at the MELD₁₀ (74 mg/m², 3/10 dogs) and at 1.5 x MELD₁₀ (120 mg/m², 6/10 dogs) in the single dose study and at 1/3 MELD₁₀ (4 mg/m², 1/10 dogs) in the five daily dose study. Clinical signs of GI toxicity and marrow toxicity were seen, as well as increased BUN. Histopathic lesions were similar to those found in the rats including lymphoid, gastrointestinal, marrow and ovarian toxicity. Liver and spleen toxicity was seen in the single dose study and testicular atrophy was observed in the five daily dose study. Based on the results of these studies, 1/30 MELD₁₀ was chosen for the starting dose in humans.

1.5 Human Phase I Trials

Topotecan has been studied in several schedules in phase I studies in the United States and Europe.

Three phase I studies have been carried out in which topotecan was administered as a 30 minute infusion daily x 5 days every 3 weeks.²³⁻²⁵ In all three trials myelosuppression, principally neutropenia was dose limiting. Nadir neutrophil counts occurred on day 8-11 and were of brief duration. The recommended phase II dose from all three studies was the same: 1.5 mg/m²/day x 5 days every 3 weeks.

Other toxic effects seen during these trials were as follows:

- mild-moderate nausea/vomiting (*infrequent*)
- occasional anorexia
- hair loss

- fatigue
- occasional diarrhea, skin rash, fever
- dysuria (*one patient*)
- occasional elevations in bilirubin or transaminases

No serious non-hematologic toxicity has been documented.

In the phase I trials several patients have experienced objective tumor regression as follows:

Ovary	1 partial response
Nonsmall cell lung cancer	1 complete response
	3 partial responses
Small cell lung cancer	1 partial response
Esophagus	1 partial response

"Minor" responses have been noted in several other tumor types. Given that most patients on phase I trials are heavily pretreated and receive what is later known to be subtherapeutic dosing, this list of documented responses is extremely encouraging.

1.6 Pharmacokinetic Studies

Pharmacokinetic studies of topotecan in humans were performed as part of the Phase I trial at JHOC (*T89-0165*).²⁴ Twelve patients received a dose of 0.5-1.5 mg/m² topotecan daily x 5. The harmonic half-lives were 3.3 and 80 minutes. The renal and plasma clearance rates were 446 ± 55 and 630 ± 106 ml/min/m², respectively. The volume of distribution (*Vd*) was 20.7 ± 4.7 L/m² on day 1, but increased to 40.3 ± 5.9 L/m² by day 5.

Pharmacokinetics were also performed at Memorial Sloan Kettering as part of a Phase I study (*T90-0003*).²³ Six patients received a dose of 1.5 mg/m². The median alpha and beta half-lives were 9.0 and 103 minutes, respectively. The clearance was 2080 mL/min/m², and the *Vd* was 186 L/m².

The optimal dose and schedule selected for phase II trials based on the results of these trials, is 1.5 mg/m² IV daily x 5 every 3 weeks.

1.7 Topotecan and Radiation

Topotecan may be a radiation sensitizer by preventing DNA repair and modifying radiation-induced DNA lesions. Topoisomerase I inhibitors can enhance radiation damage by preventing DNA repair and survival recovery in human neoplastic cells. Boothman et al reported that post-treatment exposure to camptothecin, a specific inhibitor of topoisomerase I, enhanced the lethal effects of radiation on radioresistant human malignant melanoma cells *in vitro*.²⁶ Mattern et al reported potentiation of radiation-induced cell killing by topotecan in Chinese hamster ovary or P388 murine leukemia cells *in vitro*.²⁷ The potentiation of radiation toxicity by topotecan required the presence of the topoisomerase I inhibitor during the first few minutes post-irradiation. Kim et al found potentiation of radiation response in human carcinoma cells *in vitro* and murine fibrosarcoma (*in isogenic BALB/c mice*) *in vivo* by topotecan.²⁸ The radiosensitization effect was dependent upon drug dose and on the time sequence of topotecan and radiation. The *in vivo* studies showed best potentiation when topotecan was administered 2 or 4 hours before radiation. Administration of the drug 2 hours after radiation did not produce any significant potentiation of radiation. There was no disproportionate enhanced radiation skin reaction in the mice exposed to combined topotecan and radiation. Boscia et al reported radiation sensitization by topotecan in a human squamous carcinoma cell line (*SCC-25*) resistant to cisplatin *in vitro* and in the FSaIIC fibrosarcoma cell line growing in C3H mice *in vivo*.²⁹ Various reports indicate a dose enhancement ratio of 2.0 or more. The mechanism of topotecan radiosensitization is speculated to be that topotecan inhibition of topoisomerase I prevents potentially lethal DNA damage repair leading to a conversion of repairable non-lethal DNA lesions induced by radiation into irreparable topoisomerase I bound lethal double strand breaks. The radiosensitization action of topotecan occurs at drug concentrations achievable *in vivo* without excessive toxicity.

Phase I and phase II studies of radiosensitization of topotecan in human tumors are underway, using a variety of topotecan and radiation dose/schedules. No results are available at this time.

1.8 Topotecan and Gliomas

Topotecan has demonstrated activity against a variety of pediatric and adult central nervous system tumor

xenografts growing subcutaneously and intracranially in athymic nude mice. Significant tumor regressions and growth delays were reported by Friedman et al against xenografts derived from ependymomas, childhood high grade gliomas, adult high grade gliomas, and medulloblastomas.³⁰ Blaney et al. examined the plasma and cerebrospinal fluid pharmacokinetics of topotecan in non-human primates.³¹ Peak CSF concentrations of topotecan occurred 30 minutes following intravenous drug administration. The CSF disappearance paralleled that of plasma. The mean ratio of the area under the CSF concentration-time curve to that in plasma was 0.32 (range, 0.29-0.37). Thus topotecan can penetrate CSF in potentially therapeutic concentrations, indicating reasonable penetration of the blood-brain barrier. The combination of activity against human primary brain tumor xenografts *in vivo* and good CSF penetration makes topotecan a good candidate for further study in patients with CNS tumors.

A phase I study of topotecan in pediatric patients with malignant solid tumors reported stable disease in one patient with astrocytoma and another with medulloblastoma but progressive disease in one patient with glioblastoma.³² In this study topotecan 0.75-1.9 mg/m² by continuous intravenous infusion daily for 3 days was given. The recommended pediatric phase II topotecan dose was 1.0 mg/m²/day for 3 days as a constant intravenous infusion followed by G-CSF support, with cycles repeated every 21 days. The actual doses administered to the 3 patients with primary brain tumors are unknown. There was minimal nonmyelosuppressive toxicity. Myelosuppression was dose limiting, both neutropenia and thrombocytopenia.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) has recently completed a phase II trial of topotecan in recurrent malignant glioma in adults.³³ Topotecan 1.5 mg/m² intravenously daily for 3 days, repeated every 3 weeks, was used. There were 2 objective responses (*1 complete response for 9 days until death from neutropenic sepsis, and 1 partial response ongoing at 24+ months*), 21 patients with stable disease, and 8 with progressive disease. The overall median progression-free survival was 3.3 months and median survival 6.6 months. Toxicity was primarily myelosuppression severe but brief, neutropenia was common. The median granulocyte nadir was 0.3 x 10⁹/L and 25 of 31 patients experienced grade 3 or 4 neutropenia (< 1.0 x 10⁹/L). Only 9 patients experienced grade 3 or 4 thrombocytopenia and 1 patient had grade 3 anemia. Despite this, infection was uncommon (*4 of 31 patients*), and only 12 of 109 cycles administered were given at reduced dose due to prior toxicity. Nonhematologic toxicity was uncommon. In particular, there was no excessive skin reaction in prior radiated areas on the scalp and no recognized neurologic toxicity (*such as leukoencephalopathy*) to suggest that topotecan chemotherapy increased the toxicity of prior radiation therapy. All patients had received prior radiation. The degree of hematologic toxicity may have been slightly greater in those who had received prior chemotherapy (*mainly nitrosoureas*) than in chemotherapy naive patients. Although the objective response rate (6.5%) was low, 68% had stable disease suggesting that topotecan has perhaps some activity in malignant glioma. This combined with the tolerable toxicity suggests that further investigation, either in different dose schedules, or as a radiation sensitizer, is warranted.

2.0 OBJECTIVES

- 2.1 To determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of combined topotecan and cranial radiation therapy.
- 2.2 To determine that acute and delayed treatment-related toxicity is acceptable with this study regimen.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Histologically confirmed glioblastoma multiforme; gliosarcomas are also eligible.
- 3.1.2 Diagnosis must be made by surgical biopsy or excision.
- 3.1.3 The tumor must be supratentorial in location.
- 3.1.4 Therapy must begin within five weeks of surgery.
- 3.1.5 Patients must not have received prior radiotherapy to the head and neck, chemotherapy, or radiosensitizer therapy.
- 3.1.6 Age ≥ 18 years.
- 3.1.7 Karnofsky Performance Status ≥ 50% (*Appendix II*)
- 3.1.8 Neurological Functional Status 0,1, or 2 (*Appendix II*)
- 3.1.9 Adequate bone marrow reserve (*hemoglobin*³ 10 g/dL, *absolute neutrophil count*³ 1500/mm³, *platelets*³ 100,000/mm³) and normal renal (*BUN* £25 mg/dL and *creatinine* £1.5 mg%) and hepatic (*bilirubin* £ 1.5 mg% and *SGPT or SGOT* £ twice normal range) function. **All mandatory studies specified in**

Section 4.1 must have been performed.

- 3.1.10** A diagnostic CT scan (*or MRI*) with and without contrast must be performed preoperatively and postoperatively prior to the initiation of radiotherapy.
- 3.1.10.1** A post-operative scan is not required if the extent of surgery was a stereotactic biopsy.
- 3.1.11** Patients must have signed a study-specific informed consent. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the patient's legal representative.
- 3.1.12** Women with child-bearing potential must have a negative pregnancy test (*or other definitive evidence of no pregnancy*) and all sexually active patients must practice contraception while undergoing treatment and for three months post treatment.
- 3.1.13** Steroid dose must be stable for one week prior to entry.

3.2 Ineligibility Criteria

- 3.2.1** Well differentiated or anaplastic astrocytoma.
- 3.2.2** Multifocal glioma.
- 3.2.3** Recurrent glioblastoma multiforme.
- 3.2.4** Patients with prior malignancies, except carcinoma *in situ* of the cervix or nonmelanomatous skin cancer, unless disease free ≥ 3 years.
- 3.2.5** Major medical illness(es) or psychiatric impairment(s) that will prevent completion of protocol therapy or would interfere with follow-up.
- 3.2.6** Inability to obtain histologic proof of glioblastoma.
- 3.2.7** Patients with acquired immune deficiency syndrome (*AIDS*).
- 3.2.8** Inability to meet eligibility requirements in Section 3.1.

4.0 PRETREATMENT EVALUATION

4.1 Mandatory Studies

- 4.1.1** Complete medical history and general physical examination (*to include vital signs*).
- 4.1.2** CT or MRI scan with and without contrast performed preoperative and postoperatively prior to the initiation of radiotherapy (*mandatory for eligibility*); same type of scan must be used both preoperatively and postoperatively.
- 4.1.3** CBC with differential, platelet count, blood chemistries (*SMA 12*).
- 4.1.4** Detailed neurological examination (*to include mini mental status evaluation*) immediately prior to beginning protocol treatment course.
- 4.1.5** Chest x-ray.

4.2 Additional Studies

- 4.2.1** Additional renal or liver function tests as indicated.

5.0 REGISTRATION PROCEDURES

- 5.1** 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 a.m. to 5:00 p.m. ET. The patient will be registered and a case number will be assigned and confirmed by mail.

The following information must be provided:

- Institution name and number
- Patient's name and ID number
- Verifying physician's name
- Eligibility criteria information
- Demographic data
- Treatment start date

- 5.2** Institutions with IRB approval for RTOG 94-17 (*limited participation study*) must enter eligible patients to that study until it meets accrual requirements.

6.0 RADIATION THERAPY

6.1 General Requirements

- 6.1.1** Treatment will be delivered with megavoltage photon beam machines of energy ≥ 4 MeV. Electron, particle, or implant boost is not permissible.

- 6.1.2** The patient may be treated in the supine or other appropriate position. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. The treatment volume for both the initial volume and the conedown volume will be based on the preoperative CT/MRI.
- 6.1.2.1** The initial treatment volume will include the contrast-enhancing lesion and surrounding edema (*if it exists*) demonstrated on CT/MRI plus a 2.0 cm margin. If no surrounding edema is present, the initial treatment volume should include the contrast-enhancing lesion plus a 2.5 cm margin.
- 6.1.2.2** For the first 46 Gy/23 fractions, the treatment volume should include the volume of contrast-enhancing lesion and surrounding edema on preoperative CT/MRI scan plus a 2.0 cm margin. After 46 Gy, the treatment volume should include the contrast-enhancing lesion (*without edema*) on the presurgery CT/MRI scan plus a 2.5 cm margin.
- 6.1.3** Treatment plans may include opposed lateral fields, a wedge pair of fields, or multiple field techniques. CT or MRI-guided treatment planning is necessary to assure accuracy in the selection of field arrangements. Inability to achieve field placement as defined by the protocol will result in variation scores at RTOG Headquarters review. Isodose distributions for the initial target volume and the conedown target volume are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the dose distribution to the initial treatment volume and the boost treatment volume. The inhomogeneity in dose across the target volume will be kept to a minimum. The minimum and maximum doses to the treatment volume should be $\pm 5\%$ of the dose at the center of the volume. The maximum dose should be to a cross-sectional area $\leq 2 \text{ cm}^2$. The use of vertex fields require either a diagram or photograph of treatment position to be submitted to RTOG headquarters. There must be at least two shaped treatment fields with each field treated daily. Treatment with a single beam is not acceptable. Port films of each field will be taken weekly.

6.2 Dose Definition and Schedule

- RT must begin within one week of registration. Treatment will be given in 2 Gy fractions once daily. All treatment volumes will be based on preoperative CT/MRI. The initial 46 Gy in 23 fractions (*2 Gy/fraction*) will be delivered to the initial treatment volume. The final 14 Gy in 7 fractions will be delivered to the boost treatment volume. All portals will be treated during each treatment session. Doses are specified as the treatment dose which will be to the center of the treatment volume. For the following portal arrangements, the target dose will be specified as follows:
- 6.2.1** For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
- 6.2.2** For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.
- 6.2.3** For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
- 6.2.4** Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.
- 6.2.5** The technique of using two opposing co-axial, unequally-weighted fields is not recommended due to unacceptable hot spots and unacceptable tissue inhomogeneity. However, if this technique is utilized, the dose will be specified at the center of the treatment area.
- 6.2.6** Other or complex treatment arrangements: at the center of the target area.

6.3 Dose Limitation to Critical Structures

- The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 50 Gy, the retina of at least one eye (*but preferably both*) to 50 Gy, and the brain stem to 60 Gy. When the optic chiasm must be included in the full dose, then there may be a finite unknown risk of developing blindness.

6.4 Documentation Requirements

- A copy of the pretreatment (*pre- and post-op*) CT/MRI, the treatment prescription form, treatment calculation form, simulation films, and representative portal films of each initial field must be forwarded to RTOG Headquarters within one week of treatment start. At the completion of treatment, the following will also be forwarded to Headquarters: daily treatment record, all isodose distributions including a composite plan, simulation and portal films of the reduced fields, and the Radiotherapy Form.

6.5 Acute Radiation Toxicities

- 6.5.1** Expected toxicities include loss of hair and erythema of the scalp. Reactions in the ear canals and on the ear should be observed and treated symptomatically. If significant increase (*grades ³ 3*) in reaction of the normal tissue occurs, it should be noted and reported to the Study Chairman.
- 6.5.2** Both acute and delayed or late reactions to radiotherapy are to be recorded and included in the complete toxicity evaluation. The level of radiation toxicity will be scored on a scale of 0-5 as described in Appendix IV-B.

- 6.5.3 Hematologic toxicities should be rated on a scale of 0-5 as defined in the RTOG Toxicity Criteria (*Appendix IV-B*).
- 6.5.4 Grade ≥ 3 will be reported per Appendix V.
- 6.6 **Adverse Reaction Reporting (RTOG FAX: (215) 928-0153)**
- 6.6.1 All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
- 6.6.2 All life-threatening (*grade 4*) toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
- 6.6.3 Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

7.0 Drug Therapy

7.1 Topotecan: (NSC #609699, IND#34,494)

7.1.1 Schedule

For the first two cycles of topotecan, each dose of topotecan will be administered as a 30 minute intravenous infusion immediately prior to RT. RT must be initiated up to 1/2 to 2 hours post topotecan infusion. Topotecan will be administered as 0.5 mg/m²/day five times each week every three weeks for a total of 3 cycles (*Level 1*). For the first cycle of topotecan, topotecan should be administered concurrently with the first 5 treatments, ideally 5 days a week. For the second cycle, topotecan will be administered with treatments 16-20. For the first two cycles of topotecan, topotecan must not be given on days when no radiation is given. For Level 2, the dose of topotecan will be increased to 1.0 mg/m²/day. If toxicity is acceptable

at Level 1. A further dose escalation to 1.5 mg/m²/day will take place if toxicity is acceptable at Level 2. A maximum of 3 cycles of topotecan will be administered to each patient. The time infusion starts and ends and time of radiation treatment must be recorded on flow sheets.

7.1.2 Names, Chemical Nature, Classification and Mode of Action (6/3/96)

Topotecan, AS hycamptamine, SK&F 104864-A. 9-dimethyl-10-hydroxycamptothecin. (S)-10-[dimethylaminomethyl]4ethyl-4,9,-dihydroxy-1-H-pyrano[3',4':6,7]indolizino[1,2-b] quinoline-3,14(4H,12H)-dione monohydrochloride; molecular formula: C₂₃H₂₃O₅N₃. HCl; MW: 458 daltons. Topoisomerase inhibitor. Binds to the nuclear enzyme, topoisomerase-1, causing disruption of DNA continuity and replication.

7.1.3 Physical Description (6/3/96)

It is supplied as a light-yellow lyophilized powder in vials containing 4 mg of topotecan AS(*as the base*) and 48 mg mannitol and 20 mg tartaric acid, NF. The pH is adjusted to 3.0. It has a reverse magenta label for identification purposes.

Unreconstituted topotecan should be stored at room temperature 15-30°C (59-86°F) in the light-proof packaging provided and must be protected from light until it is administered to patients. Information on expiration dates will be supplied on a lot-by-lot basis. All cancer chemotherapeutic agents should be handled with the utmost care during preparation and administration. To avoid any form of physical contact, the health care provider should wear gowns, gloves and masks when appropriate. As a parenteral agent, topotecan should be prepared in a vertical flow biologic safety cabinet. As an investigational agent, topotecan must be kept in a secure area and may be supplied only to patients treated in accordance with this protocol under the direction of the investigator. The unreconstituted vials contain no antibacterial preservative. Use within eight hours, unless the vials have been reconstituted with Bacteriostatic Water USP, in which case vials are good for 21 days at refrigerator temperatures.

7.1.4 Drug Ordering (6/3/96)

Topotecan AS is supplied through the Pharmaceutical Management Branch (*PMB*) for DCTDC-sponsored clinical trials as 4 mg vials, NSC #609699. Once eligibility is established and the individual has been registered, drug may be ordered by completing a NCI Clinical Drug Request (*NIH-986*) form and mailing it to PMB, CTEP, DCTDC, NCI, 9000 Rockville Pike, EPN Room 707, Bethesda, MD 20892, through the DMAS Electronic Clinical Drug Request System (*ECDR*) or by Fax (*301*) 480-4612. For questions call (*301*) 496-5725.

7.1.5 Drug Preparation for Clinical Administration (6/3/96)

Topotecan is to be administered intravenously after dilution in 0.9% sodium chloride injection or 5% dextrose injection. UNTIL SPECIFIC COMPATIBILITY DATA ARE AVAILABLE, MIXING TOPOTECAN WITH OTHER IV FLUIDS OR DRUGS IS NOT RECOMMENDED. TOPOTECAN MUST NOT BE DILUTED WITH BUFFERED SOLUTIONS BECAUSE OF SOLUBILITY AND STABILITY CONSIDERATIONS. The lyophilized formulation must be reconstituted with 4 ml of sterile water for injection, USP, yielding a 1 mg/ml solution of topotecan AS prior to dilution with .9% Na Cl or 5% dextrose. Because the lyophilized form contains no antibacterial preservatives, it is advised that the reconstituted (*undiluted*) solution be discarded 8 hours after initial entry. The final concentration of topotecan solution should be 10-500 µg/ml in 0.9% Na Cl or 6.7-339 µg/ml in 5% dextrose. The desired amount of drug should be added to an IV solution bag, mixed and delivered within 24 hours. Remove the needle from the syringe and replace it with a filter needle. Keep bottle or bag protected from light. The bottle or bag may be prepared the night prior to dosing day and stored at refrigerator temperature (2°-8° C).

7.1.6 Discontinuation of Topotecan

7.1.6.1 For grade 4 hematological toxicity lasting > 3 days or ≥ grade 3 nonhematological toxicity, topotecan will be withheld until resolution of the toxicity to ≤ grade 1. Topotecan administration may then be restarted if medically appropriate at a dose reduced by 25%. If topotecan must again be withheld because of topotecan-related toxicity, drug administration will be discontinued. If symptoms are not manageable the patient goes off protocol therapy. All patients in whom topotecan or radiation treatment are discontinued will continue to be monitored for survival. Patients may be treated as outpatients, but they will remain under direct observation for at least one hour following the first topotecan administration. Fever (*unrelated to infection*) may be treated with antipyretics. Patients must be supplied with a medical contact who is available 24 hours daily.

7.1.6.2 Tumor progression documented by CT/MRI scan.

7.1.6.3 Intercurrent illness which would in the judgement of the investigator require discontinuation of the drug.

7.1.6.4 Patient request to withdraw from study.

7.1.7 Drug Inventory Records

The pharmacist, as a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCT, using the NCI Drug Accountability Record Form (*see Investigators Handbook for Procedures for Drug Accountability and Storage*).

7.2 Topotecan Toxicity

Common adverse events reported include mild to moderate nausea and vomiting, which have been successfully controlled with anti-emetics (*eg. prochlorperazine, or ondansetron*). Alopecia, stomatitis, fever, anorexia, fatigue, elevations of liver function tests, flu-like symptoms, abdominal pain, dehydration, and diarrhea have been reported. Cutaneous toxicity has been mostly mild. Often this has consisted of localized erythema, with or without pruritus. The major dose-limiting toxicity is topotecan-related myelosuppression.

7.3 Dose Modification

7.3.1 Toxicity will be graded according to the criteria in Appendix IV. If any grade 4 (*platelets < 25,000 mm³, granulocytes < 500 mm³*) hematological toxicity lasting > 3 days or any grade 3 or 4 topotecan-related nonhematological toxicity is observed in any patient and is not controlled acutely by palliative measures, topotecan administration to that patient will cease immediately. Topotecan will be withheld until resolution of the toxicity to ≤ grade 1. Topotecan administration may then be restarted if medically appropriate at a dose reduced by 25%. If topotecan must again be withheld because of topotecan-related toxicity, drug administration will be discontinued. Cranial radiation will continue unless toxicity is attributed to radiation, in which case radiation will be held until toxicity resolves.

NADIR COUNTS			
Absolute Granulocyte Count (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose <u>Next</u> Cycle
≥ 0.5 or < 0.5 for ≤ 3 days	AND	≥ 25	No change
< 0.5 for >3 days	OR	< 25	Reduce by 25% of dose previous cycle.

febrile neutropenia, ≥ grade 3 infection	OR	bleeding requiring transfusion	Reduce by 25% of dose previous cycle.
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TREATMENT DAY (<i>DAY 1 COUNTS</i>)			
Absolute Granulocyte Count ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	Dose <u>This</u> Cycle
≥ 1.5	AND	≥ 100	Treat on time. Adjust dose according to nadir count previous cycle.
< 1.5	OR	< 100	Delay until recovery. Adjust dose according to nadir count previous cycle.

7.3.2 This study will involve a dose escalation of topotecan in three increments 0.5, 1.0 and 1.5 mg/m²/day x 5 days q 3 weeks x maximum 3 cycles. Ten evaluable patients will be analyzed at each dose level. To be evaluable a patient must have received treatment and be analyzed at week 15 for toxicity. After 10 evaluable cases have treatment results available, these cases will be analyzed with respect to unacceptable toxicity (*defined at ³ grade 3 nonhematological or ³ grade 4 hematological toxicity lasting >7 days*). If any fatal toxicities occur, accrual will be immediately suspended for that dose level and the study will be re-evaluated. **(1/31/96)**

7.3.3 The study chair and RTOG protocol office must be notified of each event of unacceptable toxicity (*patient number, toxicity, toxicity grade, relationship to protocol treatment, duration, outcome - if known*) within 3 working days of onset, to minimize the risk that the study will continue to inappropriately accrue patients to a dose level.

7.4 Adverse Reaction Reporting (RTOG FAX: (215) 928-0153)

7.4.1 Any Adverse Event

All adverse events, regardless of severity and whether or not ascribed to topotecan, are to be recorded on the appropriate data form. Patients withdrawn from the study due to any adverse event will be followed.

7.4.2 Serious Adverse Event

According to Federal Regulation 21 CFR 312.32, a serious adverse event is defined as any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug event includes any experience that is fatal or life-threatening, permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

7.4.2.1 Serious adverse events must be reported to:

- a. The IRB - To comply with Federal Regulations, each investigator will make an accurate and special report to the IRB on all serious adverse events, deaths, or life-threatening problems which were not previously anticipated (*in nature, severity, or degree of incidence*) and which may reasonably be regarded as caused by or associated with topotecan.
- b. IDB/NCI and RTOG - To provide IDB/NCI and RTOG with enough information to adequately assess the overall safety profile of the investigational drug, each investigator shall make an accurate and special report to IDB/NCI on all serious adverse events, deaths, or life-threatening problems whether unanticipated or not.

Investigational Drug Branch

RTOG ADR

P.O. Box 30012
 Bethesda, MD 20824
 Phone (301) 230-2330
 (available 24 hours)
 Fax (301) 230-0159

Calls to RTOG should be made to
 the Study Research Associate
 Phone (215) 574-3150
 Fax (215) 928-0153

- c. Report Time Requirements - Report to Investigational Drug Branch by telephone (301-230-2330) or fax (301-230-0159) within 24 hours:
- all life-threatening (grade 4 and 5) unknown reactions.
 - life-threatening (grade 4) and lethal (grade 5) known reactions (This does not include myelosuppression. Grade 4 myelosuppression should be submitted as part of study results).
 - grade 2 and 3 unknown reactions.
 - written report to follow within 10 working days.

In the event of any grade ≥ 3 non-hematologic toxicity or grade ≥ 4 hematologic toxicity, RTOG Headquarters is to be notified by phone within 24 hours and appropriate data forms submitted within 7 days.

Copies of each report will be kept in the investigator's files and adequate documentation provided to IDB/NCI that the IRB has been properly notified.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Corticosteroids and Other Medication

9.1.1 Corticosteroids may be utilized as deemed necessary by the individual investigator. Corticosteroids will be used in the smallest dose that will afford the patient satisfactory neurologic function and the best possible quality of life.

9.1.2 Phenytoin sodium and other anti-seizure medication may be used as indicated clinically. All medications and doses are to be documented.

9.1.3 Infections are to be treated with appropriate antibiotics and recorded. If infection precludes topotecan therapy for more than two weeks, the patient will be discontinued from the study.

9.1.4 Analgesics, antiemetics, and any other medications are to be specified, and their doses recorded.

9.2 Additional treatment for disease progression

9.2.1 Disease recurrence or progression should be documented by neurologic examination and CT/MRI. Appropriate therapy will then be administered at the discretion of the investigator. Such therapy may consist of additional chemotherapy, repeat surgery, placement of a shunt, interstitial brachytherapy, radiosurgery, or supportive care. All therapy shall be documented.

9.2.2 Every effort will be made to ensure patient comfort at all times. Patients will be informed that their elective withdrawal from this protocol will in no way jeopardize their care, and they will be encouraged to continue their follow-up therapy independent of participation in this study.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters Table

<u>Assessments</u>	<u>Prior to Therapy</u>	<u>During Radiotherapy</u>	<u>At Initiation of each Topotecan Cycle</u>	<u>Follow-up (q3 months) See Sec. 12.1</u>
Neurological exam/H&P	X	weekly	X	X
Vital Signs (TPR, BP)	X		X	
Toxicity evaluation	X	weekly	X	X
CBC, differential and platelet count	X	weekly	weekly until 3 weeks post-3rd cycle of chemotherapy	X

Serum chemistries including serum creatinine	X		X	q3 months for 1 year
Anticonvulsant levels	X		X	
Chest x-ray	X			
CT scan with contrast and/or MRI* with and without gadolinium	X Both pre-operative and post-operative pre-radiotherapy			q3 months after start of radiotherapy, and at time of neurologic deterioration unless the last CT/MRI had been done within 1 month and was compatible with recurrence
Mini mental status evaluation	X		X	q3 months from beginning of treatment

***Note: It is mandatory that patients are followed with the same study (CT or MRI) as the baseline study.**

11.2 Evaluation During Study

- 11.2.1** A neurologic examination will be performed once a week during radiation therapy, at initiation of each chemotherapy cycle and at each follow-up visit.
- 11.2.2** Skin within the treatment portal will be examined at least once per week during radiation therapy and first post-treatment visit. The degree of skin reaction should be recorded. If moist desquamation develops, or is threatening to develop in an area that is larger than 1-2 cm in diameter, then the study chairman should be notified immediately and therapy (*topotecan and RT*) should be interrupted for a few days to allow for healing.
- 11.2.3** The contrast-enhanced CT/MRI of the brain will be obtained prior to surgery and prior to radiotherapy (*post-surgery*), and at intervals specified in Section 11.1 and at the time of neurologic deterioration unless the last CT/MRI done was within one month and was compatible with recurrence. Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually with the first two weeks post-treatment and last up to 6-8 weeks. These transient adverse signs and symptoms spontaneously improve without therapy. They are considered to be due to transient demyelination.³⁶ Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first two or three months post-irradiation. CT/MRI is not required after documentation of tumor progression or recurrence.

11.3 Criteria for Evaluation of Toxicity

- 11.3.1** As per Section 13.2 this study is to evaluate toxicity and determine optimum dose of topotecan combined with cranial radiation for malignant gliomas.
- 11.3.2** Post-mortem examination for the cranial contents should be obtained at death whenever possible to evaluate effects of this therapy on malignant and normal brain tissue. It is especially important that if deaths occur on study or within 30 days of topotecan administration, an autopsy must be sought by the treating physician.

11.4 Follow-up for Cancelled and Ineligible Cases

- 11.4.1** Eligible patients who refuse all treatment will be cancelled and removed from follow-up.
- 11.4.2** All cases receiving any topotecan will be followed for survival and morbidity data.
- 11.4.3** Ineligible cases who do not receive any protocol therapy will not be followed.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 1 wk of study entry
Baseline Mini Mental Status Evaluation (MS)	
Initial Evaluation Form (I1)	Within 2 wks of study entry
Diagnostic Pathology Report (P1)	
Study-Specific Flowsheet (SF) (<i>pre-study labs</i>)	

<u>Preliminary dosimetry information:</u> RT prescription (<i>Protocol Treatment Form</i>) (T2) Films (<i>simulation and portal</i>) (T3) Calculations (T4) Pretreatment (<i>pre- and post-op</i>) CT/MRI scans (C1) and reports (C3)	Within 1 wk of start of RT
Radiotherapy form (T1) <u>Final dosimetry information:</u> Daily treatment record (T5) Isodose distribution (T6) Boost films (<i>simulation and portal</i>) (T8) Study-specific flowsheet (SF)	Within 1 wk of RT end
Post RT/CT/MR scan (C2) and reports (C3) 3 months from start of RT Study-Specific Flowsheet (SF)	One month from last dose of topotecan
Follow-up form (F1) Mini mental status evaluation (MS)	Every 3 months from treatment start for 1 yr; q4 months x 1 yr, q6 months x 3 yrs, then annually. Also at progression/relapse and at death (<i>FI only</i>).
Adverse event form (K4) Autopsy report (D3)	As applicable

12.2 Recording of Toxicity

All toxicities \geq grade 3 must be documented on the Study-Specific Flowsheets as to date of onset and date of resolution to \leq grade 2.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Toxicity

13.2 Sample Size (1/31/96)

This study will involve a dose escalation of topotecan in three increments 0.5, 1.0 and 1.5 mg/m²/day x 5 days q3 weeks x maximum 3 cycles. To be evaluable, a patient must have received treatment and be analyzed at week 15 for toxicity. After 10 evaluable cases have treatment results available, these cases will be analyzed with respect to unacceptable toxicity (*defined at ³ grade 3 nonhematological or ³ grade 4 hematological toxicity lasting > 7 days*). If any fatal toxicities occur, accrual will be immediately suspended for that dose level and the study will be re-evaluated. If there are no fatal toxicities and 0 patients with unacceptable toxicity, the dose of topotecan be escalated. If 1 of the first 5 patients or 2 of 10 patients have unacceptable toxicity, accrual will continue until 5 additional cases are evaluated with treatment results. These 5 cases will be analyzed with respect to toxicity and if 0 or 1 of these patients have unacceptable toxicity then the dose can be escalated. If there are \geq 3 patients of the first 10 patients in a cohort or \geq 4 of the 15 patients in a cohort with unacceptable toxicity, the previous topotecan dose level will be accepted as the maximally tolerated dose. **Total sample size will be maximum of 45 patients.** All treated patients will be considered for toxicity evaluation.

13.3 Patient Accrual

The patient accrual is projected to be 9 cases per month, based upon the monthly accrual for RTOG 94-11. At that rate, it will take six months for the required accrual for the phase I study. If the average monthly accrual rate is less than three patients, the study will be re-evaluated with respect to feasibility.

13.4 Suspension of Accrual Due to Morbidity

If there is any fatal treatment morbidity, the accrual will be suspended, and all data pertaining to the event will be reviewed by the study chairs and reported to the RTOG Data Monitoring Committee (DMC) for review.

13.5 Dose Escalation (1/31/96)

Dose escalation of topotecan will be in three increments of 0.5, 1.0 and 1.5 mg/m²/day x 5 days q 3 weeks x maximum 3 cycles. Each dose level will be evaluated when 10 evaluable patients have survived 15 weeks from the start of therapy. If no unacceptable toxicities are observed, then the dose of topotecan will be escalated. If 1 or 2 unacceptable toxicities are observed within the first 10 evaluable patients, then five additional evaluable patients will be accrued. If fewer than three acceptable toxicities occur within the first 15 evaluable patients then the dose will be escalated. If three or more unacceptable toxicities are observed then the previously acceptable dose of topotecan will be accepted as the maximum tolerated dose.

13.6 Analyses Plans

13.6.1 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) the quality of submitted data with respect to timeliness, completeness, and accuracy;
- c) the frequency and severity of the toxicities.

Through examining the above items, the RTOG DMC 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 RTOG Executive Committee, so that corrective action can be taken.

13.6.2 Analysis for Reporting the Initial Treatment Results (1/31/96)

This analysis will be undertaken when each patient has been potentially followed for 15 weeks. 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. Further subgroup analyses will not be undertaken due to the small sample size.

REFERENCES

1. Walker MD, Green SB, Byar DP et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med* 1980; 303: 1323-1329.
2. EORTC Brain Tumour Group. Effect of CCNU on survival rate of objective remission and duration of free interval in patients with malignant brain glioma - final evaluation. *Eur J Cancer* 1978; 14: 851-856.
3. Kornblith PL, Walker M. Chemotherapy for malignant gliomas. *J Neurosurg* 1988; 68: 1-17.
4. Fine HA, Dear KB, Loeffler JS, et al. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993; 71: 2585-2597.
5. Schold SC Jr, Herndon JE, Burger PC, et al. Randomized comparison of diaziquone and carmustine in the treatment of adults with anaplastic gliomas. *J Clin Oncol* 1993; 11: 77-83.
6. Bigner DD. Biology of gliomas: potential clinical implications of glioma cellular heterogeneity. *Neurosurgery* 1981; 9: 320-326.
7. Kornblith PL, Szytko PE. Variations in response of human brain tumours to BCNU *in vitro*. *J Neurosurg* 1978; 48: 580-586.
8. Yung WA, Shapiro JR, Shapiro WR. Heterogeneous chemosensitivities of subpopulations of human glioma cells in culture. *Cancer Res* 1982; 42: 992-998.
9. Vick NA, Khandekar JD, Bigner DD. Chemotherapy of brain tumours: the "blood-brain barrier" is not a factor. *Arch Neurol* 1977; 34: 523-526.
10. Lesser GJ, Grossman S. The chemotherapy of high-grade astrocytomas. *Sem Oncology* 1994; 21: 220-235.
11. Neuwelt EA, Howieson J, Fenkel EP, et al. Therapeutic efficacy of multiagent chemotherapy with drug delivery enhancement by blood-brain barrier modification in glioblastoma. *Neurosurgery* 1986; 19: 573-582.
12. Gumerlock MK, Belshe BD, Madsen R, et al. Osmotic blood-brain barrier disruption and chemotherapy in the treatment of high grade malignant glioma: Patient series and literature review. *J Neurooncol* 1992; 12: 33-46.
13. Mahaley MS Jr, Hipp SW, Dropcho EJ, et al. Intracarotid cisplatin chemotherapy for recurrent gliomas. *J Neurosurg* 1989; 70: 371-378.
14. Shapiro WR, Green SB, Burger PC, et al. A randomized comparison of intra-arterial versus intravenous BCNU, with or without intravenous 5-fluorouracil, for newly diagnosed patients with malignant glioma. *J Neurosurg* 1992; 76: 772-781.
15. Brem H, Mahaley MS Jr, Vick NA, et al. Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. *J Neurosurg* 1991; 74: 441-446.
16. Fine HA, Antman KH. High-dose chemotherapy with autologous bone marrow transplantation in the treatment of high grade astrocytomas in adults: Therapeutic rationale and clinical experience. *Bone Marrow Transplant* 1992; 10: 315-321.
17. NCI Annual Report to the Food and Drug Administration: Topotecan HCl (NSC 609 699), IND 34494, June 1991.
18. SmithKline Beecham Pharmaceuticals. Investigator Brochure. Topotecan SK&F 104864-A, 1994.
19. Lock RB and Ross WE. DNA Topoisomerases in cancer Therapy. *Anticancer Drug Design*, 1987; 2: 151-164.
20. Eng WK, Faucette L, Johnson RK, et al. Evidence that DNA topoisomerase I is necessary for the cytotoxic effects of

camptothecin. *Molecular Pharm*, 1989; 34: 755-760.

21. Johnson RK, McCabe FL, Faucette LF, et al. SK&F 104864, A Water-Soluble Analog of Camptothecin with a Broad Spectrum of Activity in Preclinical Tumour Models. *Proc Am Assoc Cancer Res* 1989; 30: 623.
22. Burris H, Kuhn J, Johnson R, et al. SKF 104864: Preclinical studies of a new topoisomerase I inhibitor. *Proc Am Assoc Cancer Res* 1990; 31: 431.
23. Sirott MN, Saltz L, Young C, et al. Phase I and clinical pharmacologic study of intravenous topotecan. *Proc Am Soc Clin Oncol* 1991; 10: 104.
24. Rowinsky E, Grochow L, Hendricks C, et al. Phase I and pharmacologic study of topotecan (SK&F 104864): A novel topoisomerase I inhibitor. *J Clin Oncol* 1992; 10: 647-656.
25. Verweij J, Lund B, Beynen J, et al. Clinical studies with topotecan: The EORTC experience. *Proc 7th NCI-EORTC symposium on New drugs in cancer therapy. Ann Oncol* 1992; Suppl 1, 3: 118.
26. Boothman DA, Wang M, Schea RA, et al. Posttreatment exposure to camptothecin enhances the lethal effects of x-rays on radioresistant human malignant melanoma cells. *Int J Radiat Oncol Biol Phys* 1992; 24: 939-948.
27. Mattern MR, Hofmann GA, McCabe FL, Johnson RK. Synergistic cell killing by ionizing radiation and topoisomerase I inhibitor Topotecan (SK & F 104864). *Cancer Res* 1991; 51: 5813-5816.
28. Kim JH, Kim SH, Kolozsvary A, Khil MS. Potentiation of radiation response in human carcinoma cells *in vitro* and murine fibrosarcoma *in vivo* by topotecan, an inhibitor of DNA topoisomerase I. *Int J Radiat Oncol Biol Phys* 1992; 22: 515-518.
29. Boscia RE, Korbut T, Holden SA, et al. Interaction of topoisomerase I inhibitors with radiation in cis-diamminedichloroplatinum (II)-sensitive and -resistant cells *in vitro* and in the FSaIIC fibrosarcoma *in vivo*. *Int J Cancer* 1993; 53: 118-123.
30. Friedman HS, Houghton PJ, Schold SC, et al. Activity of 9-dimethylaminomethyl-10-hydroxycamptothecin against pediatric and adult central nervous system tumor xenografts. *Cancer Chemother Pharmacol* 1994; 34: 171-174.
31. Blaney SM, Cole DE, Balis FM, et al. Plasma and cerebrospinal fluid pharmacokinetic study of Topotecan in nonhuman primates. *Cancer Res* 1993; 53: 725-727.
32. Pratt CB, Stewart C, Santana VM, et al. Phase I study of topotecan for pediatric patients with malignant solid tumors. *J Clin Oncol* 1994; 12: 539-543.
33. Eisenhauer EA, Wainman N, Boos G, et al. Phase II trials of topotecan in patients (pts) with malignant glioma and soft tissue sarcoma (abstract 488). *Proc Am Soc Clin Oncol* 1994; 13: 175.

APPENDIX I (10/13/95)

RTOG 95-07

**PHASE I STUDY OF TOPOTECAN
PLUS CRANIAL RADIATION FOR GLIOBLASTOMA MULTIFORME**

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 I have an opportunity to decide whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I understand that I have been diagnosed with a malignant brain tumor called a glioblastoma multiforme and further treatment is recommended. The usual treatment in cases such as mine is radiation therapy given once daily, five days per week for six weeks. Radiation therapy is a form of cancer treatment using high energy x-rays and can be given with or without either chemotherapy or other medications.

This study is being done to assess the side effects when topotecan, a new medicine, is given together with radiation therapy. Forty-five patients will be treated on this study.

DESCRIPTION OF PROCEDURES

This study involves daily radiation treatments to the part of my brain involved with tumor. Radiation treatments will be given five times a week for six weeks. Topotecan will be given before my radiation five times a week as an intravenous ("*i.v.*", *in my vein*) over 30 minutes. I will receive topotecan during the first and fourth weeks of radiation treatment. A third course of topotecan will be given during the week following radiation. The Division of Cancer Treatment, National Cancer Institute will provide topotecan free of charge for this study but should this agent become commercially available or approved for this indication during the course of this study, however, I may be asked to purchase subsequent doses of the medication.

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.

Risks from Radiation Therapy: include some or all of the following side effects: scalp redness, or soreness, hair loss, which may be temporary or permanent, dry mouth or altered taste, hearing impairment, fatigue, sleepiness or temporary aggravation of tumor symptoms such as headaches, seizure, or weakness. Cataracts may occur, although every effort will be made to minimize the chances of this occurring. Radiation sometimes causes late side effects such as mental slowing or behavioral change. Occasionally radiation causes severe local damage to normal brain tissue, a condition called necrosis. Radiation necrosis can mimic recurrent brain tumor or those of a stroke and may require surgery.

Risks from Topotecan: include appetite loss, sore mouth, fever, flu-like illness, abdominal pain, dehydration, severe diarrhea, and mild to moderate nausea and vomiting which have been successfully controlled with antiemetics. Hair loss and skin rashes usually with itching have been reported. A temporary drop, sometimes very severe, in the level of red blood cells, white blood cells and/or platelets in the blood occurs and this may put me at risk of infection or bleeding. Temporary changes in blood tests of liver or kidney function have been seen. Topotecan might increase the risk of early or delayed damage to the brain that can be seen with radiation therapy alone. With any treatment there is a small risk of new or unexpected side effects, including death occurring. Contraceptive precautions must be taken.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done

to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. 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.

This study may be harmful to an unborn child. There is insufficient medical information to see whether there are significant risks to a fetus carried by a mother who is participating in this study. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy test prior to participating in this study. This requires that a small amount of blood be drawn within 7 days prior to the study. The results will be made available to me prior to the initiation of this study. There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

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 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 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 either surgery or radiation therapy either alone or with chemotherapy 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. 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 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

NEUROLOGIC FUNCTION (NF) STATUS

<u>N F</u>	<u>Definition</u>
0	No neurologic symptoms; fully active at home/work without assistance.
1	Minor neurologic symptoms; fully active at home/work without assistance.
2	Moderate neurologic symptoms; fully active at home/work but requires assistance.
3	Moderate neurologic symptoms; less than fully active at home/work and requires assistance.
4	Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

APPENDIX III

NEUROLOGICAL FUNCTIONAL CLASSIFICATION

A neurological evaluation and assignment to a functional class will be performed for each patient in the study. The patient will be classified as below:

- Class I - Able to work, neurological findings minor or absent.
- Class II - Able to be at home although nursing care may be required. Neurological findings present but not serious.
- Class III - Requiring hospitalization and medical care with major neurological findings.
- Class IV - Requiring hospitalization and in serious physical or neurological state including coma.

Class	Ability to Work	Hospital (<i>bed</i>)	Neurologically Impaired
I	+	-	0,1
II	-	- to ±	2
III	-	+ to +	3
IV	-	-	4

NEUROLOGICAL PERFORMANCE

Neurological Symptoms

(to be scored as follows: 0-absent, 1-mild, 2-moderate, 3-severe)

Headache
Visual Disturbance
Speech Impairment
Sensory Symptoms
Motor Symptoms
Memory Lag
Personality Change
Seizures
Other (*specify*)

Neurological Signs

(to be scored as follows: 0-normal, 1-mildly impaired, 2-moderately impaired, 3-severely impaired)

Mental Status
Papilledema
Motor Deficit
Reflexes
Cranial Nerves (*specify abnormal one*)
Sensory Deficit
Cerebellar Deficit
Visual Fields
Other (*specify*)

APPENDIX V

ADVERSE REACTION REPORTING GUIDELINES

A. GENERAL 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. **When a protocol toxicity requires special handling, study-specific reporting procedures supercede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
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), 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 submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. 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.

Unknown toxicities are those thought to have resulted from the agent but have 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 (\geq *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. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *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. 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 a reasonable suspicion that the effect is due to protocol treatment.

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 FAX # 301-230-0159

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 (<i>grade 4</i>) | As above |

events which may be due to agent.

- 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 within 24 hours
**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*) unknown adverse reactions resulting from or suspected to be related to investigational agent.

Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.
**A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

Report **in writing to RTOG Headquarters and IDB within 10 working days.

** See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form

APPENDIX VI

RADIATION THERAPY PARAMETERS

The 2.5 cm margins (*for the boost fields*) are three-dimensional: superiorly, inferiorly, medially and laterally as well as anteriorly and posteriorly. (*See Diagrams A & B*)

Please note that it is important that the dose inhomogeneity be minimized particularly between the central axis dose and the tumor minimum dose. The protocol dose should be prescribed at the center of the target volume.

The inferior margin of the temporal lobe follows the outline of the sphenoid sinus. In order to encompass a 2.5 cm margin around most temporal lobe tumors, the entire temporal fossa usually needs to be included. In order to deliver a full dose to the inferior portion of the temporal fossa, the inferior border of the treatment portals should be below the bottom of the sphenoid sinus. (*See Diagram B*).

APPENDIX VI
(continued)

Diagram 1 illustrates that even with 6 MV photons utilizing parallel opposed portals, if the treatment portal encompasses the posterior occiput or the frontal region, it is obvious that without wedges the target minimum dose is 10% lower than the prescribed central axis dose, and there is a hot spot in the thinner portion that can be 10% to 15% hotter. These differences can be minimized with the use of wedges as in Diagram 2. The tumor minimum is only 2% lower than the central axis dose, and the hot spots are smaller and of lower dose. Isodose distributions are required for parallel opposed fields.

APPENDIX VI
(continued)

Diagram 3 is an example of a composite plan for an anteriorly located lesion with significant edema. By combining large 15 wedged parallel opposed fields to 57.60 (*Diagram 4*), it was possible to even out hot spots and treat the target volume to a high dose throughout with minimal gradient. Optimization of individual plans and the submission of composite plans is an essential requirement of this study.

APPENDIX VI
(continued)