

RADIATION THERAPY ONCOLOGY GROUP

RTOG BR-0119

A RANDOMIZED PHASE II STUDY OF A.M. AND P.M. MELATONIN FOR BRAIN METASTASIS IN RPA CLASS II PATIENTS

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RTOG Headquarters/Statistical Center

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SCHEMA

S		R	<u>Arm 1</u>
T	Chemotherapy Planned After Whole Brain Irradiation	A	Whole brain radiation therapy with concurrent a.m. melatonin
R		N	
A	1. No	D	
T	2. Yes	O	<u>Arm 2</u>
I		M	Whole brain radiation therapy with concurrent p.m. melatonin
F		I	
Y		Z	
		E	

Whole brain irradiation: 3 Gy daily between 2 p.m. – 6 p.m., five days a week for two weeks for a total dose of 30 Gy

Melatonin: 20 mg (*two capsules*) taken orally between 8 a.m.-9 a.m. **OR** between 8 p.m.-9 p.m. beginning on Day 1 of RT and continuing for six months or until disease progression

Protocol therapy must begin within 14 days of radiographic documentation of brain metastases. (11/5/02)

Eligibility: (*See Section 3.0 for details*) [11/5/02]

- Brain metastases from histologically-documented solid tumors (*except germ cell tumors*)
- RPA class II patients: Zubrod Performance status of 0-1 and any of the following: \geq 65 years of age; extra-cranial metastases; or uncontrolled primary malignancy
- Ineligible for or unwilling to enroll in current RTOG stereotactic radiosurgery trials
- No previous radiation to the brain
- No planned concurrent chemotherapy during the two weeks of whole brain irradiation (*Concurrent chemotherapy after irradiation, in patients with known disease, is allowed.*); prior chemotherapy is allowed if $>$ 30 days prior to registration
- Ability to participate in Mini-Mental Status Examination
- Ability to swallow pills
- Patients who are of reproductive age and/or who are sexually active must practice an effective method of birth control while on study.
- Patients must sign a study-specific informed consent form prior to study entry.

Required Sample Size: 128

RTOG Institution # _____

RTOG BR-0119

ELIGIBILITY CHECK (11/5/02)

Case # _____

(page 1 of 2)

- _____(Y) 1. Brain metastasis from histologically documented solid tumors (*except germ cell tumors*)?
- _____(Y) 2. Zubrod Performance status of 0-1 at the time of enrollment?
- _____(Y) 3. Any of the following: ≥ 65 years of age; extra-cranial metastases; or uncontrolled malignancy?
- _____(Y) 4. Ineligible for or unwilling to enroll in alternative RTOG stereotactic radiosurgery trials?
- _____(Y) 5. Able to participate in the Mini Mental Status Examination?
- _____(Y) 6. Able to swallow pills?
- _____(N) 7. Previous radiation to the brain?
- _____(N) 8. Planned concurrent chemotherapy during the two weeks of whole brain irradiation?
- _____(Y) 9. If the patient is of reproductive age and/or is sexually active, is the patient practicing an effective method of birth control while on study?
- _____(Y) 10. Pretreatment evaluations in accordance with Section 4.0 requirements?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Initials (*Last, First*) [Initials Only effective 2/2/02]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth

(cont'd on next page)

RTOG Institution # _____

RTOG BR-0119

ELIGIBILITY CHECK (11/5/02)

Case # _____

(page 2 of 2)

- _____ 9. Ethnic Category (*Hispanic or Latino; Not Hispanic or Latino; Unknown*)
- _____ 10. Race
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (*U.S. Residents*)
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ (Y/N) 17. Blood for research in current study?
- _____ (Y/N) 18. Allow contact for future research?
- _____ (Y/N) 19. Chemotherapy planned after whole brain irradiation?

_____ Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____

Date _____

1.0 INTRODUCTION

The RTOG has performed multiple studies for patients with brain metastases but none has shown any ability to improve length of survival or quality of life.¹ Studies for patients with a single or limited number of brain metastases and no other disease have shown an advantage for surgery combined with radiation^{2,3} and radiosurgery with radiation.⁴ However, such presentations are rare. For the general patient who presents with multiple brain metastases and/or disease elsewhere in the body, the standard approach of whole brain radiotherapy has not been improved upon in over fifty years.

Recursive partitioning analysis of the combined RTOG data of three trials run from 1979 through 1993 revealed that patients can be divided into three prognostic groups⁵: patients with a Karnofsky Performance Status (*KPS*) of at least 70 and age less than 65, a controlled primary and the brain as the only site of metastases had a median survival of 7.1 months; patients with a *KPS* of less than 70 had a median survival of 2.3 months; all of the other patients had a median survival of 4.2 months.

Increasing numbers of patients are using alternative approaches.^{6,7} Standard practitioners' reluctance to encourage or accept such treatments arises from the lack of solid clinical research supporting their efficacy. It is therefore important to begin rigorous trials of proposed treatments.

1.1 Melatonin Background

Melatonin, or N-acetyl-5-methoxytryptamine, is secreted by the pineal gland.⁸ Photic information from the retina is transmitted to the pineal gland. Specifically, darkness stimulates melatonin production, and light inhibits melatonin production. In humans, melatonin secretion increases soon after the onset of darkness and reaches a peak early in the morning (*2 a.m. to 4 a.m.*) The circadian rhythm of melatonin secretion, in a 24-25 hour cycle, persists even in continuous darkness. Sufficiently bright nocturnal light will suppress melatonin production.

Intravenously injected melatonin has a serum half-life of approximately 0.5 to 6 minutes. It is metabolized primarily in the liver to 6-hydroxymelatonin and then conjugated with sulfuric or glucuronic acid and secreted in the urine.⁹ The bioavailability of orally administered melatonin varies. After an 80 mg dose of melatonin given orally, the serum melatonin levels are 350 to 10,000 times higher than usual nighttime levels when they peak 60 to 150 minutes later. However, all of these levels are higher than the 0.2 ng/ml—2 ng/ml levels needed to achieve a radiosensitizing effect.¹⁰

There are no known interactions between the metabolism of melatonin and anticonvulsants or corticosteroids. It has been suggested that melatonin may inhibit the action of corticosteroids;¹¹ however, all of the previous clinical trials of melatonin for brain metastases or primary brain tumors have been done with the patients being allowed to take corticosteroids, and no complications were reported. The possibilities of the interactions of corticosteroids and melatonin are myriad. This protocol will address this by using standard practices, and thereby determine if melatonin is active within the present standard of care.

No serious side effects or risks have been reported with the ingestion of melatonin. Reported side effects include hypothermia, increased sleepiness, and decreased alertness. Toxicity has not been evaluated in people taking large doses for extended times.

Melatonin has several separate biological activities. There are receptor-mediated effects related to the induction of sleep, and in some species, the control of seasonal breeding. Non-specific effects are related to free-radical scavenging. *In vitro* and *in vivo* studies have shown melatonin to be a potent scavenger of hydroxyl radicals and other oxygen radicals.¹²⁻¹³ Melatonin may also enhance immune response. Specifically, melatonin receptors have been found on T lymphocytes (*CD4 cells*) but not B lymphocytes.¹⁴

Melatonin has also been shown to be an important nocturnal, circadian growth inhibitory signal to rodent tumors *in vivo*.¹⁵ The essential fatty acid, linoleic acid (*LA*), is required for optimal growth and metabolism of a variety of experimental murine and human tumors, particularly tissue-isolated rat hepatoma 7288CTC. *LA* is taken up by this tumor and metabolized to the mitogenic signaling molecule, 13-hydroxyoctadecadienoic acid (*13-HODE*)¹⁶ Eliminating endogenous melatonin production via either pinealectomy, exposure to constant light, or the presence of dim light during darkness increases the rates of growth, *LA* uptake, and 13-HODE production by this tumor.¹⁷⁻¹⁹ Daily afternoon (*but not morning*) melatonin injections, dietary melatonin ingestion, or short photoperiod exposure have the opposite effects.

Perfusion of tissue-isolated tumors with physiological concentrations of melatonin results in a direct, rapid, and reversible inhibition of tumor uptake of LA and metabolism to 13-HODE as well as suppression of tritiated-thymidine incorporation into tumor DNA. These effects are reversed by either a melatonin receptor antagonist, pertussis toxin, forskolin or cAMP. These findings indicate that the melatonin signal inhibits tumor growth via a melatonin receptor-mediated suppression of cAMP levels resulting in decreased tumor transport and metabolism of LA to 13-HODE.¹⁹

In addition to its membrane receptor-mediated actions, melatonin has been shown to be a potent antioxidant and free radical scavenger. Melatonin has been shown to be a radioprotective agent in the experimental setting presumably by virtue of its ability to scavenge hydroxyl radicals.²⁰ Human peripheral blood lymphocytes pre-treated *in vitro* with pharmacological levels of melatonin, as well as blood lymphocytes collected from human volunteers who had ingested a single oral dose of 300 mg of melatonin, exhibit a significantly reduced amount of DNA damage when the cells were subsequently exposed *in vitro* to gamma radiation.^{21,22} Furthermore, mice that were given *i.p.* injections of melatonin prior to whole-body exposure to a LD50 dose of ionizing radiation experienced significant increases in their survival at 30 days post radiation as compared with controls not pre-treated with melatonin.²³ Additionally, mice that were pre-treated with melatonin were protected against whole-body ionizing radiation-induced genetic damage in peripheral blood and bone marrow cells.²⁴

Preliminary studies²⁵ examined the hypothesis that melatonin is a radiosensitizer of hepatoma 7288CTC and a radioprotectant of normal tissues in the radiation field. Furthermore, we tested the hypothesis that the radiosensitizing effects of melatonin are circadian stage-dependent. Rats bearing tissue-isolated tumors and maintained on 12L:12D light: dark cycle (*lights on 0600-1800 h*) were treated with daily p.m. (*1600-1800 h*) s.c. injections of either melatonin (*20 ug/day*) or placebo for two weeks. Two days after the injections were stopped, groups of placebo or melatonin-pretreated rats received a single dose of 624 cGy from a cobalt-60 teletherapy source administered (*RT*) at 1700-1830 h with the lights on. Other placebo or melatonin-pretreated rats did not receive RT. Placebo or melatonin-pre-treated tumors not receiving RT grew at the same rapid rate. Placebo-pretreated tumors receiving the RT initially grew slowly for the first few days following RT but subsequently grew as rapidly as control tumors not receiving RT. In contrast, melatonin pre-treated tumors began to regress a few days after RT and were completely absent two weeks later. Tumors were still undetectable at necropsy eight weeks later. Tumors pre-treated with daily a.m. (*0800-1000 h*) melatonin injections two weeks prior to RT grew at a rate identical to controls receiving placebo and no RT. Melatonin pre-treatment enhanced RT-induced lipid peroxidation in tumor tissue while it reduced lipid peroxidation in adjacent normal tissues within the RT field. The mechanism may involve melatonin enhancement of RT-induced free radical generation in tumor tissue while normal tissues are protected by melatonin.

1.2 Clinical Trials

Paolo Lissoni, of the Instuti Tumori of Italy, has published a series of articles showing a remarkable efficacy of high dose melatonin for improving the length of survival and quality of life of patients with advanced metastatic disease.^{26,27} Two trials are of particular interest. In the first, patients with recurrent symptoms from brain metastases after treatment with radiation therapy were randomized to receive 20 mg of melatonin at 9 p.m. each night or placebo.²⁴ Although a very small study, 26 patients in the control arm and 23 patients in the melatonin arm, it showed a significant improvement in median survival (*5.5 months vs. 9.2 months*) and in the number of patients displaying an improvement in Karnofsky Performance Status. The second trial utilized concurrent melatonin or placebo and radiation therapy for glioblastoma multiforme²⁷ Again, 20 mg of melatonin was used each evening. The one-year survivals were 8/16 in the melatonin arm and 2/14 in the placebo arm.

Thus, there are strong preclinical and clinical data that melatonin may be active as either a radiosensitizer for radiation or active in its own right in inhibiting tumor growth. Because melatonin is a circadian hormone, the proper timing of melatonin for treating neoplastic disease is not known.

2.0 OBJECTIVES

- 2.1** To determine if overall survival is improved and clinical deterioration (*as measured by the Mini-Mental Status Exam*) is decreased by the administration of morning (*a.m.*) or evening (*p.m.*) melatonin when combined with external irradiation in patients with brain metastasis;
- 2.2** To estimate serum melatonin levels at the end of radiation therapy in a subset of patients.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (11/5/02)

- 3.1.1 Brain metastasis from histologically documented solid tumors (*except germ cell tumors*); Biopsy proof from the brain metastases is preferred when clinical history and radiographic findings are equivocal;
- 3.1.2 RPA class II patients: Zubrod Performance status of 0-1 at the time of enrollment and any of the following: ≥ 65 years of age; extra-cranial metastases; or uncontrolled primary malignancy;
- 3.1.3 Able to participate in the Mini-Mental Status Examination;
- 3.1.4 Able to swallow pills;
- 3.1.5 Prior chemotherapy is allowed if > 30 days prior to registration;
- 3.1.6 Since it is unknown what effects melatonin may have on an unborn child, participants who are of reproductive age and/or who are sexually active must practice an effective method of birth control while on study.
- 3.1.7 Pretreatment evaluations must be completed as in Section 4.0.
- 3.1.8 Patients must sign a study-specific informed consent prior to study entry.

3.2 Ineligibility Criteria

- 3.2.1 Eligible for and willing to participate in alternative RTOG stereotactic radiosurgery trials;
- 3.2.2 Prior radiotherapy to the brain.

4.0 PRETREATMENT EVALUATIONS

4.1 Required Evaluations (within 14 days prior to registration)

- 4.1.1 History and physical
- 4.1.2 Contrast CT or MRI for radiographic documentation of brain metastases
- 4.1.3 Staging of degree of metastases: absence or presence of active disease outside of the brain; the staging only requires determination if such disease is present, not the extent of disease.
- 4.1.4 Zubrod Performance Status
- 4.1.5 Mini-Mental Status Exam

5.0 REGISTRATION PROCEDURES

- 5.1 Each institution must submit a Study Agent Shipment Form (*Appendix V*) to RTOG Headquarters prior to the registration of its first case. Allow adequate processing time (*7-10 days*) before calling to register the first patient.
- 5.2 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 to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY

6.1 Whole Brain Radiation Therapy—Treatment must begin within 14 days of radiographic documentation of brain metastases (11/5/02)

- 6.1.1 Total Dose:
3 Gy will be given daily five days a week for two weeks for a total of 30 Gy. **PATIENTS SHOULD BE TREATED BETWEEN 2 P.M. AND 6 P.M. DAILY, MONDAY THROUGH FRIDAY**, preferably as close to 6 p.m. as possible. If a patient starts treatment on a Friday, a Saturday treatment may be given between 2 p.m. and 6 p.m. and then treatment resumed on Monday.
- 6.1.2 Physical Factors:
Patients may be treated on Co-60 or linear accelerators. The treatment distance should be at least 80 SSD.
- 6.1.3 Simulation, Blocking and Immobilization
A simulation should be done on all patients. This simulation can be done on a dedicated simulator or on the treatment machine. Blocking and immobilization may be done at the preference of the treating Radiation Oncologist.
- 6.1.4 Treatment Planning
Port films should be taken at least once during treatment. The entire cranial contents should be treated using only opposing lateral fields. Care should be taken to minimize the dose to the orbits. No cone down or boost should be given. Central axis dose calculations are sufficient for dosimetry.

6.2 Radiation Toxicities

- 6.2.1** *Acute, ≤ 90 days from treatment start:* Expected toxicities include hair loss, erythema of the scalp, headache, nausea and vomiting, lethargy, and transient worsening of neurological deficits. Reactions in the ear canals and on the ear should be observed and treated symptomatically. *Late, > 90 days from treatment start:* Possible toxicities include radiation necrosis, cognitive dysfunction, accelerated atherosclerosis, and radiation-induced neoplasms.
- 6.2.2** Effects of radiotherapy are to be recorded and included in the toxicity evaluation. Reaction within 90 days of treatment start date will be scored using the revised NCI Common Toxicity Criteria, version 2.0, which can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). For reactions appearing or persisting beyond 90 days, refer to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (*Appendix III*).

7.0 DRUG THERAPY

7.1 Treatment Plan—Treatment must begin within 14 days of radiographic documentation of brain metastases (11/5/02)

7.1.1 Drug Description

The melatonin capsules required for a patient to complete the study will be supplied to the institution in one shipment (*See Section 7.1.3*). Each capsule will contain 10 mg of melatonin. The institution will dispense the capsules to each patient as specified in Section 7.1.7.

7.1.2 Storage

Melatonin must be stored at room temperature, away from direct sunlight.

7.1.3 Supply and Distribution

Each institution must submit a Study Agent Shipment Form (*Appendix V*) to RTOG Headquarters prior to the registration of its first case. Allow adequate processing time before calling to register the first patient. Upon receipt of the Melatonin Shipment Form from each institution, RTOG will notify Biologics, Inc. to initiate shipment of melatonin for each patient registered by that institution. The melatonin required for a patient to complete the study will be delivered in one shipment. All packages are shipped for second business day delivery, with the exception of Canadian deliveries, which will require a 4-5 day window. Institutions can contact Biologics, Inc., if necessary, as noted below:

Kim Adams, Director of Pharmacy Biologics, Inc.
625 Oberlin Road
Raleigh, NC 27605
1-800-850-4306
(919) 546-9810
FAX (919) 546-9816

After all study patients have completed protocol treatment at the site, the institution will be responsible for destroying any remaining supplies of melatonin on site.

7.1.4 Administration

Two capsules (*a total of 20 mg*) are to be taken at the specified time, either 8-9 a.m. OR 8-9 p.m., based on the patient's randomization. If the patient misses taking a dose at the specified time and is within two hours of the proper time, the patient should take it. Otherwise the patient should resume on the regular schedule the next day.

7.1.5 Duration of Treatment

The patient will begin the melatonin with the first day of treatment and continue for six months or until disease progression or death.

7.1.6 Toxicities

Melatonin is usually well tolerated. Side effects that can occur include altered sleep patterns, confusion, headache, hypothermia, pruritis, sedation, dysphoria, and tachycardia. Patients should not operate heavy machinery or drive a car for at least 4 hours after taking melatonin. Concomitant use of succinylcholine is prohibited; concomitant use of benzodiazepines should be avoided.

7.1.7 Study Agent Accountability

The institution will dispense one bottle of capsules (28-day supply) to the patient at each visit for the first 3 visits; three bottles of capsules will be dispensed to the patient at the three-month follow-up visit. The patient is to bring in the pill container at each follow-up visit to determine the number of pills consumed in the previous period. Unused capsules will not be re-dispensed.

Patients will be issued diaries to record daily doses of melatonin. Melatonin compliance and toxicity data will be recorded by the institution on the Treatment Summary Form (*See Section 12.1*).

7.2 Dose Modification

If the patient does not tolerate the full dose of melatonin, i.e., has severe headache not responsive to standard analgesic regimens, increased dysphoria in depressed patients, or has other severe reactions thought to be secondary to the melatonin, then one capsule (*10 mg*) should be taken for one week and then the full dose resumed. If the patient cannot tolerate the full dose thereafter, the patient should stop taking the melatonin.

7.3 Adverse Drug Reaction Reporting

7.3.1 This study will utilize the Common Toxicity Criteria (*CTC*) version 2.0 for grading of chemotherapy and acute radiation (≤ 90 days) toxicity. A copy of the CTC version 2.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0. See Appendix IV for Adverse Event Reporting Guidelines. This study will be monitored by the Clinical Data Update System (*CDUS*) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.3.2 The following guidelines for reporting adverse drug reactions (*ADR's*) apply to any research protocol that uses commercial anticancer agents. The following ADR'S experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported by telephone to RTOG Headquarters within 24 hours of discovery and then a written report sent to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within ten working days:

7.3.2.1 Any ADR which is both serious (*life-threatening [grade 4] or fatal [grade 5]*) and **unexpected**;

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

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

7.3.3 The ADR report should be documented on FDA Form 3500 and mailed or faxed to the address on the form, as well as to the IDB and RTOG Data Management Department:

Investigational Drug Branch P.O. Box 30012 Bethesda, MD 20824 (301) 230-2330, available 24 hours Fax (301) 230-0159	RTOG Data Management 1101 Market Street, 14 th floor Philadelphia, PA 19107 Phone (215) 574-3214 Fax (215) 923-1737
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All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

7.3.4 Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters Data Management department within ten days of discovery.

7.3.5 Acute myeloid leukemia (*AML*) or myelodysplastic syndrome (*MDS*) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at <http://ctep.info.nih.gov>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed within 30 days of AML/MDS diagnosis to the address on the form and to the RTOG Data Management Department:

Investigational Drug Branch (<i>NCI/CTEP</i>) P.O. Box 30012 Bethesda, MD 20824	and	RTOG Headquarters AML/MDS Report 1101 Market Street, 14 th floor Philadelphia, PA 19107
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All forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Concurrent chemotherapy during the two weeks of whole brain irradiation is not allowed; however, chemotherapy after irradiation, in patients with known disease, is acceptable.

9.2 Concurrent use of benzodiazepines should be avoided; however, if used, the patient will require close monitoring by the physician. Concurrent use of corticosteroids and anticonvulsants will be at physician discretion.

10.0 PATHOLOGY/SPECIMEN COLLECTION (11/5/02)

10.1 Pathology

10.1.1 Histologic proof of the original malignancy is required. Biopsy proof from the brain metastases is preferred when clinical history and radiographic findings are equivocal. A pathology report documenting the original malignancy and the brain metastasis should be submitted. No tissue or slides are to be submitted.

10.2 Serum Specimens

For patients who have consented to participate in the serum component of the study (See Appendix IB)

10.2.1 This blood work is not mandatory but is encouraged. The goal of this blood work is to estimate the serum melatonin levels in the first 25 patients per arm that are enrolled on this optional component.

10.2.2 Specimen Collection

Blood should be collected on the last day of radiation therapy, at approximately 12 noon, if possible. Blood samples should be centrifuged, serum aspirated, and placed into cryo-vials (freezing vials). Do NOT collect blood into serum separator tubes since the separator plug deteriorates with freezing. Samples should be labeled with the RTOG protocol number and the patient's case number.

Place the cryo-vials containing the serum samples into a -80°C freezer until the samples are shipped. If an 80° freezer is not available, storage in a -20° freezer is acceptable, if the freezer is NOT a frost-free freezer. If multiple samples from multiple patients are collected at a site, the samples can be batched for shipment, as long as they are stored at -80° . When blood sampling is completed at a site, then all samples can be shipped as described in Section 10.3.

10.3 RTOG Tissue Bank

10.3.1 The following must be provided in order for the case to be evaluable for the Tissue Bank:

10.3.1.1 Specimens must be clearly labeled with the RTOG study number, the patient's case number and the date and time of collection.

10.3.1.2 A Specimen Transmittal Form (ST) for each patient's specimens that are shipped; the form must include the RTOG protocol number and patient's case number. The specimens will be analyzed by David Blask, M.D., Ph.D., Basset Research Institute.

10.3.1.3 A copy of the patient tissue consent form; the consent form must include the RTOG protocol number and patient's case number. The patient's name and/or identifying information should be removed from the consent form.

10.3.1.4 Institutions should ship specimens on dry ice (at least 8 lbs.) for next day delivery; therefore, no specimens should be shipped on a Friday or on the day prior to a major holiday. Call Holly Flinn at the number in Section 10.3.2 prior to shipping specimens.

10.3.2 Submit materials to:

**LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
ldhflinn@ihc.com**

10.4 Reimbursement

10.4.1 RTOG will reimburse pathologists from submitting institutions \$200 per case if proper materials are submitted. After confirmation from the Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution.

10.5 Confidentiality/Storage (See RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/tissuebank/tissuefaq.html> for further details)

10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 The specimens will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the Tissue Bank should be notified in writing. The notification must include the RTOG protocol number and the patient's case number. Material will be discarded, unless a specific request is made for specimen return, including a shipping address.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (11/5/02)

	Pre-Entry	End of RT	Interval in Months from Start of RT					
			1 ^a	2	3	6	12	18
History and Physical	X							
Contrast CT or MRI	X			X				
Staging of degree of metastases	X							
Zubrod Performance Scale	X	X	X	X	X	X	X	X ^b
Mini-Mental Status Exam (MMSE)	X	X	X	X	X	X	X	X ^b
Optional blood collection for melatonin level		X ^c						

- The patient is to bring in the pill container at each follow-up visit to determine the number of pills consumed in the previous period.
- Also every six months thereafter, until progression of neurological problems or death
- Blood should be collected on the last day of RT (*at approximately 12 Noon, if possible*) in the first 25 patients per arm (*See Section 10.2.2*).

11.2 Evaluation During Treatment (11/5/02)

11.2.1 Patients will be assessed utilizing the MMSE and Zubrod Performance Scale at the end of RT, every 4 weeks from the start of RT for 3 months, then every 3 months until 6 months, then every 6 months thereafter.

11.3 Evaluation of Therapy Effectiveness

11.3.1 Survival and time to clinical deterioration will be measured from the time of registration.

11.3.2 The MMSE will be used to determine neurocognitive deterioration. Patients with MMSE at or below an established cutoff will be considered a cognitive failure (*See Section 13.4*).

11.3.3 Ineligible patients and those patients who do not receive any of the experimental component of this study will be removed from follow up and excluded from analysis.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 wks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1) (primary site)	
Baseline Mini-Mental Status Exam (MS)	
<u>Final Dosimetry Information:</u> Radiotherapy Form (T1)*	Within 1 week of RT end
Mini-Mental Status Exam (MS)	
Pill Diary (DP)	Every 4 wks for the first 3 months of drug administration, then at completion of therapy (Section 7.1.5)
Treatment Summary Form (TF)	Every 4 wks for first 3 months of drug administration, then at completion of therapy
Follow-up Form (F1)	Month 12 from start of RT, then every 6 months thereafter; also at progression/relapse and at death.
Mini-Mental Status Exam (MS)	Every 4 weeks for 3 months following completion of RT, then every 6 months thereafter
Autopsy Report (D3)	As applicable

*NOTE: Copies of simulation and port films and the RT Daily Treatment Record for the whole brain irradiation will be submitted to RTOG Headquarters ONLY if specifically requested.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Overall survival

13.1.2 Clinical deterioration as measured by the Mini-Mental Status Exam (MMSE)

13.1.3 Serum melatonin levels

13.2 Background

RTOG recursive partitioning analysis (RPA) has found that the survival of brain metastases patients is highly influenced by prognostic factors (*Performance status, age, metastases outside of brain, control of primary tumor*).⁵ RPA class II patients are defined as having a Zubrod of 0-1 and any of the following: age ≥ 65 , extracranial metastases, or uncontrolled primary malignancy. These patients historically have a median survival time (MST) of 4.2 months. The RTOG brain metastases database (*historical control*) contains 765 RPA class II patients.

13.3 Randomization

13.3.1 Patients will be randomized to a.m. or p.m. melatonin according to a permuted block design, balancing by institution. The randomization will be stratified by planned chemotherapy (*yes vs. no*). Each arm will be compared separately to historical control.

13.4 Sample Size

The primary objective of this study is to compare the overall survival of brain metastases RPA class II patients treated with radiation therapy (RT) and concurrent morning (*a.m.*) or evening (*p.m.*) melatonin to corresponding patients from the RTOG database. For each arm, an increase in MST of two months compared to the historical MST of 4.2 months will be considered a meaningful improvement in survival. A sample size of 60 evaluable patients followed for 8 months will provide at least 90% probability of detecting a two month (48%) improvement in MST compared to the historical control at a one-side

significance level of 0.10.²⁸ Adjusting for an expected 95% eligibility/evaluability results in 64 patients for each arm. **This study requires a total sample size of 128 patients, 64 per arm.**

13.5 Reporting of Secondary Endpoints

13.5.1 Mini-Mental Status Exam

The MMSE will be used to determine neurocognitive deterioration. An age- and education-adjusted cutoff (*see table below*) will be used to define patients with possible cognitive dysfunction.^{29, 30} The educational levels from the cited sources have been translated to agree with the RTOG Demographic Data Form (A5). Patients without educational level data will be considered to have completed high school. MMSE scores at or below the cutoff value will be considered a cognitive failure. The cutoff points have been shown to have a sensitivity of 82% and specificity of 98% for identifying cognitive dysfunction by MMSE. The cumulative incidence model will be used to analyze the time to neurocognitive deterioration.

CUTOFF SCORES FOR MINI-MENTAL STATUS EXAMINATION

Age (yr)	Educational Level			
	Up to Grade 8	Some high school, did not graduate	Graduated high school or received GED	Attended college or technical school after high school
<55	26	28	28	29
55-59	26	28	28	28
60-64	26	27	27	28
65-69	25	26	27	27
70-74	24	25	26	27
75-79	23	24	25	26
80-84	23	23	24	24
85-89	23	23	23	24
90-95	23	23	23	23

13.5.2 Serum Melatonin Levels

Serum melatonin levels will be measured at the end of radiation therapy for the first twenty-five patients on each arm (*See Section 10.2.1*). A 95% confidence interval of the melatonin level will be calculated for each arm.

13.6 Inclusion of Women and Minorities

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into brain metastases trials failed to show any treatment interaction with gender or race.²⁶ Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races. The projected gender and minority accruals are shown below:

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Total
Female	0	1	6	3	0	54	64
Male	0	1	6	3	0	54	64
Total	0	2	12	6	0	108	128

13.7 Patient Accrual

The patient accrual is projected to be 26 cases per month, based upon the monthly accrual for prior RTOG brain metastases studies. At this rate, it will take 5 months to accrue 128 patients. If the average monthly accrual rate is less than five patients, the study will be re-evaluated with respect to feasibility.

13.8 Analyses Plans

13.8.1 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, and compliance rate of treatment delivery with respect to protocol prescription;
- 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 statistician and study committee can identify problems with the execution of the study. If necessary, problems will be reported to the RTOG Executive Committee, so that corrective action can be taken.

13.8.2 Analysis for Reporting the Initial Treatment Results

This analysis will be undertaken when each patient has been potentially followed for a minimum of 8 months. 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 of institutional accrual;
- c) distribution of important prognostic baseline variables – (*age, KPS, neurologic function, extent of surgery, mental status*);
- d) observed results with respect to the endpoints described in Section 13.1.
- e) Overall survival of patients will be compared separately for each arm to RPA class II historical control patients using a one-sided log-rank test with a significance level of 0.10. If this testing indicates both arms to have improved survival compared to the historical control, then the arm with the best survival will be selected. If only one arm is shown to improve survival, then that arm will be selected. If neither arm is shown to improve survival over the historical control, then both schedules will be regarded as inactive.

REFERENCES

1. Berk L. An overview of radiotherapy trials for the treatment of brain metastasis. *Oncology*. 9: 1205-1210, 1995.
2. Patchell R, Tibbs P, Walsh J, et al. A randomized trial of surgery in the treatment of single metastasis to the brain. *N Engl J Med*. 322:494-500,1990.
3. Smally S, Laws E, O'Fallon J, et al. Resection for solitary brain metastasis. *J Neurosurg*. 77:531-540,1992.
4. Flickenger J, Kondziolka D, Lunsford L, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. *Int J Radiat Oncol Biol Phys*. 28:797-802, 1994
5. Gaspar L, Scott C, Rotman M, et al. Recursive Partitioning Analysis (RPA) of Prognostic Factors in Three Radiation Therapy Oncology Group (RTOG) Brain Metastases Trials. *Int J Radiat Oncol Biol Phys*. 37(4):745-51, 1997.
6. Eisenberg DM, Kessler RC, Foster C, et al. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *JAMA*. 280:1569-1575, 1998.
7. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *Cancer*. 73:699-701, 1994.
8. Reiter, RJ. Pineal melatonin: cell biology of its synthesis and of its physiological interactions. *Endocr Rev*. 12:151-180, 1991.
9. Lynch HJ, Wurtman RJ, Moskowitz MA, et al. Daily Rhythm on Human Urinary Melatonin. *Science*. 187:169-171, 1975.
10. Demuro RL, Nafziger AN, Blask DE, Menhinick AM, Bertino JS. The absolute bioavailability of oral melatonin. *J Clin Pharmacol*. 40:781-784, 2000.
11. Maestroni GJ, Conti A. Anti-stress role of the melatonin-immuno-opioid network: Evidence for a physiological mechanism involving T cell-derived, immunoreactive beta-endorphin and MET-enkephalin binding to thymic opioid receptors. *Int J Neurosci*. 61(3-4):289-98, 1991.
12. Tan DX, Chen LD, Poeggeler B, et al. Melatonin: A Potent Endogenous Hydroxyl Radical Scavenger. *Endocr J*. 1:57-63, 1993.
13. Tan DX, Poeggeler B, Reier RJ, et al. The Pineal Hormone Melatonin Inhibits DNA-adduct Formation Induced by the Chemical Cargingoen Safrole *in vivo*. *Cancer Lett*. 70:65-71, 1993.
14. Gonzales-Haba MG, Garcia-Maurino S, Calvo JR, et al. High-Affinity Binding of Melatonin by Human Circulating T Lymphocytes (CD4+). *FASEB J*. 9:1331-5, 1995.
15. Blask, DE. Melatonin in oncology. In: H.S. Yu and R.J. Reiter, (eds). *Melatonin - Biosynthesis, Physiological Effects, and Clinical Implications*. Boca Raton: CRC Press; 1993: 289-310.
16. Sauer, LA, Dauchy, RT, Blask, DE, Armstrong, BJ, Scalici, S. 13-Hydroxyoctadecdienoic acid is the mitogenic signal for linoleic acid-dependent growth in rat hepatoma 7288CTC *in vivo*. *Cancer Res*. 59:4688-4692, 1999.
17. Dauchy, RT, Sauer, LA, Blask, DE, Vaughan, GM. Light contamination during the dark phase in photoperiodically controlled animal rooms: effect on tumor growth and metabolism in rats. *Lab Animal Sci*. 47:511-518, 1997.
18. Dauchy, RT, Blask, DE, Sauer, LA, Brainard, GC, Krause, JA. Light during darkness stimulates tumor progression by enhancing tumor fatty acid uptake and metabolism. *Cancer Lett*. 144:131-136, 1999.
19. Blask, DE, Sauer, LA, Dauchy, RT, Holowachuk, EW, Ruhoff, MS, Kopff, HS. Melatonin inhibition of cancer growth *in vivo* involves suppression of tumor fatty acid metabolism via melatonin receptor-mediated signal transduction. *Cancer Res*. 59:4693-4701, 1999.
20. Reiter, RJ. Antioxidant actions of melatonin. *Adv Pharmacol*. 38:103-117, 1997.
21. Vijayalaxmi A, Reiter, RJ, Sewerynek, E, Poeggler, B, Leal, BZ, Meltz, ML. Marked reduction of radiation-induced micronuclei in human blood lymphocytes pre-treated with melatonin. *Radiat. Res*. 143:102-106, 1995.
22. Vijayalaxmi, A, Reiter, RJ, Herman, TS, Meltz, ML. Melatonin and radioprotection from genetic damage: *in vivo/in vitro* studies with cells from human volunteers. *Mutat Res*. 71:221-228, 1996.
23. Vijayalaxmi, A, Meltz, ML, Reiter, RJ, Herman, TS, Sree Kumar, K. Melatonin and radioprotection from whole-body irradiation: survival studies in mice. *Mutat Res*. 425:21-27, 1999.

24. Vijayalaxmi, A, Meltz, RL, Reiter, RJ, Herman, TS Melatonin and protection from genetic damage in blood and bone marrow: whole-body irradiation studies in mice. *J Pineal Res.* 27:221-225, 1999.
25. Blask, DE, Barthold, HJ, Dauchy, RT, et al. Melatonin radiosensitizes tumors and radioprotects normal tissues: time-of-day dependency. 91st Ann Mtg *Amer Assoc Cancer Res.* (abstract submitted).
26. Lissoni P, Barni S, Ardizzoia A, et al. A randomized study with the pineal hormone melatonin versus supportive care alone in patients with brain metastasis due to solid neoplasms. *Cancer.* 73:699-701, 1994.
27. Lissoni P, Meregalli S, Nosetto L, et al. Increased survival time in brain glioblastoma by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. *Oncology.* 53:43-46, 1996.
28. Dixon DO, Simon R. Sample size considerations for studies comparing survival curves using historical controls. *J Clin Epidemiol.* 41:1209-1231, 1988.
29. Tangalos EG, Smith GE, Ivnik RJ, et al. The Mini-Mental State Examination in general medical practice: Clinical utility and acceptance. *Mayo Clin Proc.* 71:829-837, 1996.
30. Crum RM, Anthony JC, Bassett SS, et al. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA.* 269: 2386-2391, 1993.

APPENDIX IA

RTOG BR-0119

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A RANDOMIZED PHASE II STUDY OF A.M. AND P.M. MELATONIN FOR BRAIN METASTASIS IN RPA CLASS II PATIENTS

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have cancer that has spread to the brain.

WHY IS THIS STUDY BEING DONE? (11/5/02)

The usual treatment in cancer that has spread to the brain (brain metastases) is radiation therapy. A research study done in Italy suggests that melatonin, a natural human hormone, may help patients with brain metastases live longer and maintain a better quality of life. In this study, radiation therapy will be combined with this hormone, melatonin, to see if the melatonin improves the effectiveness of the radiation. The study will also gather information about the effects (good and bad) melatonin has on you and the cancer.

In some patients with cancer that has spread to the brain, chemotherapy is used in addition to radiation therapy. This is not encouraged for patients thirty days before participating in this study and is not allowed during the two weeks of radiation therapy of this study. You may receive chemotherapy after radiation therapy is finished, if you and your doctor feel that chemotherapy is appropriate.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 128 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Before comparing melatonin and radiation therapy to radiation therapy alone, we need to learn the best way to give the melatonin. This study will gather information about taking melatonin in the morning versus the evening during radiation treatment. Therefore, this study involves assignment to one of two treatments. It is not clear at the present time if either of these two treatments is better. For this reason the therapy offered to you will be based upon a method of selection called randomization. Randomization means that you are put into a group by chance. A computer will assign you to one group. You will have an approximately equal chance of being assigned to one of the following treatments:

Treatment 1

You will receive radiation therapy once a day, between 2 and 6 p.m., five days a week, for two weeks. In addition, you will begin taking melatonin on the first day of radiation therapy, two capsules **between 8-9 a.m. each morning**, and will continue taking melatonin for a maximum of six months or until there is evidence that therapy is not helping or your disease grows. You will be provided with a pill diary and asked to keep track of your daily doses of melatonin. Melatonin will be provided free of charge for this study.

Treatment 2

You will receive radiation therapy once a day, between 2 and 6 p.m., five days a week, for two weeks. In addition, you will begin taking melatonin on the first day of radiation therapy, two capsules **between 8-9 p.m. each evening**, and will continue taking melatonin for a maximum of six months or until there is evidence that therapy is not helping or your disease grows. You will be provided with a pill diary and asked to keep track of your daily doses of melatonin. Melatonin will be provided free of charge for this study.

If you take part in this study, you will have the following tests and procedures:

(11/5/02)

- A physical examination before you begin treatment
- A CT scan or MRI of the brain before you begin treatment and two months after radiation therapy ends
- A brief questionnaire before you begin treatment, after radiation therapy, and at each follow-up visit; You will be asked to answer questions and follow a few directions to measure your thinking abilities.
- If you are asked and agree to participate in the research about melatonin levels in the blood, you will have your blood drawn once on the last day of radiation therapy.
- Follow-up visits with your doctor every 4 weeks from the start of radiation therapy for 3 months, then every 3 months until 6 months, then every 6 months thereafter.

HOW LONG WILL I BE IN THE STUDY?

You will receive radiation therapy for two weeks. You will begin taking melatonin on the first day of radiation therapy and will continue taking melatonin for a maximum of six months or until there is evidence that therapy is not helping or your disease grows. Follow-up visits with your doctor will take place every 4 weeks from the start of radiation therapy for 3 months, then every 3 months until 6 months, then every 6 months thereafter.

The researcher may decide to take you off this study if your doctor decides it is in your medical best interest, if your condition worsens, or if new information becomes available that this therapy is not in your best interest. Rarely, you may be taken off a study if funding or drug supply is stopped.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Whole Brain Radiation Therapy

Very Likely

- Hair loss, which may be permanent
- Dry mouth and/or change in taste
- Nausea and/or vomiting
- Scalp reddening or tanning and irritation
- Tiredness

Less Likely

- Headaches

Less Likely But Serious

- Temporary aggravation of tumor symptoms such as seizures or weakness
- Drainage from the ears or plugging of the ears with decreased hearing

Memory loss, behavioral change and/or increased sleepiness (occurring four to ten weeks after the radiation therapy is completed and lasting for several days up to two weeks)

Cataracts and eye damage with the possibility of blindness

Severe local damage to normal brain tissue (*necrosis*), which may require surgery

Melatonin

Very Likely

Decreased alertness and reaction time

Increased sleepiness

Altered sleep patterns

Headache

Feeling cold

Itching

Rapid heartbeat

Less Likely But Serious

Confusion

Due to decreased alertness and reaction time and/or increased sleepiness, you should not drive a car or operate heavy equipment for at least 4 hours after taking melatonin.

(11/5/02) It is unknown what effects melatonin may have on an unborn child. For this reason, if you are a woman able to have children and have not been surgically sterilized or if you are a man able to father children, you will be asked to practice an effective method of birth control while you are participating in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with cancer that has spread to the brain. Treatment with radiation (with or without melatonin) may keep the brain tumor from growing and may shrink it. This may provide relief from symptoms and improve your quality of life. Melatonin may improve control of the brain tumor. However, neither of these benefits is guaranteed.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: radiation therapy alone

or no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as 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 this study.

WHAT ARE THE COSTS?

Melatonin will be provided free of charge for this study.

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT? (11/5/02)

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A group of experts in brain cancer from the RTOG Brain Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study. **We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.**

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI's Web sites for comprehensive clinical trials information
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ
<http://cancernet.nci.nih.gov>.

SIGNATURE (11/5/02)

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient's Name

Signature

Date

Name of Person Obtaining Consent

Signature

Date

APPENDIX IB (11/5/02)

RTOG BR-0119

CONSENT FORM FOR USE OF BLOOD FOR RESEARCH

ABOUT USING BLOOD FOR RESEARCH

This study will gather information about melatonin levels in the blood in some of the patients who participate in this study. You may be asked for permission to send a small amount of your blood to a central office for future research. If you are asked and give your permission, your blood will be drawn once on the last day of your radiation therapy.

The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your blood before it is given to a researcher. Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

THINGS TO THINK ABOUT

The choice to let us use your blood for research is up to you. **No matter what you decide to do, it will not affect your care.**

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood and then any blood that remains will no longer be used for research; or, you may request that we dispose of your blood.

In the future, people who do research may need to know more about your health. While _____ (doctor/institution) may give researchers reports about your health, your doctor/institution will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your blood will be used only for research. . However, the research done with your blood may help to develop new products in the future. If this occurs, you will not be financially compensated.

BENEFITS

The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

RISKS

Physical Risks

If your blood is drawn, you may experience some discomfort, bruising, and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

Social-Economic Risks

There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your _____ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

MAKING YOUR CHOICE

If you have any questions about the research involving your blood or about this form, please talk to your doctor or nurse, or call the institution’s research review board at _____(IRB’s phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. **No matter what you decide to do, it will not affect your care.**

1. My blood may be used for the research in the current study.

Yes No

2. Someone from [treating institution/treating physician] may contact me in the future to ask me to take part in more research.

Yes No

Participant statement:

I have read and received a copy of this consent form. I have been given an opportunity discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

Patient's Name

Signature

Date

Witness statement:

I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient's signature.

Name of Person Obtaining Consent

Signature

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

ZUBROD PERFORMANCE SCALE

- 0 Fully active, able to carry on all predisease activities without restriction (*Karnofsky 90-100*).
- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (*Karnofsky 70-80*).
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (*Karnofsky 50-60*).
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (*Karnofsky 30-40*).
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (*Karnofsky 10-20*).

APPENDIX IV

ADVERSE EVENT REPORTING GUIDELINES

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

A. Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

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

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

Definite:	The adverse event is <i>clearly related</i> to the treatment/procedure.
Probable:	The adverse event is <i>likely related</i> to the treatment/procedure.
Possible:	The adverse event <i>may be related</i> to the treatment/procedure.
Unlikely:	The adverse event is <i>doubtfully related</i> to the treatment/procedure.
Unrelated:	The adverse event is <i>clearly NOT related</i> to the treatment/procedure.

B. Grading of Adverse Events

Unless specified otherwise, the NCI Common Toxicity Criteria (CTC) version 2.0 is used to grade severity of adverse events. Protocols approved prior to March 1998 will use one of several different morbidity grading systems. To grade severity of adverse events in studies prior to this date, consult the protocol document for the appropriate rating system.

C. General Guidelines

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. **When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines.** A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.

2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.

3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.

a. The Group Chair in consultation with the Study Chair will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. **Copies must include the RTOG study and case numbers.**

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.

5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local Institutional Review Board (IRB).

6. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, **the study number and the case number must be recorded** so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).

8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) **within 10 working days** of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.

9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.

10. All neuro-toxicity (\geq grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

D. Adverse Event Reporting Related to Radiation Therapy

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.

2. All grade 4, (CTC v 2.0 and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.

3. All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

E. Adverse Event Reporting Related to Systemic Anticancer Agents

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE¹	Hospitalization During Treatment²	Secondary AML/MDS³
FDA Form 3500 ^{4,5} within 10 days	X	X	X	
NCI/CTEP Secondary AML/MDS Form within 30 days of diagnosis ^{4,5}				X
Call RTOG within 24 hrs of event ⁷	X ⁶			

- 1 Any increased incidence of a known AE.
- 2 Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTC Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
- 3 Reporting required during or subsequent to protocol treatment.
- 4 Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012.
- 5 Copy to RTOG Data Management labeled: Attention: Adverse Event Report.
- 6 All grade 5 known toxicity.
- 7 Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents

An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, <http://ctep.info.nih.gov> for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses "decentralized" notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators' reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOG Registrar upon faxed request (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures.

Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: **An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).**

Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): **When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.**

b. Expedited Reporting for Phase 1 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Grade 2: Expedited report within 10 working days. Grade 3: Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. Grade 1: Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of last dose of treatment with an investigational agent.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent.

1 Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.

2 Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. Expedited Reporting for Phase 2 and Phase 3 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Expedited report within 10 working days. Grade 1: Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited including Grade 5 aplasia in leukemia patients within 10 working days. Grade 4 myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

1 Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.

2 Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

APPENDIX V

RTOG BR-0119

STUDY AGENT (*MELATONIN*) SHIPMENT FORM

Melatonin will be shipped only to institutions that have identified a single individual associated with the investigational drug unit of the institution. This form must be completed and returned to RTOG Headquarters prior to registering any patient on study. Allow adequate processing time (*7-10 days*) before calling to randomize your first patient.

SHIP TO:

Name: _____

Address: _____

(no P.O. addresses)

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____

Investigator (*PI*) Signature _____ Date: _____

Investigator Name (*Print*) _____

Investigator NCI # _____

Send Completed Form to:

*RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107*

**ATTN: PROTOCOL OFFICE
FAX 215-574-0300**

RTOG Headquarters Approval _____

Date: _____