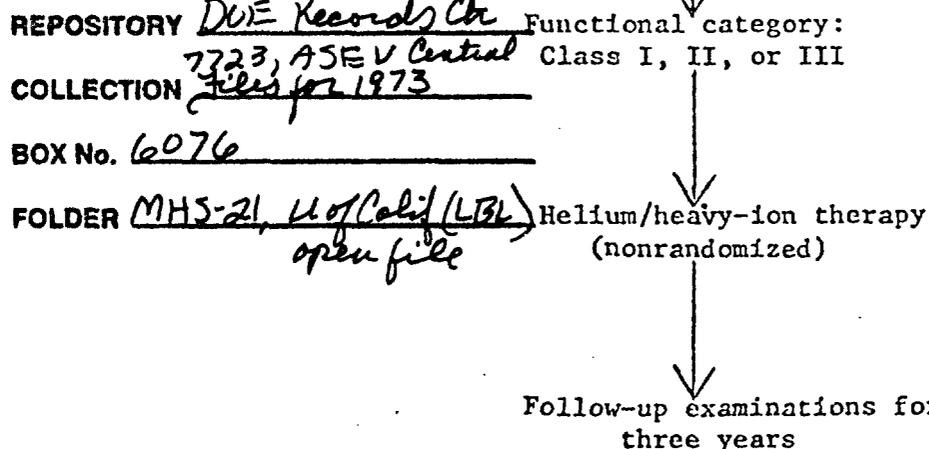


PHASE III PROTOCOL: HELIUM/HEAVY-ION RADIOTHERAPY OF  
MALIGNANT GLIOMA OF THE BRAIN

0.0 Schema

Eligible patients: Malignant glioma, astrocytoma  
Grade III or IV, of brain above tentorium



Endpoints:

- o Morbidity of treatment
- o Gross tumor response
- o Disease free interval
- o Characteristics of local recurrence
- o Length of survival
- o Quality of survival

1.0 Introduction

This study is designed to evaluate the effectiveness of helium/heavy-ion therapy of malignant glioma, astrocytoma Grade III or IV of the brain above the tentorium. Experience with such tumors has shown very poor cure rates following surgery or surgery combined with conventional radiation therapy. Bouchard (1966) who's results are among the best reported shows survival rates at one, three, five and ten years of 44%, 13%, 7%, and 4% respectively. In his series 95% of those patients receiving adequate irradiation had a quality of survival graded as good or fair.

Because of the poor survival rate associated with this disease a nonrandomized study is proposed.

## 2.0 Objectives

The objectives of this study are 1) To determine whether helium/heavy-ion therapy will increase the frequency of local tumor control and ultimately improve the survival of patients with malignant glioma of the brain, and 2) To evaluate the tolerance of helium/heavy-ion therapy in terms of decreased morbidity of treatment and decreased radiation injury of the brain because of the improved dose localization capability thereof.

The primary endpoints of the study are:

1. Disease free survival
2. Absolute survival
3. Quality of survival
4. Tumor response judged by serial diagnostic studies and/or surgical/autopsy findings
5. Incidence of distant metastasis (this is probably unnecessary considering the number of patients we will see).

## 3.0 Eligibility of patients

3.1 General conditions of eligibility. All institutional, Food and Drug Administration, National Cancer Institute regulations regarding submission to the institutional human experimentation committee and the use of procedures for obtaining and recording informed consent will be followed. A patient may be removed from the study at any time if the study is not in the best interests of the patient. A patient also may withdraw voluntarily from the study at any time, as indicated in the consent form.

3.2 Specific conditions for patient eligibility. In addition to the above, the following conditions must be met before the patient can be admitted to the study:

1. Biopsy proven malignant glioma, astrocytoma Grade III or IV, of the brain above the tentorium
2. The patient must be functionally classed as Class I, II, or III of the four classes shown below (Order, et al, 1968):

<u>Class</u>	<u>Definition</u>
I	Intellectually and physically able to work; neurological findings minor or not present.
II	Intellectually intact and physically able to be at home, although nursing care may be required; neurological findings present, but not a major factor.
III	Major neurological findings requiring hospitalization and medical care and supervision.
IV	Requires hospitalization and is in serious physical and neurological state
3.	Patient's general condition must be such that there is a reasonable expectation of his completing the study treatment, and the required follow-up

examinations (including travel for treatment as well as annual follow-up examinations at Lawrence Berkeley Laboratory).

4. Agreement of the patient and his physician to the conditions of the study.
5. Agreement of the patient's physician to relinquish management of the patient's treatment to the study team (it is hoped that the patient's physician will be a member of the study team in many cases).
6. Unequivocal understanding by the patient of the provisions of the study and willing completion of the required investigational treatment consent form.
7. Eligibility for the protocol is not effected by adequate surgical decompression and/or steroid administration. Steroids may be administered before and during radiotherapy. The surgeon may in his judgment remove greater or lesser amounts of the tumor depending upon its location and the patients condition.

3.3 Conditions for patients ineligibility. The following conditions are cause for exclusion of the patient from the study.

1. Previous definitive therapy of the primary tumor including prior definitive radiation therapy or potentially curative surgical procedures (surgical decompression is not considered a potentially curative procedure).
2. Previous chemotherapy which in the opinion of the study team might compromise treatment or evaluation.
3. Previous radiation therapy to regions overlapping the study treatment portals.
4. Active uncontrollable infection in the area of contemplated radiation.
5. Medical, psychological, or other contraindications to the contemplated diagnostic or therapeutic measures, and their evaluation.
6. Less than an eight year disease free interval after diagnosis and treatment of a second malignancy other than skin cancer (for patients with skin cancer the disease must have been under control for at least three years, and not have been melanoma or cancer of the lip).

4.0 Pretreatment evaluation. Insofar as possible the pretreatment evaluation of patients will be standardized among the participating institutions. The evaluation will include the following:

1. Medical history:
  - a. Age
  - b. Sex
  - c. Race
  - d. Date of onset of disease related symptoms and description thereof.
  - e. Date of definitive diagnosis of disease.
  - f. Previous therapy, if any.
  - g. Other significant illnesses.
  - h. Current medications
2. Physical examination:
  - a. Height
  - b. Weight
  - c. Temperature
  - d. General physical examination
  - e. Neurological examination
  - f. Assessment of performance status (Karnofsky function assessment)
3. Laboratory tests and routine x-rays:
  - a. Complete blood count with WBC, differential and platelets
  - b. Urinalysis
  - c. Serum electrolytes and chemical screening battery
  - d. Chest x-ray
4. Tumor localization studies. Tumor localization studies will be obtained as necessary to precisely define the tumor volume. Studies may include one or more of the following:
  - a. Plain skull x-rays
  - b. Computerized tomographic scan with and without contrast
  - c. Arteriography
  - d. Pneumoencephalography
  - e. Brain scan
  - f.
5. Surgery. Surgical decompression with biopsy and/or subtotal excision may be performed at the participating institution. Tumor margins will be clipped by the surgeon to aid in treatment planning.

5.0 Radiation therapy.

5.1 Following completion of the diagnostic evaluation including surgery, the study team, participating surgeon, and radiotherapist will review the available information and define the volume of tissue to be given the maximum amount of radiation.

5.2 Treatment alternatives. The recommended tumor dose in glioblastoma, according to Bouchard, is 6500 rads given in 50 to 60 days with multiple fractions using megavoltage irradiation. The current standard practice in the community is to deliver approximately 4000-4500 rads to the whole brain with a boost of 2000 rads to a reduced tumor volume.

Alternative 1: Whole brain irradiation including the entire cranial vault (anterior, middle and posterior fossa) will be given at the referring institution to a dose level of 4500 rads. A reduced volume with appropriate shaping of the helium/heavy-ion beam to cover the primary tumor will be given at Lawrence Berkeley Laboratory. Because of the average RBE of 1.2 in the broadened (6 cm wide) Bragg peak region of the helium ion beam the boost radiation therapy to the reduced volume will be limited to 1670 rads (ten fractions of 167 rads each).

Alternative 2: Patients will be given whole brain irradiation (anterior middle and posterior fossa) with the plateau region of the helium ion beam to a total dose of 4500 rads in four and one-half weeks. Boost irradiation using the broadened Bragg peak (6 cm) will be given to a reduced tumor volume to a total dose of 1670 rads (ten fractions of 167 rads each) over two weeks.

Final total and incremental helium and heavy ion doses will be determined by clinical experience and pretherapeutic heavy ion studies.

#### 6.0 Post irradiation evaluation.

6.1 Additional therapy. If the primary tumor is not controlled subsequent therapy should proceed at the discretion of the patient's responsible physician. Clinical evidence of lack of tumor control should be documented by radiographic studies and so entered in the patient's records. In the event that surgery or biopsy is performed the excised tissue or biopsy specimen should be carefully examined by a study pathologist with assistance from the involved radiation oncologist.

6.2 Follow-up schedules. Follow-up examinations will be scheduled with the referring physician at the following periods after treatment: Monthly for the first six months, every two months for the next six months, every three months for the next twelve months, and every four months during the next year. Patients will also receive an annual physical examination at the study center at Lawrence Berkeley Laboratory; with the consent of the primary physician this examination may be substituted for one of his evaluations.

If the study patient cannot return to the participating hospital where he was entered in the study, arrangements will be made to have him examined at another hospital by his private physician and a report of this examination submitted to Lawrence Berkeley Laboratory.

6.3 Follow-up information. The following information will be recorded on the follow-up form at each visit:

1. Brief interval history related to disease.
2. Physical examination:
  - a. Weight
  - b. Temperature
  - c. Appropriate aspects of physical examination
  - d. Appropriate aspects of neurological examination
  - e. Performance status (Karnofsky function assessment)
3. Laboratory tests and routine x-rays: Appropriate studies indicated in section 4.
4. Specific diagnostic studies, or studies which gave the most reliable information regarding the initial extent of tumor will be repeated electively at one year intervals and may be repeated sooner if indicated by the patient's status.
5. Complications of treatment.

## 7.0 Administration

7.1 Admission to study. Any patient who meets the required eligibility in pre-treatment evaluation criteria will be admitted to the protocol for helium/heavy-ion radiotherapy at the Donner Laboratory, Lawrence Berkeley Laboratory. The necessary study forms to support data collection and analysis are currently being designed under the direction of the senior statistician assigned to the study team. The following records will be generated by the study team and participating institutions for storage, retrieval and analysis at the study center:

1. Forms to be submitted upon acceptance of the patient into the protocol.
  - a. Patient eligibility form (submitted for both eligible and ineligible patients entering each participating institution). Patients who are determined by their physician as obviously ineligible will be eliminated at this point. The patient eligibility form listing the reason(s) for ineligibility will be forwarded to the study center for use in statistical population control.
  - b. Pre-treatment evaluation form. This form, documenting the history and physical information, laboratory tests and special studies, including surgery will be submitted only on those patients referred for treatment.
  - c. Study entrance form (patient name, address, referring institution, referring physician, etc.).
  - d. Patient consent form
2. Radiation treatment summary. A standardized radiation treatment summary will be used by participating institutions for those patients who receive the whole brain megavoltage radiation therapy at the

participating institutions. A daily schedule of helium/heavy-ion therapy will be prepared at Lawrence Berkeley Laboratory. This report will also include an end of treatment examination to include weight, pertinent general physical examination and neurological examination findings, performance status, current medications, and if possible, an assessment of tumor response.

3. Follow-up examination form (see section 7).
4. Pathology forms (see section 9).

## 8.0

Statistical considerations.

- 8.1 Randomization. Based on available literature and their own experience the Regional Clinical Committee and Sub-committee for Human Trials of Pion Radiation Therapy estimated the current accumulative 5 year survival rate for malignant glioma of the brain at approximately 6%. Because of this low survival rate a nonrandomized study is proposed. Any patient meeting eligibility and pre-treatment evaluation criteria will be accepted for helium/heavy-ion radiotherapy.
- 8.2 Number of patients required. It is estimated that 6-10 patients treated with helium ions would provide sufficient information to undertake similar radiation therapy with heavy ions. This number of patients also would demonstrate the feasibility of whole brain irradiation with helium ions insofar as cutaneous and subcutaneous reactions and irradiation tolerance (nausea, vomiting, etc.) are concerned.

If the feasibility study with Grade III and IV astrocytoma is encouraging it is reasonable to expect that a full-scale program could be undertaken with a goal of treating approximately 100 patients.

In order to demonstrate an improvement in the five year survival rate from 6% to 20% with helium/heavy-ion it will be necessary to treat 105 patients in order to demonstrate statistical significance ( $P=0.01$ ).

## 9.0

Pathology.

- 9.1 Initial surgical (biopsy) specimens. Biopsy specimens will be examined by pathologists at the participating institutions to confirm the diagnosis. Representative slides and copies of biopsy reports will be submitted to the study center for review by the study pathologists. Copies of the reports from the study pathologists will be forwarded to the referring and/or follow-up physician.
- 9.2 Subsequent surgical specimens. Any tissue surgically removed from anatomical sites will be examined by pathologists at the participating institution where surgery was performed. Appropriate microscopic slides and pathological reports will be forwarded to the study center for review by the study pathologists.

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9.3 Autopsies. Autopsies should be performed on all study patients by pathologists at the participating institutions. Post mortem studies should include a description of irradiated tissues and the character and extent of persistent, recurrent or metastatic tumor. Autopsy reports and representative microscopic slides will be forwarded to the study center for review by the study pathologists.

10.0 References

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Order, S.E.; Hellman, S.; von Essen, C. F.; and Kligerman, M.M. Improvement in quality of survival following whole brain irradiation. Radiology 81 (July 1968): 149.

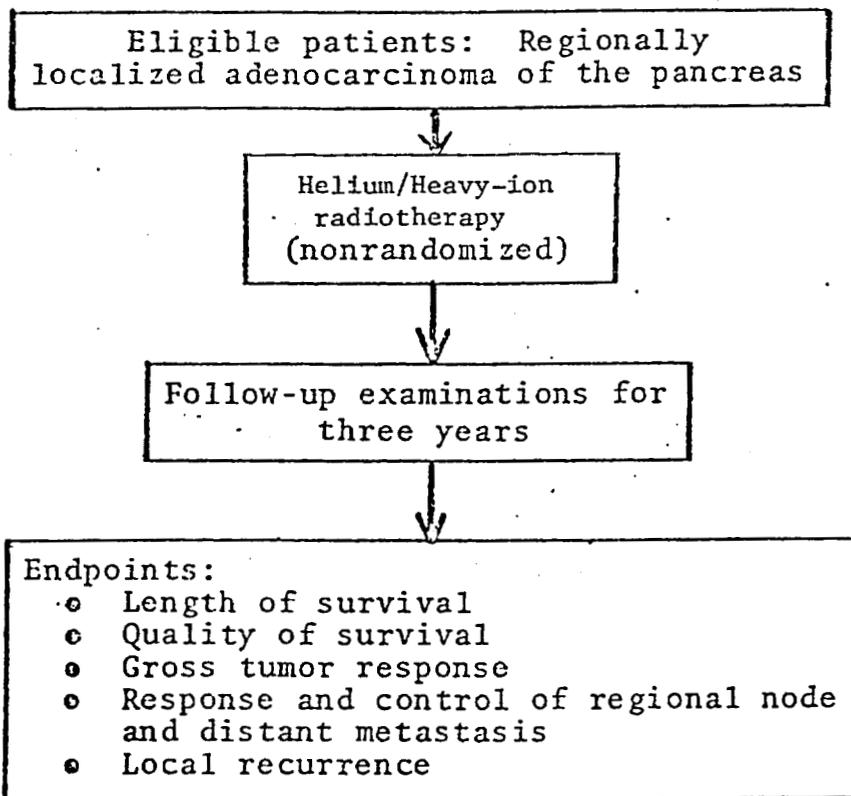
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PHASE III PROTOCOL: HELIUM/HEAVY-ION RADIOTHERAPY OF  
ADENOCARCINOMA OF THE PANCREAS

0.0 Schema



1.0 Summary of the Study

This study is designed to evaluate the effectiveness of helium/heavy-ion radiotherapy of regionally localized adenocarcinoma of the pancreas (disease confined to pancreas, peripancreatic tissues, and regional lymph nodes). Because of the very low survival rate associated with this disease, a nonrandomized study is proposed. Any patient who meets the required eligibility and pretreatment evaluation criteria will be admitted to the protocol for helium or heavy-ion radiotherapy at the Lawrence Berkeley Laboratory (LBL).

Primary endpoints of the study will be derived from patient survival time, quality of survival, study of gross tumor response, a record of response and control of regional node and distant metastasis, and a record of local recurrence. Patients will receive follow-up examinations (with study parameters and progress toward endpoints recorded for statistical analysis) for three years, since available literature indicates a very low two-year survival rate for these patients.

A survival rate of 10 percent will be sought as a minimally acceptable improvement in patient survival probability with helium/heavy-ion therapy. Adequate measurement of such a rate would require 159 evaluable patients for the study ( $p = 0.01$ ), based on current survival of approximately 1 to 2 percent for operable cases and 0 percent for inoperable cases, as estimated by the Regional Clinical Committee and Subcommittee for Human Trials of the Los Alamos Meson physics facility pion radiotherapy project.

## 2.0 Introduction and Objectives

2.1 Staging. This study will evaluate the effectiveness of helium/heavy-ion therapy of regionally localized adenocarcinoma of the pancreas (disease confined to pancreas, peripancreatic tissues, and regional lymph nodes). The American Joint Committee on Cancer Staging and End Results Reporting (AJC) has not developed an appropriate staging system for this site.

2.2 Rationale. Carcinoma of the pancreas is not satisfactorily treated by currently known methods. Localized or regionally localized involvement can on occasion be resected (Whipple procedure) but the morbidity of the procedure is high. Evidence is weak or lacking that patients treated radically fare better than those undergoing palliative biliary bypass surgery or no treatment. Conventional forms of radiation have not been successful. An alternate form of local therapy is badly needed, since the disease often remains localized for prolonged periods, the symptoms and signs of localized disease may be devastating, and existing therapy is inadequate.

2.3 Objectives. The objectives of the study are to determine whether helium/heavy-ion therapy can improve local control and survival in patients with adenocarcinoma of the pancreas. The morbidity and complications of this therapy, particularly to the gastrointestinal tract, will be assessed. Because of the very low survival rate associated with this disease, a nonrandomized study is proposed.

The study will evaluate the effects of helium/heavy-ion therapy upon:

1. Length of survival
2. Quality of survival
3. Change in tumor size
4. Incidence and response of metastasis in regional nodes
5. Incidence of distant metastasis
6. Incidence of local recurrence.

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### 3.0 Eligibility of Patients

3.1 General condition of eligibility. Only patients with adenocarcinoma of the pancreas are eligible for this study.

3.2 Conditions for patient eligibility. In addition to the above general condition, the following conditions must be met before a patient can be admitted to the study:

1. Biopsy proof of adenocarcinoma (with biopsy material obtained from the pancreas or an adjacent lymph node if the gross surgical findings are typical of pancreatic carcinoma).
2. Performance of a palliative biliary bypass does not affect patient eligibility for the protocol.
3. Reasonable expectation of completing the study treatment and the required follow-up examination (including travel to and treatment at LBL, as well as an annual follow-up examination at the study center at LBL.
4. Agreement of the patient and his physician to the conditions of the study.
5. Understanding by the patient of the provisions of the study, and completion of the required investigational treatment consent form.

3.3 Conditions for patient ineligibility. The following conditions are cause for exclusion of the patient from the study:

1. Clinical evidence of metastatic disease to the liver, peritoneal surfaces remote from the pancreas, or extra-abdominal sites (supraclavicular nodes, thorax, or skeleton).
2. Previous definitive therapy of the primary tumor and regional adenopathy, including prior definitive radiation therapy or potentially curative surgical procedures.
3. Previous chemotherapy, which, in the opinion of the study team, might compromise treatment or evaluation.
4. Previous radiotherapy to areas overlapping the projected treatment portals.