

Use of the Bragg Peak for Brain-Tumor Therapy

Alexander Gottschalk, John T. Lyman and Larry W. McDonald

The early work in this laboratory demonstrated that the biological effect of tissue ionization produced by the heavy particles from the first cyclotron was greater than that of X rays. This led to the setting up of safety standards for workers around accelerators and also to the investigation of neutron irradiation in cancer therapy (1,2,3). The interest in the relationship between the density of ionization and biological effect, from the standpoint of both basic radiobiology and radiation therapy, has continued here. Since World War II, when larger cyclotrons and linear accelerators were constructed and higher energy, heavy charged particle beams became available, extensive biological and medical research has been carried out with various heavy particles in this laboratory and elsewhere (4), and the work is now leading to advances in the therapy of several diseases (5).

Accelerated heavy particles from the Berkeley 184-inch synchrocyclotron have been used for patient therapy since 1954. Numerous papers have described clinical studies using heavy particles for radiosurgical suppression or ablation of the hypophysis in the treatment of diseases such as metastatic breast carcinoma, diabetic retinopathy, acromegaly, and Cushing's disease, and also for direct irradiation of a soft-tissue lesion and recently for three brain tumors (6-11).

Experiments started already in 1948 included the successful treatment of animal tumors with the Bragg peak and thus demonstrated the unusual clinical implications of heavy particles in therapy using this portion of the heavy particle beam (12). In these investigations it became evident that heavy-particle beams are of great clinical interest. Unlike X rays or gamma rays, they penetrate tissue with little scatter, and the higher linear energy transfer (LET) as the particles slow down produces the Bragg peak, by which it is possible to deliver a cancerocidal dose to deep-seated tumors. This can be achieved with relatively little skin dose, the depth-dose to skin-dose ratio being opposite to that of X rays or gamma rays. In addition, each unit of energy delivered at the Bragg peak has a greater relative biological effect (RBE) per unit of ionization present (4,13) as compared to 250-kVp X rays. Furthermore, factors such as temperature, fractionation, protective agents and oxygen saturation, which all modify electromagnetic or other low-LET radiations, alter to a lesser degree

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the effect of higher LET irradiation (14,15,16). This report describes the case histories of three patients suffering from brain neoplasms treated with the Bragg peak, discussing the dosimetry and technical aspects of therapy.

CASE HISTORIES

CASE 1. A four-year-old white male had the onset of neurological symptoms December 6, 1960, consisting of a fall, morning vomiting, diplopia, papilloedema, and a palsy of the left abducens nerve. Increased intracranial pressure was also present at this time. Subsequent ventriculography and carotid angiography revealed a right parasagittal mass. A craniotomy was performed and a lemon-sized, grade 2 oligodendroglioma was removed. In the interval, February 13 through March 9, 1961, 3,100 rads were delivered to the tumor site with a 250-kVp apparatus of HVL (half-value layer) 2.28 mm Cu.

In May of 1961 signs of increased intracranial pressure again developed, and at a second craniotomy, recurrent tumor was found. Histologically, this also was a grade 2 oligodendroglioma. In October of 1961, because of a developing left hemiparesis, a third craniotomy was performed with a recurrent neoplastic mass once more excised. At this time, the tumor had become a grade 3 oligodendroglioma.

In December of 1961 the patient first manifested right hemiparesis and had a right-sided Jacksonian seizure. Consequently, he was believed to have tumor spread across the midline. In the interval from December 20, 1961, to January 12, 1962, the patient was treated with Bragg-peak irradiation from the alpha-particle beam of the 184-inch synchrocyclotron. He slowly improved and over a period of the next five months experienced a good palliative result. He then gradually began to show a steady deterioration with obvious regrowth of tumor and expired on October 15, 1962.

The autopsy revealed a recurrent oligodendroglioma extending widely into both cerebral hemispheres and into the thalamus. Hemorrhage and necrosis within the tumor were interpreted as being caused either by the irradiation or by the tumor outgrowing its blood supply. Metastases from the intracranial tumor were found in the lungs.

CASE 2. A 50-year-old white male was initially suspected of having a brain tumor in April 1962 after a two-and-a-half year history of progressive weakness in the right hand, a short history of difficulty with speech and right hemiparesis. A left carotid arteriogram demonstrated a left temporal-parietal tumor. On May 21, 1962, a subtotal resection of a grade 3 astrocytoma was performed. Postoperative irradiation using the Bragg peak was started on June 29, 1962, but following the initial two treatments, the patient became unresponsive and suffered from a progressive right hemiparesis, nausea, and

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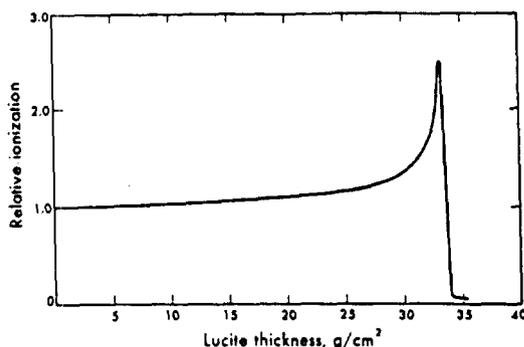


Figure 1. Bragg curve of 910-MeV alpha-particle beam. Mu-31722

vomiting. He was then reoperated, and a lemon-sized tumor was again removed. Bragg-peak therapy was resumed on July 9 and completed on July 13, 1962. In spite of considerable neurologic deficit consisting of aphasia and a persistent hemiparesis, his status improved until October of 1962. He then gradually began a progressive down-hill course and expired in January of 1963. Terminally, the patient appeared to be suffering from bilateral bronchopneumonia for which he was hospitalized. He was treated with antibiotics and seemed to improve when he suddenly became unresponsive and died three days later.

A grade 4 astrocytoma was found extensively involving the left cerebral hemisphere at autopsy. Sections from the more superior portions of the tumor showed some eosinophilic coagulum which was PAS positive; a similar type of coagulum has been noted in radionecrosis of nerve tissue. The greater part of the tumor showed focal necrosis and some vessel thrombosis which are common in grade 4 astrocytomas. Pressure effects produced encephalomalacia of the right occipital lobe and hemorrhage in the brain stem. The hemorrhage in the brain stem and bronchopneumonia were the terminal events.

CASE 3. A 38-year-old white male first noted the onset of left-sided headache and nausea in January, 1962. The symptoms progressed in severity and were associated with rather vague personality change with at least one episode of loss of contact with his surroundings.

Papilledema was evident in June 1962, and on June 9, 1962, a ventriculogram demonstrated a left frontal mass. A left frontal craniotomy was performed the same day with subtotal removal of a grade 2 astrocytoma from the region of the left sylvian fissure. From July 6 to July 13, 1962, the patient was treated with alpha-particle Bragg-peak irradiation. In the immediate post-operative and post-irradiation period a right hemiparesis and pronounced aphasia were evident. The hemiparesis has now (one year later) completely disappeared.

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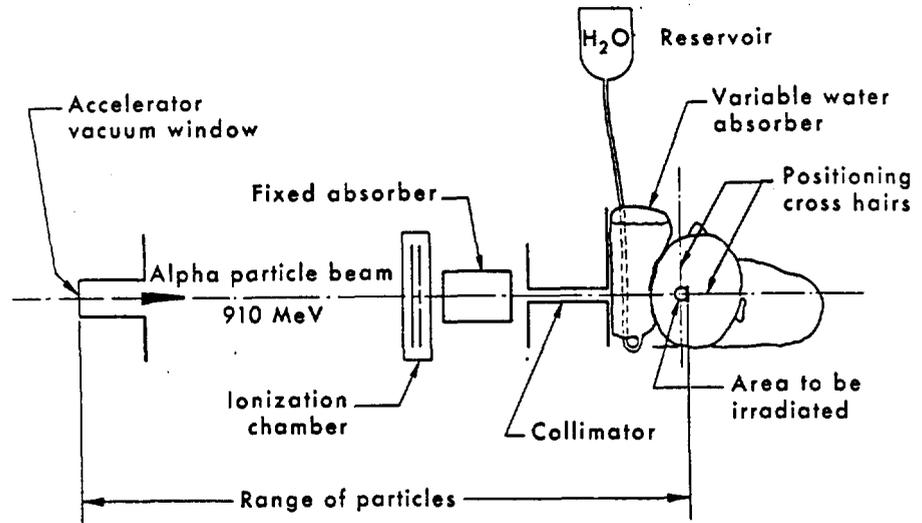


Figure 2. Schematic diagram of treatment setup.

The aphasia has improved, but is still present. The patient is working regularly as a stock clerk and is able to drive his car. At this time there is no evidence of recurrent neoplasm.

METHOD OF THERAPY AND DOSIMETRY

The three patients were all irradiated at the 184-inch synchrocyclotron, utilizing the 910-MeV alpha-particle beam. As this beam of particles is slowed down by interactions with an absorbing medium, an increase in ionization in the medium takes place. This is shown in Fig. 1. This Bragg curve shows the increase in ionization of the nitrogen gas in an ionization chamber as a function of the amount of absorbing medium in front of the ionization chamber, the absorber in this case being lucite.

Relative mass-stopping powers of various materials were calculated or measured (17) so that suitable combinations of absorbers could be used to permit maximum ionization to occur at required depth below the surface of the scalp. A fixed absorber of lucite or copper was used in conjunction with a variable water absorber enclosed in a pliable plastic bag conforming with the patient's head (Fig. 2). The beam was monitored before the first absorber, and from Bragg curves (obtained by using various combinations of absorbing materials) the dose delivered to various depths in the brain was determined.

Isodose curves were obtained by graphically summing the depth-dose curves for the individual treatment fields. In case 3, isodose curves were also obtained by simulating the treatment schedule on the IBM 7090 computer (see Fig. 3).

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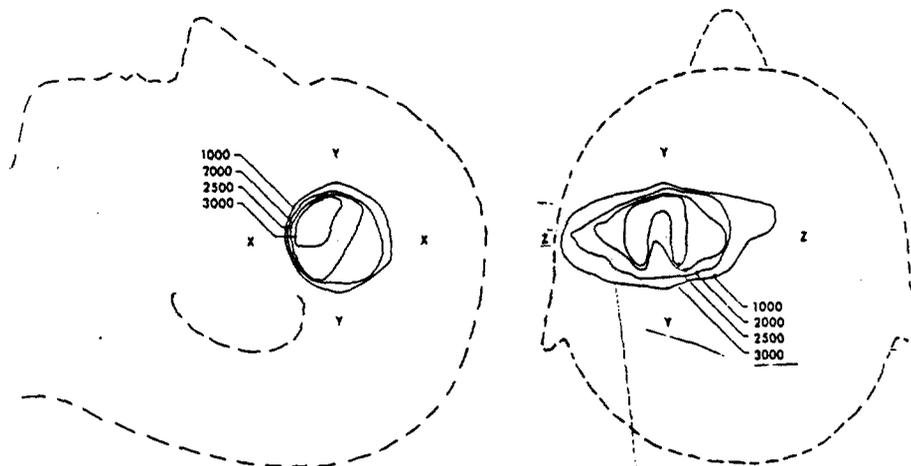


Figure 3. Isodose curves for case 3, calculated by IBM computer. MU-33279 and 33280

Case 1: Treatment was given on eight separate occasions within a 24-day period. Irradiation was delivered through 13 separate portals. The maximum dose delivered to the tumor was 8,500 rads, with the majority of the treatment field receiving more than 6,000 rads.

Case 2: Treatment was given on five separate occasions during a 15-day period. Irradiation was delivered through nine portals. Maximum dose delivered to the tumor was 5,250 rads, with the majority of the treatment field receiving greater than 4,000 rads.

Case 3: Treatment was given on four separate occasions during an 8-day period. Irradiation was delivered through five different portals. Three of the portals were used more than once, but the beam was allowed to penetrate to a different depth each time. The maximum dose was 4,450 rads. Most of the field received more than 2,500 rads.

DISCUSSION

The largest beam now available for heavy-particle therapy is a circle 6 cm in diameter. Therefore, it is currently possible to treat only a relatively small volume of tissue with a cancerocidal dose. However, modifications that will permit larger treatment fields are presently underway. Nevertheless, effective therapy with the Bragg peak does depend upon precise localization of the residual neoplasm. The surgeon can often help by localizing tumor-containing areas in relation to bony landmarks in the skull; and in most cases, radio opaque clips can be placed around the margins of the operative field to provide a

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target visible on alignment X rays. Unfortunately, highly malignant gliomas tend to infiltrate widely, often sending out microscopic tumor strands into brain tissue that grossly appears normal. Consequently, the likelihood of a geometric miss with the heavy particle beam (also a problem when X rays are used (18)) is great, although it may be possible to deliver tumorocidal doses to all the tissue obviously invaded by neoplasm.

In both case 1 and 2 this situation almost certainly occurred. It is noteworthy, however, that in case 1 palliation was achieved with the Bragg peak in spite of the fact that a conservative dose of conventional irradiation had no apparent effect. Whether this was due to the higher dose given with the heavy particles, the greater efficacy of the high LET irradiation, or both, is not known. The relative good health enjoyed by case 3 more than one year after treatment is encouraging but as yet permits no ultimate prognosis; because, in a large series of patients with comparable tumors, Kernohan and Sayre (19) found an average survival of almost two years following surgery alone.

SUMMARY AND CONCLUSIONS

Three patients with brain tumors have been treated by the Bragg peak of the 910-MeV alpha-particle beam from the 184-inch synchrocyclotron. All had had subtotal tumor resection prior to therapy. The case histories are presented; the technique of dosimetry, and the method of irradiation are discussed. The series is too small to judge whether or not this form of therapy holds great promise for the future.

ACKNOWLEDGEMENTS

Drs. John H. Lawrence and Cornelius A. Tobias provided both motivation and guidance for this project. Mr. Richard W. Pratt was responsible for constructing the mechanical devices necessary for therapy and was of incalculable aid in helping to position patients. Mrs. Jeannette Cornell provided nursing care. Physicist Jerry Howard and Mr. James Vale and the cyclotron crew were responsible for the proper operation of the therapy beam.

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BRAIN TUMORS

During the past six years, we have used 910-MeV. alpha particles to irradiate brain tumors in six patients, employing the Bragg peak in five cases and the plateau of the Bragg curve in one (27). One of these patients, a thirty-eight year-old man who had a grade II astrocytoma partially excised one month prior to Bragg-peak alpha-particle irradiation in July 1962, continues to do well. He works full time, and has had no headaches or neurological signs of tumor recurrence, and it is now over five years since completion of his therapy. Treatment was carried out using five fields to deliver a tumor dose of two thousand five hundred rads in four doses over an eight-day period. The other four patients had brief periods of improvement, but died at intervals ranging from six to twenty-two months following therapy. In these cases there was evidence of tumor recurrence outside of the radiation field, and in the cases where post-mortem results are available, this tumor extension was shown. Thus, while cessation of tumor growth in the treated area may be achieved, there is often recurrence later, outside of the radiation field. This points out a major difficulty in treating these cases -- namely, the exact delineation of the tumor area. Even though, by taking advantage of the heavy particle's favorable radiobiological characteristics we are able to deliver greater tumor doses while sparing the skin and intervening tissues, unless we

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can place the radiation throughout the entire tumor area, we cannot expect to obtain improved results.

Heavy particles were used to treat one other patient with a brain tumor (pinealoma); in this case, because of the central location and small size of the tumor, a technique was employed similar to that for pituitary irradiation, using the plateau of the alpha-particle beam with rotation. The patient, a fifty-five year-old man, had been in good health until August, 1965, when he first experienced diplopia. Medical work-up revealed a 2-cm. mass in the posterior part of the third ventricle causing partial obstruction to the cerebrospinal fluid pathways. Following two shunting procedures in September and in October, 1965, his visual symptoms disappeared, apparently because of temporary relief of the hydrocephalus and the direct pressure from the mass. It was then decided, hoping to achieve a more permanent result, to irradiate this tumor with heavy particles; in December, 1965, a total tumor dose of five thousand three hundred and fifty rads was given in two increments separated by a three-day interval. The patient was essentially asymptomatic until late October, 1966, when he again noted diplopia. During the next few months he also experienced progressive loss of visual acuity and hearing sense; in January 1967 he was hospitalized and ventriculography revealed a third ventricular mass which was interpreted as tumor recurrence (in retrospect, however, this actually represented a hematoma). The patient became stuporous and

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developed left homiparesis. Following a right occipital craniotomy, he remained permanently comatose and five days later, January 14, 1967, the patient expired. At autopsy, the essential cranial findings were post-surgical hemorrhagic necrosis of the right occipital lobe, right and left thalamus, and pulvinar; there were post-irradiation changes in the target area, but notably, none outside the target area. There was no evidence of residual tumor cells.

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the other one did well for a period of 5 years. However, in each of these patients there was subsequently evidence of tumor recurrence outside of the radiation field, and the patients died at intervals ranging from 6 months to 6 years after treatment. In the 4 cases where post-mortem results are available, the tumor extension outside the radiation field was shown. Thus, while cessation of tumor growth in the treated area may be achieved, there is often recurrence later outside of the radiation field, and this points out a major difficulty to overcome in treating these cases—the exact delineation of the tumor area must be known. Even though one can take advantage of the heavy particle's favorable radiobiological characteristics and thereby deliver greater tumor doses while sparing the skin and intervening tissues, unless one can place the radiation throughout the entire tumor area improved results cannot be expected.

In the case of the sixth patient with a brain tumor (pinealoma), because of the central location and small size of the tumor it was decided to employ a technique similar to that for pituitary irradiation using the plateau of the alpha-particle beam with rotation. This patient was essentially asymptomatic for 10 months following therapy, but then again noted diplopia. Ventriculography revealed a third ventricular mass which was interpreted as tumor recurrence, but which in retrospect actually represented a hematoma. He died 5 days after a right occipital craniotomy, and at autopsy the essential cranial findings were postsurgical hemorrhagic necrosis of the right occipital lobe, right and left thalamus, and pulvinar, there were postirradiation changes in the target area, but notably none outside the target area. There was no evidence of residual cells.

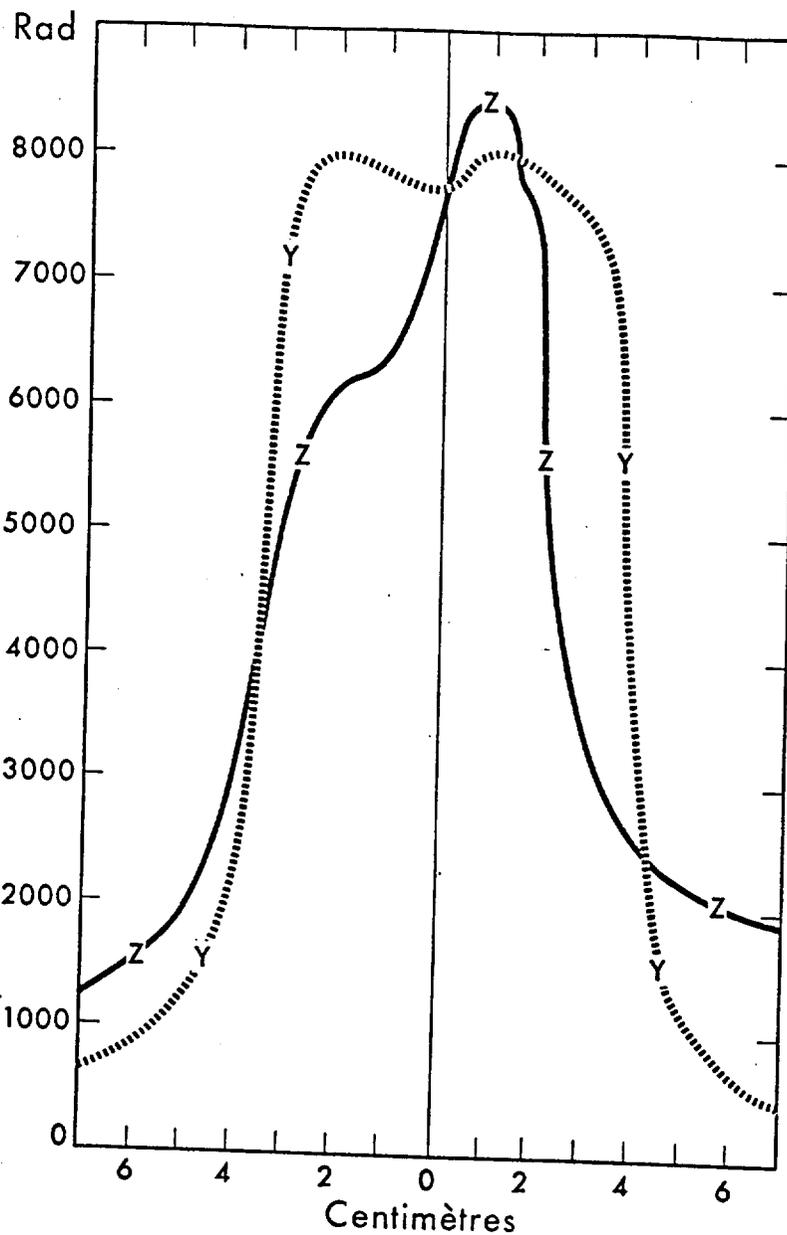
We have also used the Bragg peak of the 910-MeV alpha-particle beam to perform thalamotomies in 2 patients with Parkinson's disease [132] but there are not sufficient data to discuss the results. More recently we have used the Bragg peak to treat pulmonary metastases in 3 patients; following is a case history of the first patient.

Case history. A 44-year-old woman with a 6-year history of cylindroma of the palate was referred in September, 1969, for treatment of pulmonary metastases. Resection of the hard and soft palate without radical neck dissection (no cervical nodes were palpable) had been done in March, 1963, the pathological section showing adenoid cystic carcinoma in all margins except one. Postoperative radiation therapy with 2-MeV x ray was administered, the total dose being 5000 rads in 25 days. Multiple follow-up examinations revealed no evidence of local recurrence nor distant metastases until February, 1969, when both were detected. The primary site was treated with implantation of two radon

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Dose profiles along lateral ZZ and anterior-posterior axis YY

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Case Summary: Peter Lassen #1
First Brain-Tumor Patient
Bragg-Peak Therapy

This four-year old boy with a recurrent parasagittal oligodendroglioma had undergone surgery three times within nine months for excision of a lemon-sized brain tumor. He had also received one course of x-ray therapy (estimated tumor dose, 3,130 rads delivered to the tumor site from February 13 through March 9, 1961). When referred to us in December 1961, there was evidence that the tumor had spread across the midline, bilateral involvement of the motor cortex being present.

Bragg peak alpha particles were used to treat the tumor, using 13 fields in eight treatments over a 24 day period. The maximum dose delivered to the tumor was 8,500 rads with a majority of the treatment field receiving more 6,000 rads (less than 2,000 rads went to any of the skin areas).

There was good palliation for eight months; however, the tumor then recurred outside the radiation field and the patient died nine months following completion of therapy.

Autopsy revealed recurrent oligodendroglioma extending widely into both cerebral hemispheres and into the thalamus.

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HEAVY PARTICLES (BRAGG PEAK) IN TREATMENT OF BRAIN TUMORS

Patient	Type of tumor	Previous treatment	Heavy-particle therapy Rads/days Date finished	No. Rxs. No. portals	Palli- ation survival	Postmortem findings
1. 	Oligodendroglioma	12/60 Surgery 3/61 3,100 r 5/61 Surgery 10/61 Surgery	6,000/24 1-12-62	8 13	8 mon. 9 mon.	Extension of tumor beyond radiation field. <i>PM</i>
2. 	Astrocytoma III	6/62 Surgery 7/62 Surgery	4,000/15 7-13-62	5 9	3 mon. 6 mon.	Extension of tumor beyond radiation field. <i>PM</i>
3. 	Astrocytoma II	6/62 Surgery	2,500/8 7-13-62	4 5	60 mon. 73 mon.	Extension of tumor beyond radiation field. <i>PM</i>
4. 	Oligodendroglioma	1961 Co-60 1963 Nitrogen mustard	4,000/7 6-14-65	2 14	12 mon. 14 mon.	No postmortem examination.
5. 	Astrocytoma III	7/65 Surgery	6,000/10 10-15-65	5 8	10 mon. 23 mon.	Extension of tumor beyond radiation field. <i>PM</i>
6. 	Pinealoma	9/65 Shunting 10/65 procedures	5,350/3* 12-23-65	2 --	13 mon. 13 mon.	Hemorrhagic necrosis (post-surgery) <i>PM</i>

* Rotation only -- no Bragg peak.

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Brain Tumor Case #2: [REDACTED]

Previous history: [REDACTED] year old white male, initially suspected of having a brain tumor in April 1962, after a 2 1/2 year history of progressive weakness in the right hand and a short history of difficulty with speech and right hemiparesis. A left carotid arteriogram demonstrated a left temporal-parietal tumor. On May 21, 1962, a subtotal resection was performed. the pathological diagnosis being a grade 3 astrocytoma.

Postoperative Bragg peak heavy particle irradiation was started on June 29, 1962. This therapy was interrupted after the first two treatments, and a second craniotomy performed with removal of a massive amount of recurrent glioblastoma. Bragg peak heavy particle therapy was then resumed on July 9 and completed on July 13, 1962. There were five treatments during the 15 day period, using 9 portals. Maximum tumor dose delivered was 5,250 rads; the majority of the treatment field received greater than 4,000 rads.

The patient subsequently improved; he was subjectively better and skull x-rays taken three months after therapy revealed no particular change in the multiple silver clips and the bone flap appeared to be in satisfactory condition. However, after these three months he gradually began a progressively downhill course and expired in January of 1963 (six months after the end of treatment).

Postmortem findings showed a grade 4 astrocytoma extensively involving the left cerebral hemisphere. There was again similar recurrence beyond the area of radiation.

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Brain Tumor Case #3: [REDACTED]

History: a [REDACTED] year old man, first noted symptoms in January 1962 which progressed in severity and were associated with vague personality changes, and at least one episode of loss of contact with his surroundings. Papilledema was evident in June of 1962 and a ventriculogram demonstrated a left frontal mass. A left frontal craniotomy was performed on June 9, 1962 with subtotal removal of a grade 2 astrocytoma from a lesion of the left silvian fisher.

Bragg peak heavy particle irradiation was carried out between July 6 and July 13, 1962. There were four treatments during the 8 day period, the irradiation being delivered through five different portals (three of the portals were used more than once, but the beam was allowed to penetrate to a different depth each time). The maximum dose was 4,450 rads; most of the field received more than 2,500 rads. The hemiparesis disappeared one year later, aphasia was improved but still present. and the patient was working regularly at that time and was able to drive his car. He continued to do well, and 4 1/2 years after treatment examination revealed no headaches or neurological signs of tumor recurrence. However, within the next year there was tumor recurrence, and in July of 1968 he underwent a left frontal craniotomy with lobectomy. The tissue was glioblastoma multiforma, grade 4. The patient did well for 10 days but then had a grand mal seizure. and declined until death on August 23, 1968.

The autopsy showed right frontal and corpus collosum involvement with intracranial hemorrhage. . We are still waiting the details of the microscopic findings.

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Brain Tumor Case #4: [REDACTED]

A [REDACTED] year old female with a clinical diagnosis of slowly growing oligodendoglioma. History: Onset of symptoms in 1951. In 1961 she received cobalt 60 therapy (5,400 rads in 8 weeks) and responded very well for two years. Symptoms then recurred and she was given a brief course of nitrogen mustard, with no resulting improvement.

Bragg peak heavy particle irradiation was administered in June 1965. A tumor dose of 4,000 rads was given in two treatments over a one-week interval (using 7 portals on each side).

One year later there was no evidence of tumor recurrence but the patient died 14 months after treatment. Unfortunately no autopsy was performed, and the results of the radiation therapy could not be fully assessed.

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Brain Tumor Case #5: [REDACTED]

[REDACTED] year old man who had grade 3 astrocytoma. History: Symptoms first noted in May 1965. On July 27, 1965 craniotomy performed and a five centimeter tumor was removed just posterior to the left postcentral gyrus. The improvement was dramatic and his only residual abnormality was minimal right hemiparesis. However, in view of pathological evidence of presence of tumor cells at the margins at the excised specimen, it was felt that post-operative heavy particle therapy was indicated.

Bragg peak heavy particle therapy was administered in five treatments over a 10 day period, using 8 portals. The treatment ended on October 15, 1965. The total tumor dose was 6,000 rads.

Following treatment the patient had a fair remission for about a year. However, about December 1967 he started to show signs of deterioration, and the patient expired in August of 1967. Cause of death was acute and organizing bronchopneumonia, cachexia, astrocytoma of left parietal lobe (recurrence with extension to left frontal and temporal lobes).

Microscopic findings at postmortem revealed in the brain, (1) glioblastoma multiforme; (2) radiation necrosis of tumor and some adjacent white matter and (3) mineralization of blood vessels.

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1160113

Brain Tumor Case No. 6: [REDACTED] (Pinealoma)

[REDACTED] year old male who had been in good health until August 1965 when he first experienced diplopia. The medical workup revealed a 2 centimeter mass in the posterior part of the third ventricle, causing partial obstruction to the cerebral spinal fluid pathways. Following two shunting procedures in September and October 1965, his visual symptoms disappeared, apparently because of temporary relief of the hydrocephalus and the direct pressure from the mass. It was then decided, hoping to achieve a more permanent result, to irradiate this tumor with heavy particles.

In this case, Bragg peak heavy particles were not used because of the central location and small size of the tumor -- a technique was employed similar to that for pituitary irradiation using the plateau of the alpha particle beam with rotation. A total tumor dose of 5,350 rads was given in two treatments over a three-day period (initial plan had been to deliver 8,000 rads in three increments over eight days; however, increased diplopia developed and it was decided to stop after two treatments with 5,350 rads probably being an adequate dose). Therapy was completed on December 27, 1965.

The patient did well and was essentially asymptomatic until late October 1966 when he again developed diplopia. There was no evidence of increased intracranial pressure, and the shunt valve was working well. In early January 1967 he was hospitalized with an episode of progressive somnolence, associated with deafness and third nerve paralysis. The patient underwent ventriculography on 1/3/67 and 1/5/67 after the ventriculo-atrial shunt had been ligated. This revealed what at first was interpreted to be a

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	Accession No.	42-92-0066
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