Neutron interstitial brachytherapy for malignant gliomas: a pilot study

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Fifty-six patients with malignant glioma were treated with implantation of the neutron-emitting element californium-252 ($^{252}$Cf) within 2 weeks after surgical debulking of the tumor. Implantation was performed using computerized tomography-guided placement of afterloading catheters, and the $^{252}$Cf sources were removed after approximately 300 neutron rads were delivered. Patients then received 6000 to 7000 conventional photon rads by external beam. The total photon-equivalent dose to the tumor ranged from 8100 to 9100 rads. The median survival time was 10 months, with 18- and 24-month survival rates of 28% and 19%, respectively. The results of reoperation or autopsy showed that patients had recurrence of the tumor but that radiation necrosis was restricted to the area of the original tumor. Serious complications occurred in five patients (9%) and consisted of wound infections in three, cerebral edema in one, and radiation necrosis beyond the original tumor margin in one.

Previous studies using external-beam neutron radiation have shown that neutrons are capable of totally eradicating malignant gliomas; however, in most cases, unacceptable widespread radiation necrosis has resulted. Neutron implants are a logical way to increase the dose to the tumor and decrease the dose to normal brain. Interstitial neutron radiation can be given safely with $^{252}$Cf, and the survival results achieved by radiation alone using relatively low doses of interstitial neutron radiation from $^{252}$Cf implants plus conventional photon radiation were equal to the results attained with any currently available conventional therapy.

KEY WORDS: brain neoplasm □ astrocytoma □ interstitial brachytherapy □ californium-252 □ neutrons □ glioblastoma

Malignant gliomas respond poorly to currently available treatment. Other than surgery, irradiation is the only method of treatment that unequivocally increases survival time. However, conventional external-beam photon (x-ray) radiation only prolongs life and does not provide a cure.

Neutron radiation has theoretical advantages over conventional photon therapy. Preliminary investigation with external-beam neutron therapy has shown that neutrons can completely eradicate gliomas but that unacceptable radiation damage to normal brain frequently follows. Neutron radiation has the potential to cure brain tumors if a way can be found to limit toxicity to normal brain tissue. Interstitial irradiation (from implanted radioactive sources) is a logical way to increase the dose to the tumor and decrease the dose to normal brain. Californium-252 ($^{252}$Cf) is a radioactive isotope that emits fast neutrons and is suitable for implantation therapy. Use of this isotope allows the delivery of large doses of neutron radiation directly to the tumor with relative sparing of normal brain tissue. We report the results of the first 56 patients with malignant gliomas treated with interstitial neutron therapy plus external-beam photon therapy.

Clinical Material and Methods

Patient Selection

Selection criteria for treating patients with $^{252}$Cf included: 1) no previous treatment had been given (other than attempted surgical resection or debulking); 2) there was a histologically confirmed diagnosis of malignant glioma (Kernohan grade III or grade IV astrocytoma); 3) the tumor was restricted to one cerebral hemisphere and did not extend into midline structures or show evidence of subependymal spread; and 4) the patient had a Karnofsky performance score greater than 50%.

From December, 1980, to December, 1985, 56 pa-
patients with malignant gliomas were implanted with $^{252}$Cf sources and then treated postoperatively with conventional external-beam photon radiation therapy. All patients received adrenocorticosteroids prior to surgery and implantation. Dexamethasone, 2 to 4 mg every 6 hours, was started 48 hours before implantation and was tapered off within 1 week after the procedure when possible.

**Implantation Technique**

The technique for implantation of a $^{252}$Cf source in brain tumor has improved steadily over the last 5 years. In general, there has been an evolution from the use of a single afterloading tube to multiple tubes. There have also been improvements in the localization of tumors and the accuracy of placement of the sources.

During the 1st year (1981), 11 patients were treated using a single interstitial afterloading tube loaded with two $^{252}$Cf sources. Because the effect of interstitial neutron irradiation on brain tissue was unknown, the intent of the initial studies was to keep the dose of neutron radiation delivered to normal tissue as low as possible. This limited approach was used to concentrate the efficient cell-killing ability of $^{252}$Cf neutrons on the central part of the tumor only. No attempt was made to totally cover the entire tumor with neutron radiation, and all patients received conventional external-beam photon radiation therapy in conjunction with neutron implantation.

Beginning in 1982, an attempt was made to tailor the shape of the neutron field of radiation to conform to the shape of the tumor. A template attached directly to the skull was used to position the implant tubes. The positioning of the tubes was guided by (nonstereotaxic) computerized tomography (CT), and up to four flexible plastic tubes (each containing two sources) were used. This arrangement allowed a larger dose distribution and a higher dose rate at the periphery of the field. Eighteen patients were treated with this early multiple-tube system.

Although localization was aided by CT scanning in the multiple-tube series, a more accurate localization system was needed to ensure total coverage of the tumor and accurate calculation of the dose delivered to the tumor and to normal tissue. In 1984, a Brown-Roberts-Wells stereotaxic frame that allowed CT-guided placement of the tubes was obtained. For 1 year this system was used in 17 patients to localize the depth and trajectory of the soft tubes. The head frame was removed once the tubes were in place. Although the stereotaxic system allowed much greater accuracy in placement, the soft tubes did not allow secure source placement because they would often become deformed after placement. Rigid tubes were needed to guarantee that the sources would remain in place.

In 1985, we designed a system for locking a set of rigid tubes into a template. This allowed the stereotaxic frame and template to remain in place throughout treatment and guaranteed accurate source placement. A stereotaxic frame system was obtained that allowed placement using either magnetic resonance (MR) imaging or CT; this has further increased the accuracy and flexibility of the implantation and evaluation procedure. With this system, up to seven tubes with a total of 14 sources have been used. The last 10 patients were treated with this apparatus. An idealized isodose distribution is shown in Fig. 1, and a typical distribution in a patient is shown in Fig. 2.

In all cases, after implantation of the afterloading catheters, the patients were taken to the department of radiation medicine where the $^{252}$Cf sources were inserted into the tubes. The sources remained in place for a total of 4 to 6 hours, depending on tumor size and age of the sources, until 300 neutron rads (equal to

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**Fig. 1.** An idealized isodose diagram showing the distribution from a six-tube array with 14 sources of radiation. Crosses indicate target points.

**Fig. 2.** Typical isodose distribution of neutron radiation from implanted californium-252 overlaid on a computerized tomography scan from a patient in this series.
about 2100 photon-equivalent rads) were delivered to the tumor. The sources were then removed along with the afterloading catheters, and the wounds were closed.

Beginning 7 to 10 days after $^{252}$Cf implantation, all patients received whole-brain external-beam photon radiation therapy. External-beam therapy was delivered using parallel opposed bilateral ports treating both fields every day. Total external-beam radiation doses ranged from 6000 to 7000 rads given over 5 to 7 weeks. The total photon-equivalent dose to the tumor (including radiation from $^{252}$Cf and external-beam photon therapy) ranged from 8100 to 9100 rads.

**Californium-252**

Californium-252 is a transplutonium radioactive isotope that emits fast neutrons of 2.3 MeV energy. The penetration characteristics are similar to those of photons and follow the inverse-square distribution. The isotope has a half-life of 2.7 years and is suitable for implantation therapy for brain tumors. The sources used in this study consisted of 15-mm long solid wires of $^{252}$Cf double clad in platinum/iridium.* The actual $^{252}$Cf platinum/iridium cylinders were 23 mm long × 2.8 mm in diameter.

**Calculation of Dose**

A small amount of gamma radiation is emitted along with the neutrons from $^{252}$Cf. The photon-equivalent dose from $^{252}$Cf is calculated as follows:

Equivalent Dose = (RBEn × DOSEn) + (RBEg × DOSEG),

where n signifies neutrons, g signifies gamma radiation, and RBE is the relative biological effectiveness. RBEn = 6 (based on animal data and previous work with other tumor systems), 1,9,17,18,23,32 and RBEg = 1.

**Safety Precautions**

Neutron radiation required somewhat different safety procedures from those used with conventional radiation. Lucite plastic and water (rather than lead) were used for shields from the neutrons. All personnel wore neutron-sensitive film badges, although only the physicians who loaded the sources into the afterloading tubes and the nurses who attended the patient from behind radiation shields while the implants were placed were at any risk of exposure. If the patients required attention from within the shield, the afterloading sources were removed from the implanted tubes and placed in a safe. The sources were then reinserted after the nurses had completed their work. Exposure to personnel was kept to less than 60 seconds per day per person.

**Evaluation of Patients**

Patients were evaluated by neurological examination, Karnofsky score, and CT scanning at intervals of approximately 8 weeks. In addition, MR imaging was used with patients treated in 1985. Progression of disease was defined as an increase in size of the lesion on CT or MR imaging or a decrease in the Karnofsky score. Time to progression of disease was measured from the first day of treatment (debulking surgery in every case) until progression was documented. Survival time was measured from the first day of treatment until the day the patient died or the date of the last follow-up examination (for censored observations).

**Data Analysis**

Survival curves were drawn using the Kaplan-Meier product limit method. 19 The log-rank test 22 was applied to detect late differences in survival between two or more groups, and the Breslow statistic 2 was used to compare early differences in survival between two or more groups. Cox regression analysis 8 was used to simultaneously evaluate the effects of several prognostic variables on survival through a proportional hazard model.

**Results**

Fifty-six patients were treated with $^{252}$Cf implants followed by external-beam photon radiation therapy. There were 33 men and 23 women. At treatment the patients ranged in age from 27 to 75 years, with a median age of 57 years (standard deviation ± 11.2 years). Forty-eight patients (86%) had Kernohan grade IV tumors, and eight patients (14%) had Kernohan grade III astrocytomas. The median age was 58 years for patients with grade IV tumors and 48 years for patients with grade III tumors.

The median time to recurrence was 34 weeks. The overall median survival time was 10 months, with 18- and 24-month survival rates of 28% ± 6% and 19% ± 6%, respectively (Fig. 3). All patients received

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* The sources were obtained (on loan) from the United States Department of Energy, Savannah River Operations.
a minimum of 10 months' follow-up, except for one patient who died from a self-inflicted gunshot wound 2 months after treatment. The median survival time was 17 months for patients with grade III tumors versus 10 months for those with grade IV tumors. The overall survival time of patients with grade III astrocytomas was only marginally better than that of patients with grade IV tumors (p < 0.12 for the Mantel-Cox statistic). However, when the difference was analyzed using the Breslow statistic, there was a significant difference (p < 0.05), indicating that early deaths occurred more frequently in patients with grade IV tumors.

To calculate the effect on survival, major demographic and clinical factors were examined by fitting the proportional hazards regression model to these data. The factors examined as possible explanatory regressor variables were: age, sex, tumor grade, pretreatment Karnofsky score, location of tumor, and presence of seizures. Several versions of the model were fitted. In all models fitted, a stepwise procedure was used to determine which regressor variables affected survival. In all cases, age was the only variable that entered the model, indicating that only the age of the patient made a significant impact on survival. Older patients had shorter survival times than younger patients. Specifically, the estimated beta coefficient for age in the Cox model had the value 0.0633 with a standard error of 0.0175 (p < 0.0003). Therefore, the risk of dying for individuals increased by a factor of 1.065 for each unit increase in age at first treatment (age measured in years).

Complications

Out of 56 implantation procedures, complications occurred in nine (16%). In four patients (7%) the complications were minor and consisted of skin redness (two patients) and transient worsening in focal neurological symptoms due to edema (two patients). In five patients (9%) the complications were more severe. Three patients (6%) developed wound infections, and in one meningitis resulted. One patient developed radiation necrosis of brain outside the borders of the original tumor, diagnosed by needle biopsy. The necrosis began inside the tumor margin and extended outward. There was no widespread necrosis similar to the type found after external-beam neutron therapy. One patient suffered a permanent hemiparesis caused by massive edema after implantation.

Findings at Reoperation

Eight patients underwent reoperation after CT or MR imaging showed evidence of tumor recurrence or radiation necrosis. Seven patients had necrotic masses in the area of the 252Cf implant, and one patient had a solid tumor mass in the area of the original tumor. All eight patients had recurrent tumor at the margins of the original tumor. In all cases, the predominant tumor type was low-grade astrocytoma with inflammatory cells and gemistocytic astrocytes. Microscopic foci of grade IV astrocytoma were also present in all patients at reoperation. No patient had evidence of radiation necrosis beyond the margins of the original tumor.

Autopsy Findings

Autopsies were performed on two patients. One patient died from a self-inflicted gunshot wound to the chest 49 days after implantation. Examination of the brain showed necrosis and giant cells in the center of the tumor with grade IV astrocytoma at the outer margins of the necrotic area. The second patient died 14 months after treatment. The brain showed extensive radiation necrosis confined to the implant area with scattered inflammatory cells, gemistocytic astrocytes, and fibroblasts. One microscopic focus, 4 cm away from the original tumor margin, contained viable grade IV astrocytoma. No other evidence of tumor was present. Neither patient had evidence of radiation damage beyond the original tumor margins.

Discussion

Malignant gliomas usually respond poorly to conventional cancer treatment methods. With surgery alone, the median survival time is about 4 months; with photon radiation therapy, the median survival is significantly increased to 9.5 months. The addition of chemotherapy does not significantly extend the survival period; in the best arm of the Brain Tumor Study Group, patients treated with surgery, radiation, and BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) had a median survival time of only 11.5 months. The reasons for the general failure of treatment are many. Although over 90% of tumors appear to be localized to a single area of the brain, surgery is not curative because the tumor usually infiltrates beyond the visible margins of the tumor or into contiguous vital structures that cannot be totally resected. Chemotherapy has failed because of difficulties with achieving tumoricidal concentrations of drug in the brain and problems with resistance to specific drugs. Radiation is limited by tumor insensitivity and toxicity to normal brain tissue. Necrosis of normal brain has prevented the delivery of more than 6000 to 7000 rads by conventional external-beam photon methods, and these doses are too low to totally eradicate most tumors. Attempts to improve conventional radiation therapy using changes in fractionation or radiation cell sensitizers have not significantly increased periods of survival. The search for improvements in radiation therapy has led to the investigation of different types of radiation, including particle radiation. With heavy charged particles or unchanged particles such as neutrons, the ionization produced is very dense because the rate of energy deposited into tissue is much greater along the length of the tract that the particle travels. These types of radiation are, therefore, classified as high linear energy transfer (LET) radiation. Conventional photon radiation (x-ray) is low LET radiation and produces much less dense ionization.

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Neutron radiation has several theoretical advantages over low LET radiation including: 1) a greater ability to damage hypoxic cells; 2) a lesser ability of cells to repair sublethal and potentially lethal high LET-induced damage; and 3) less variation in radiation sensitivity relative to the cell cycle.\textsuperscript{11,35} With photon radiation, there is a dependence on tissue oxygenation for radiation response; well-oxygenated tumors are relatively more easily damaged while hypoxic tissue is radioresistant. This difference in response between oxygenated and hypoxic tissue is quantified as the oxygen enhancement ratio (OER), defined as the ratio of the dose required for equivalent cell killing of anoxic cells compared with the dose required for oxygenated cells. The OER for photon radiation is 3, while the OER for neutrons is between 1.1 and 1.6.\textsuperscript{3}

The theoretical basis for the superiority of neutrons is based on the way that each type of radiation produces cell damage. Photon radiation is thought to interact with tissue and produce free radicals. These free radicals then react with DNA (deoxyribonucleic acid) to produce radiation damage. Oxygen is believed to stabilize the production of free radicals and is necessary for photon radiation to produce maximum effect. With neutrons and other high LET radiation, the damage to DNA is produced by direct collision rather than free radical formation; therefore, oxygen is not required. In addition, photon radiation produces damage mainly to DNA while neutrons cause damage at multiple sites that is more difficult for the cell to repair. Photon radiation is more effective against cells in certain phases of the cell cycle, being most effective against cells in the M and G\textsubscript{2} phases and less effective during the S phase. Neutron radiation is equally effective throughout the cell cycle. All of the above factors are likely to be even more pronounced in malignant gliomas where extensive necrosis (with hypoxia) and a relatively low percentage of cycling cells make conventional photon radiation less effective.

Despite the theoretical attractiveness of neutron therapy for brain tumors, studies using external-beam neutron radiation have not resulted in an increase in survival times. Laramore, et al.,\textsuperscript{31} treated 36 patients with neutron beam alone or neutron beam plus photon beam, and compared the results with historical control patients treated with photon beam alone. No survival advantage for patients with neutron beam radiation therapy could be demonstrated. However, autopsies in 14 of 15 neutron-treated patients showed no evidence of tumor. The brains showed evidence of diffuse radiation damage, and damage to the normal brain was determined to be the cause of death. Catterall, et al.,\textsuperscript{4} studied 30 patients treated with neutron beam alone. The 1-year survival rate was 30%. However, 69% of patients examined at autopsy (or second craniotomy) showed either no tumor or only microscopic tumor foci. Again, diffuse damage to the brains was present, and most patients died from radiation damage. These studies showed that neutrons are capable of totally destroying malignant gliomas but that damage to normal brain must be minimized if the therapy is to be of practical use.

The dose of radiation that can be given safely is limited by tissue tolerance of the normal brain that surrounds the tumor. With external-beam therapy, radiation must always pass through normal tissue to reach the tumor. Intermittent radiation (from implanted radioactive sources) is a logical way to increase the dose to the tumor and decrease the dose to normal brain. Intermittent photon radiation has shown promise and allows large doses (> 10,000 rads) to be delivered directly to the bulk of the tumor while sparing the surrounding tissue.\textsuperscript{10,13,14} Since most malignant gliomas apparently are confined to one part of the brain and 90% recur within 2 cm of the tumor margin,\textsuperscript{46} local therapy with interstitial radiation has the potential to be curative.

Our own experience with \textsuperscript{252}Cf shows that neutron brachytherapy for the treatment of brain tumors is feasible and relatively safe. Implantation of \textsuperscript{252}Cf allows high doses of neutrons to be given while preserving the normal brain. In the few autopsied patients in our series, none had the widespread radiation damage found in patients who received external-beam neutron therapy. Californium implants have proved to be a safe way to deliver neutron radiation.

While the main purpose of our study was to determine the feasibility of \textsuperscript{252}Cf implants for brain tumor therapy, the survival results were encouraging. The technique of implantation and localization improved over the course of the study, and even using relatively unsophisticated procedures in the earliest patients, the overall survival result of 10 months was the same as results achieved with the best available combination therapies (consisting of resection, photon radiation, and chemotherapy).\textsuperscript{34} Virtually all patients in our study developed recurrence of their tumors, indicating that the dose of radiation used was too low to destroy the tumor. Technical improvements in the delivery of \textsuperscript{252}Cf therapy now allow this isotope to be used as the sole source of radiation. Much larger doses of neutron radiation can be given. A formal phase I trial (a dose-searching study) is currently in progress to determine the optimum dose for potentially curative brain tumor therapy. It is possible that with neutron implants, a dose will be found that will destroy the tumor without causing unacceptable radiation damage to the normal brain.

References


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