CHAPTER

20 Neutron Radiotherapy

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The neutron was discovered by Sir James Chadwick in 1932 during an analysis of certain nuclear reactions. Shortly thereafter, investigators proposed using it to treat various human malignant diseases. There have been two main areas of clinical investigation: fast neutron radiotherapy and boron neutron capture therapy (BNCT). We briefly describe the underlying physics of each type of therapy, summarize the historical development, and discuss current clinical usage. Space permits only a brief discussion of neutron brachytherapy using californium-252 (^{252}Cf) sources, which is in limited clinical use today. We will restrict our review to the clinical arena and not discuss ongoing basic research.

FAST NEUTRON RADIOTHERAPY

Overview

Fast neutron radiotherapy uses neutrons having typical energies of several tens of megaelectron volts (MeV) that are generated by accelerating either protons or deuterons with cyclotrons or particle accelerators and then delivering them to an appropriate target, most generally beryllium. The resulting distribution of neutrons is approximately spherically symmetric, and the beams used in therapy are collimated in much the same manner as the photon therapy beams generated by electron linear accelerators. Fission neutrons from nuclear reactors that have energies in the range of 1 MeV to 2 MeV can also be used to treat patients. Neutrons are neutral particles and interact directly with the atomic nuclei in tissue, producing recoil protons and nuclear fragments, which in turn create dense chains of ionization events. For neutrons of energies used in radiotherapy, about 85% of the deposited energy is via a "knock-on" reaction ("billiard-ball" type of collision) involving the hydrogen-1 (^{1}H) nucleus, meaning that the kinetic energy release in matter (KERMA) is larger in high-hydrogen-content tissue such as fat or myelin.

The resulting energy transfer is in the range of 20 keV/μm to 100 keV/μm compared with 0.2 keV/μm to 2 keV/μm for the megavoltage photons and electrons used in conventional radiotherapy. It is this higher energy transfer that gives rise to the different radiobiologic properties of fast neutrons, which are advantageous in certain clinical situations. The higher relative biologic effectiveness (RBE) accounts for the different clinical response observed with neutrons as opposed to conventional photon irradiation. Fast neutrons have RBEs in the range of 3 to 3.5 in terms of most normal tissue late effects, RBEs in the range of 4 to 4.5 in terms of damage to the central nervous system, and RBEs in the range of 8 for salivary gland malignant tumors.[1-3] High–linear energy transfer (LET) radiation causes a dense chain of ionizing events affecting both strands of the DNA and therefore makes DNA repair more difficult. Other cellular targets are similarly affected to a greater degree by high LET radiation. Furthermore, high-LET radiation from fast neutrons is less sensitive to the reduced cell-killing effects of hypoxia, with there being nearly equal cell killing under normoxic and hypoxic conditions.

Historical Perspective

Patients were first treated with fast neutron radiotherapy in 1938 by Robert Stone et al[4] at the Crocker Radiation Laboratory (later to become Lawrence Berkeley Laboratories). Two hundred forty patients were treated between 1938 and 1942. Many of these patients had received prior photon irradiation. There were significant radiation sequelae in the few long-term survivors such that clinical interest in fast neutron radiotherapy dropped off significantly for the next 20 years. Brennan and Phillips[5] subsequently reviewed the initial work by Stone et al and showed that an inappropriate value for the neutron RBE had been used in the dose calculations. Hence, many of those initial patients had been inadvertently overdosed.

With a better understanding of the RBE of fast neutron radiotherapy in different tissue types, in the 1970s Catterall et al[6-8] resumed neutron clinical trials at Hammersmith Hospital in London, England. Their results indicated that many advanced head and neck cancers exhibited a good response with acceptable side effects. The interest in fast neutron radiotherapy grew and to date, approximately 30,000 patients have been treated in 41 centers in North America, Europe, Asia, and Africa. Clinical utility has been elucidated through clinical trials and single-institution experiences, and neutron radiotherapy now has fairly well defined and limited indications. There are currently only four operating fast neutron radiotherapy centers throughout the world. These are listed in Table 20-1, along with some of their more important characteristics.

A summary of clinical situations and tumor histologic types for which neutrons have been shown to be advantageous compared with standard photon irradiation follows.

Salivary Gland Tumors

The therapeutic advantage of fast neutron radiotherapy compared to conventional radiotherapy is best established in salivary gland tumors. The RBE for salivary gland tumors is approximately 8, whereas for surrounding normal tissues, the RBE is 3 to 3.5.[1] A typical neutron dose for a salivary gland cancer is approximately 18 nGy (neutron Gray) to 20 nGy. The approximate equivalent photon dose is 60 Gy equivalents (GyE) to 70 GyE as far as normal tissues are concerned but it is in the range of 150 GyE to 160 GyE as far as the tumor is concerned. The therapeutic gain factor for salivary gland tumors is therefore in the range of 2.3 to 2.6.

Early single-institution studies showed neutrons to be beneficial in the treatment of salivary gland tumors. These results led to a prospective randomized trial sponsored by the Radiation Therapy Oncology Group (RTOG) and the Medical Research Council (MRC) of Great Britain.[9] Local control at 10 years was improved in the neutron arm (56% versus 17%; $p = 0.009$). The final report showed a trend toward increased median survival of about 8 months in the neutron arm, but this was not statistically significant. However, the cause of death differed between the two subgroups. Metastatic disease

TABLE 20-1 Location of Operating Fast Neutron Radiotherapy Centers, 2013

Location	Beam Reaction	Comments
United States		
University of Washington Medical Center, Seattle, Washington	50 MeV p→Be	Isocentric gantry and multileaf collimator
Europe		
Tomsk Polytechnical University, Tomsk, Russia	Cyclotron	Mean neutron energy 6.3 MeV
Technisch Universtät Munich, Munich, Germany	Fission neutrons	FRMII reactor, horizontal beam with multileaf collimator, mean neutron energy 1.9 MeV
Africa		
National Accelerator Centre, Faure, South Africa	66 MeV p→Be	Isocentric gantry and jaw collimator

Be, *Beryllium;* d, *deuteron,* FRMII, *Forschungs-Nuetronenquelle Heinz Maier-Leibnitz;* MeV, *million electron volt;* p, *proton.*

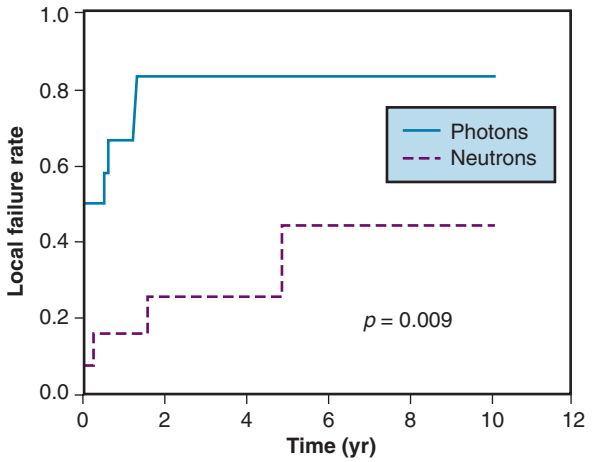

Figure 20-1 Actuarial locoregional control curves for patients with unresectable salivary gland tumors from the Radiation Therapy Oncology Group/Medical Research Council (RTOG/MRC) randomized study (80-01). The difference between the neutron curve *(purple dashed line)* and the photon curve *(blue solid line)* is statistically significant at the $p = 0.009$ level.
Adapted from Laramore GE, Krall JM, Griffin TW, et al: Neutron versus photon irradiation for unresectable salivary gland tumors. Final report of an RTOG-MRC randomized clinical trial. Int J Radiat Oncol Biol Phys 27:235, 1993.

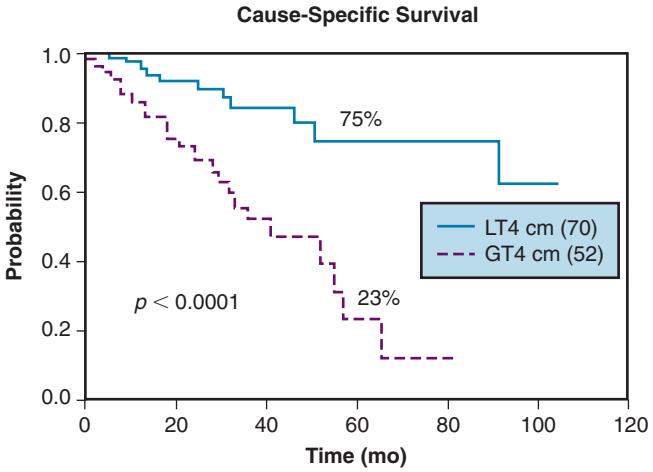

Figure 20-2 Actuarial cause-specific survival curves as a function of tumor size for patients with major salivary gland tumors treated with curative intent at the University of Washington neutron treatment facility. The *blue solid curve* depicts the results for patients with tumors smaller than 4 cm in the greatest diameter, and the *dashed purple curve* depicts the results for patients with tumors larger than 4 cm in the greatest diameter. The difference between the two curves is statistically significant at the $p < 0.0001$ level.
Adapted from Douglas JG, Lee S, Laramore GE, et al: Neutron radiotherapy for the treatment of locally advanced major salivary gland tumors. Head Neck 21:255, 1999.

was the main cause of death for the neutron patients, whereas locoregional tumor failure was the main cause of death for the photon patients. Of note, the study was stopped early for ethical reasons when 2-year survival data showed a strong trend in favor of the neutron patients. Local tumor recurrence curves for this study are shown in Figure 20-1.

The University of Washington experience was reviewed by Douglas et al.[10,11] Two hundred seventy-nine patients treated with curative intent were included in the analysis. A majority (263 patients) had evidence of gross disease, with 141 having major salivary gland neoplasms and 138 having minor salivary gland neoplasms. The 6-year actuarial cause-specific survival rate was 67%. On multivariate analysis, stage I/II disease, minor salivary gland primary tumors, lack of base-of-skull involvement, and primary (rather than recurrent) disease were associated with improved survival rates. Improved locoregional control was associated with tumors having the following characteristics: greatest diameter less than 4 cm, no base-of-skull invasion, prior surgical resection, or no previous radiation therapy. The 6-year actuarial rate for freedom from the development of metastases was 64% for patients without lymph node involvement or base-of-skull involvement. There was a 6-year actuarial rate of 10% for developing RTOG grade 3 or 4 toxicity. Cause-specific survival curves for the patients with major salivary gland cancer as a function of tumor size are shown in Figure 20-2.

The poorer outcome of salivary tumors with base-of-skull involvement appears to be the need to reduce the dose to portions of tumors that are adjacent to critical central nervous system structures (recall that the RBE for fast neutrons for central nervous system tissue is 4 to 4.5). With a standard 20 nGy dose to the involved site, the dose to the temporal tips could be approximately 80 photon GyE. Reducing the temporal lobe dose to a safe level sometimes required blocking portions of tumor. In an attempt to compensate for the reduced neutron dose, a stereotactic radiosurgical boost with photon radiation has been instituted at the University of Washington. At 40 months there was improved local control compared with historically treated patients with skull-base invasion who did not receive a stereotactic radiosurgical boost (82% versus 39%; $p = 0.04$).[12] Complications appear to be acceptable.

The use of both neutrons and photons in a composite "mixed beam" treatment has been explored by Huber et al[13] in a series of patients with advanced adenoid cystic carcinomas treated at the Heidelberg neutron facility. They found a

5-year local control rate of 75% for patients treated with neutrons alone compared with 32% for patients treated with "mixed beam" irradiation or with photons alone. It appeared that patients who had a greater portion of their treatment with neutrons fared better. Distant metastatic disease once again prevented improved local control from translating into an increase in overall survival rates.

The neutron facility in Orleans has reported similar results for 59 patients treated with fast neutron radiotherapy.[14] The 5-year local control rate was 69.5%, with a crude 5-year survival rate of 66% and a 5-year tumor-free survival rate of 64.5%.

Adenoid cystic carcinomas arising in uncommon locations are also amenable to treatment with fast neutron radiotherapy. Thirty-four patients with adenoid cystic carcinomas of the trachea received neutron radiotherapy at the University of Washington.[15] Those patients who received neutron radiotherapy as their primary treatment had a 5-year survival of 89%, whereas those who received postoperative neutron radiotherapy following surgery had a 5-year survival of 60%. There was no significant advantage to adding a brachytherapy (HDR) boost following the neutron radiotherapy. Gensheimer et al reported on 11 high-risk patients with adenoid cystic carcinomas of the lacrimal gland who were treated with fast neutron radiotherapy.[16] Most had undergone a surgical resection but gross disease was present in eight patients at the time of treatment. Disease extending to the skull base was treated with a Gamma Knife radiosurgery boost in four patients and with a proton radiotherapy boost in one1 patient. Median overall survival was 11.1 years and median disease-free survival was 6.3 years. Kaplan-Meir local control at 5 years was 80%. Long-term, ipsilateral vision preservation was not possible in most cases, although only two patients required an enucleation for treatment-related side effects.

Prostate Cancer

Prostate cancer is another tumor for which there has been significant clinical work using fast neutron radiotherapy. The National Cancer Institute (through RTOG 77-04) conducted a randomized trial for patients with T3, N0/N1 disease.[17] One arm received a mixed beam (neutron/photon) dose to 70 GyE versus a second arm that received standard photons to 70 Gy. Pelvic lymph nodes were treated to doses appropriate for microscopic disease. At the 10-year endpoint, survival rates (46% versus 29%, $p = 0.04$) were improved in the mixed beam arm. There was also improved locoregional control (70% versus 58%, $p = 0.03$) for the mixed beam subgroup. There was no difference in the rate of significant complications between the two arms. Survival curves for the patients in this study are shown in Figure 20-3.

A follow-up randomized trial was conducted that compared 70-Gy standard photon irradiation with 20.4-nGy fast neutron therapy. Pelvic lymph nodes were treated to doses appropriate for microscopic disease. This study was carried out by the National Cancer Institute (NCI)–sponsored Neutron Therapy Collaborative Working Group (NTCWG) and included patients with high-grade T2 tumors or T3 to T4, N0 to N1, M0 tumors of any grade.[18] With a median follow-up of 68 months, the 5-year actuarial locoregional failure rate was 11% for neutrons versus 32% for photons ($p < 0.01$). Actuarial overall survival and cause-specific survival rates were statistically equivalent. The incidence of severe complications was higher in the neutron group than in the photon group (11% versus 3%). Complications were fewer and less severe in the centers that had more sophisticated beam-shaping abilities. Local failure curves for the patients in this study are shown in Figure 20-4.

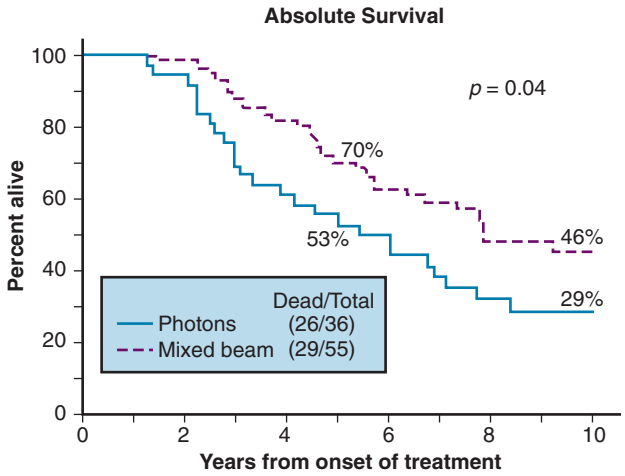

Figure 20-3 Actuarial survival curves for patients with locally advanced prostate cancer treated on Radiation Therapy Oncology Group (RTOG) protocol 77-04. The mixed (neutron and photon) beam group is shown by the *dashed purple curve,* and the photon control arm is shown as the *solid blue curve.* The difference between the curves is statistically significant at the $p = 0.04$ level.
Adapted from Laramore GE, Krall JM, Griffin TW, et al: Fast neutron radiotherapy for locally advanced prostate cancer. Am J Clin Oncol 16:164, 1993.

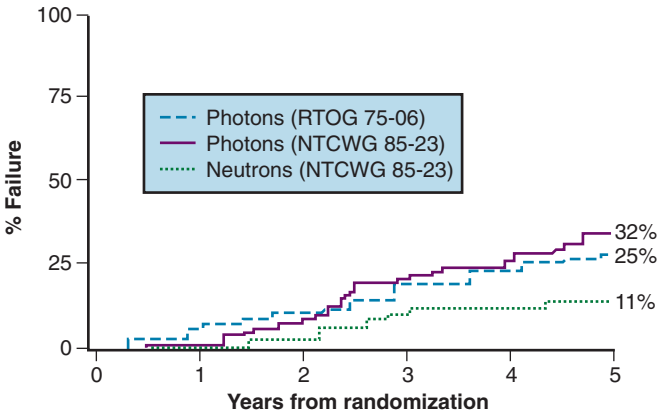

Figure 20-4 Actuarial percent local failure curves for patients with locally advanced prostate cancer treated on Neutron Therapy Collaborative Working Group (NTCWG) protocol 85-23. The group treated with neutrons is shown as the *dotted green curve,* and the group treated with photons is shown as the *dashed blue curve.* The difference between these two curves is statistically significant at the $p < 0.01$ level. A local control curve *(solid purple line)* for photon-treated patients from another Radiation Therapy Oncology Group study (RTOG 75-06) is shown for comparison. There is no statistical difference between the latter curve and the photon control arm of the neutron study.
Adapted from Russell KJ, Caplan RJ, Laramore GE, et al: Photon versus fast neutron external beam radiotherapy in the treatment of locally advanced prostate cancer. Results of a randomized prospective trial. Int J Radiat Oncol Biol Phys 28:47, 1993.

Following the randomized trials, additional studies were conducted at several centers in the United States,[19-23] Europe,[24,25] and Asia.[26,27] These single-institution results showed good locoregional control and appeared to corroborate the results of the randomized trials described previously.

Sarcomas

Sarcomas are generally considered to be among the more "radioresistant" histologic types of tumors and so would fall into the category of tumors thought to be more responsive to high-LET radiation.[1] A retrospective review by Schwarz et al[28] reports on 1171 patients with soft-tissue sarcomas from 11 European centers treated with fast neutron radiotherapy. In those patients with either inoperable tumors or gross disease after surgery, the local control rate was approximately 50%. Toxicity was higher than what was generally seen with photon irradiation. The local control rates were thought by the authors to be better than what would have been expected with standard radiotherapy. This conclusion is supported by other single-institution studies.[29]

Other Tumor Types

Fast neutron radiation has been tested on a variety of other tumor types. Generally, the rationale for the use of fast neutrons came from trying to overcome a perceived limitation of standard photon irradiation. A good example of this is malignant glioma of the brain. Dose-escalation studies with photons have failed to increase overall survival rates.[30] By definition, *glioblastoma multiforme* tumors have associated areas of necrosis that are often surrounded by regions of hypoxia, which might make the tumors more radioresistant. Studies of malignant gliomas in the 1970s and 1980s used neutrons either alone or in combination with photons.[31] None of these initial trials showed an improvement in overall survival rates with the addition of neutrons. However, with relatively high doses of fast neutrons alone, autopsy and second-look surgical data indicated that tumor cells were sterilized in the treated region.[32] Unfortunately, there was also significant coagulative necrosis caused by the neutron irradiation, which indicated too much damage to normal brain tissue. A more recent study used fluorodeoxyglucose–positron emission tomography (FDG-PET) scanning to determine the final boost volume that received 18 nGy.[33] Only 10 patients were treated and all exhibited tumor progression by 39 weeks, perhaps because of the restricted fields that were employed. Gliosis and microvascular sclerosis consistent with radiation injury were noted in regions of the contralateral brain receiving 6 nGy to 10 nGy. Much of the current interest in neutron radiotherapy for malignant gliomas is focused on boron neutron capture therapy (BNCT), which is discussed later in this chapter.

Squamous cell carcinoma of the head and neck region is another tumor for which neutrons have been used to try to overcome the relative radiation resistance of hypoxic cells. However, randomized studies and several single-institutional trials in Europe and the United States failed to show a significant improvement in locoregional control with the use of neutrons compared with standard photons. Furthermore, the side effects were generally more severe.

Summary

Neutron radiotherapy is best used in the treatment of certain tumors that exhibit a "resistance" to standard low-LET radiotherapy. The niche that it occupies is small, but it remains a highly important treatment option for a small number of patients for whom it appears to be better than more traditional forms of treatment. Examples are patients with inoperable or recurrent salivary gland malignant tumors or in high-risk situations where there has been an incomplete surgical extirpation or patients with inoperable or incompletely resected sarcomas of bone, cartilage, and soft tissue or locally advanced prostate cancers, particularly those that are not hormonally responsive. In highly selected circumstances, it may also be beneficial in the treatment of metastases from melanoma and renal cell cancer. Future research may extend these indications. The declining number of active treatment centers is attributable to the aging of the equipment and the narrow niche indications making it not economically feasible to build new centers.

BORON NEUTRON CAPTURE THERAPY

Overview

Conceptually, BNCT is a "magic bullet" approach to treating tumors. Pure beams of very low energy neutrons do not directly deposit much energy in tissue via collisions but rather interact via nuclear transmutation reactions. The basic idea is to selectively attach to the cancer cells a nuclide having a large cross section for capturing a thermal neutron. The nuclide then undergoes a nuclear reaction with the localized release of a substantial amount of energy. In principle, this kills the "tagged" cell but does not damage the surrounding "untagged" normal cells. Although there is ongoing work in developing high-current particle accelerators to produce low-energy thermal or epithermal beams for BNCT, at the present time, all clinical work is being done using moderated neutron beams from nuclear reactors. There are other nuclides besides boron-10 (^{10}B) that have a high neutron capture therapy cross section, and some of these (e.g., gadolinium-157 [^{157}Gd]) are of interest in neutron capture therapy for cancer. The ^{157}Gd neutron capture reaction produces high LET Auger electrons rather than nuclear fragments and so the agent must be in close proximity to the cellular DNA to be effective. There is little data on the clinical use of ^{157}Gd and so we will confine our discussion to BNCT. Space limitations preclude our describing ongoing research in radiobiology, compound development, or physics research into nonreactor sources of appropriate beams.

Historical Perspective

The basic idea for BNCT dates to 1936, when Locher[34] proposed treating malignant tumors with low-energy thermal neutrons via a capture process with ^{10}B. A few years later, Kruger[35] and Zahl et al[36] experimentally verified some of the basic tenets of this concept and demonstrated the high RBE of the resulting helium-4 (^{4}He) and lithium-7 (^{7}Li) fission fragments. The theoretical advantage of "tagging" the tumor-specific carrier with an innocuous substance such as ^{10}B and then activating it, rather than tagging it with a toxic compound such as ricin, is that the "binary approach" is more forgiving of other body tissues that might also display some avidity for the carrier agent.

In the real world, the thermal and epithermal beams produced by nuclear reactors are contaminated with gamma rays and fast neutrons, which can cause considerable normal tissue damage even in the absence of a high ^{10}B concentration.[37] Moreover, even in the absence of such beam contaminants, nuclear species such as ^{1}H, nitrogen-14 (^{14}N), and chlorine-35 (^{35}Cl), which are commonly found in tissue, interact with thermal neutrons via capture events of their own, and their reaction products cause biologic damage to non–^{10}B-containing normal tissues. Although the respective capture cross sections for these commonly found nuclei are much lower than for ^{10}B and other nuclear species of interest for neutron capture therapy, the concentrations of these commonly found nuclei are many orders of magnitude greater than the concentrations of ^{10}B. Hence, reactions involving these nuclides can result in an appreciable tissue dose, even in the absence of ^{10}B. The key to BNCT as a practical therapy is the development of compounds that localize specifically in tumors and deliver

sufficient ^{10}B concentrations to yield a significant therapeutic advantage compared with the radiation doses delivered to normal tissues.

Early Clinical Studies

The first set of human clinical trials was carried out in the 1950s at Brookhaven National Laboratory using ^{10}B-enriched, boric acid derivatives.[38,39] These compounds yielded high concentrations of ^{10}B in the blood at the time of irradiation and unfortunately produced relatively low ^{10}B levels in the tumors. This resulted in considerable blood vessel endothelial damage and no therapeutic benefit from treatment either in these trials or in subsequent trials that were carried out in the 1960s.[40-42] Interest in the technique waned until Hatanaka et al in Japan[43] reinstituted BNCT for malignant gliomas using a different ^{10}B-carrier, ^{10}B-sodium-mercaptoundecahydrododecaborate (BSH). This compound produced better tumor-to-blood boron ratios than the compounds used in the prior Brookhaven National Laboratory studies and the treatments caused less damage to normal brain tissue. Favorable reports regarding the efficacy of BSH[43-45] led to renewed worldwide interest in the technique.

Many patients have received BNCT treatments using thermal neutron beams from various reactors in Japan, but to date, no randomized clinical trials have been carried out. An analysis of the RTOG database by Curran et al[46] demonstrated that there are some subsets of patients with high-grade gliomas who will do well with conventional photon irradiation. A few years ago, an analysis of a subset of patients from the United States who were treated with BNCT in Japan showed no improvement over that which would have been expected with conventional therapy after correcting for the appropriate prognostic factors.[47] A comparison of the survival rates of these patients with a pseudo-matched group from the RTOG database is shown in Figure 20-5. The prognostic factors identified by Curran et al[46] were used to generate these curves. There is no statistical difference between the two curves.

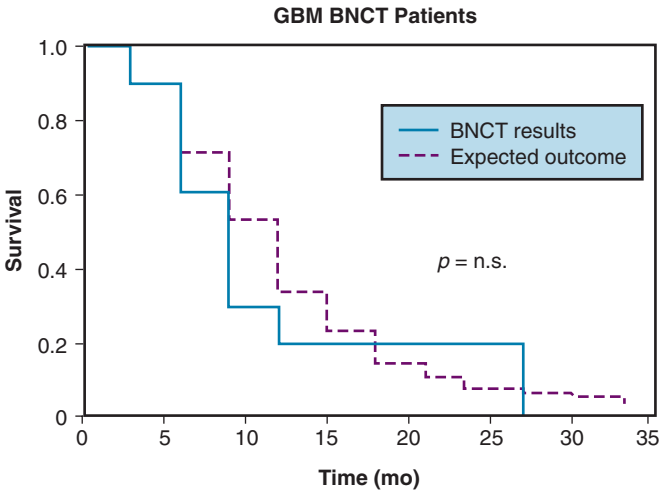

Figure 20-5 Actuarial survival curves for a group of 10 patients from the United States with glioblastoma multiforme (GBM) histology who were treated with boron neutron capture therapy (BNCT) *(solid blue curve)* and the expected survival curve for a matched cohort who received conventional treatment according to various Radiation Therapy Oncology Group study (RTOG) protocols *(dashed purple curve)*. There is no statistically significant difference between the two curves.
Adapted from Laramore GE, Spence AM: Boron neutron capture therapy [BNCT] for high grade gliomas of the brain. A cautionary note. Int J Radiat Oncol Biol Phys 36:241, 1996.

Moreover, review of the data for the entire group of evaluable patients showed that in all except one patient there was a documented tumor recurrence within the primary radiation field.[47] The only long-term survivor in this group of American patients had an anaplastic astrocytoma and fell into the most favorable category I of Curran et al.[46]

There is no doubt that many aspects of the early Japanese BNCT clinical research program were suboptimal. The use of a poorly penetrating beam of thermal neutrons meant that an open craniotomy was required to expose the tumor bed. Because of the low neutron fluxes, treatment times of 4 to 8 hours were required to deliver a surface fluence of approximately 10^{13} neutrons/cm^2, and during treatment the patient had to be under general anesthesia with the brain exposed in a converted operating room adjacent to the nuclear reactor. Although BSH is conceptually attractive as a ^{10}B-carrier agent in that it is excluded from normal brain tissue by the blood-brain barrier, typical tumor boron concentrations for glioblastoma multiforme were in the range of only 15 μg/g to 25 μg/g. It is now possible to improve on many of these shortcomings.

Modern Clinical Trials

In the modern era, clinical trials have been conducted in Japan, Europe, Argentina, and the United States. Most of this work has dealt with the treatment of malignant brain tumors and metastatic melanomas, but there is increasing interest in using this modality to treat recurrent head and neck cancers and high-grade meningiomas

In Japan, there have been three reactor facilities involved in patient treatments: (1) KURRI in Osaka, (2) MITR in Musashi, and (3) JRR-4 at the Japan Atomic Energy Research Institute in Ikargi.[48] Although most patients have been treated using thermal neutron beams, the KURRI facility has been modified to produce a higher-energy epithermal beam allowing treatment through the intact skull. The majority of the patients have been treated for various types of brain tumors using BSH as the ^{10}B-carrier agent and with a single fraction of neutron radiation. A report by Nakagawa et al[49] shows that in the subset of glioblastoma multiforme patients, 12% of treated patients lived longer than 2 years. Depending on other prognostic factors, this may or may not be better than expected with more conventional forms of treatment. A report by Kawabata et al shows a modest survival benefit in 21 glioblastoma patients treated with either BNCT alone or in combination with standard photon radiotherapy when compare to patients having similar RTOG prognostic factors.[50] Currently only the KURRI and JRR-4 reactors are treating patients.

There were several reactor facilities in Europe with BNCT clinical programs for malignant brain tumors, all using epithermal neutron beams. The program that treated the most patients was based at the HFR reactor in Petten (the Netherlands) and was directed by the European Collaboration on Boron Neutron Capture Therapy. BSH at 100 mg/kg was used as the ^{10}B-carrier. Researchers conducted a phase I dose-searching study restricted to the subsets of patients with glioblastoma multiforme whose expected median survival time with conventional radiotherapy would be less than 10 months. Unlike the other ongoing treatment regimens, which employed a single BNCT treatment, the Petten program used four fractions requiring multiple administrations of the boron-carrier compound. BNCT dose reporting is complex, and the Petten group has chosen to specify each component of the radiation field separately rather than state a Gray-equivalent dose.[51] The starting dose from the ^{10}B component was set at 80% of the dose that produced neurologic changes in a dog brain study, D_B = 8.6 Gy. The other components of the radiation dose were limited

to $D_n < 0.9$ Gy, $D_N < 1.1$ Gy, and $D_g < 5.8$ Gy, where D_n is the neutron-absorbed dose delivered by the thermal, epithermal, and fast neutrons and the charged particles produced by their reactions, D_g is the gamma ray absorbed dose, and D_N is the absorbed dose from the protons produced by the ^{14}N capture reaction. Twenty-five patients were entered into the initial dose arm of the study, with 21 actually receiving BNCT treatment.[52] The median survival time of the BNCT-treated patients was 31 weeks, with 6 patients alive at the time of a preliminary report. All 21 patients exhibited tumor recurrence.

A second BNCT program is based at the FiR No. 1 reactor in Helsinki, Finland. The initial protocol was a Phase I dose-searching study that used l-*para*-boronophenylalanine (BPA) in a fructose solution at 290 mg BPA/kg as the B-carrier. Only a single treatment was given using two radiation fields. Thus far, 10 patients have been treated with tumor doses between 35.1 and 66.7 GyE. This effective dose has been determined using weighting factors for each of the radiation components (see Kankaanranta et al[53] for specific details). With a median follow-up of 9 months, 7 of 10 patients had recurrent or persistent tumor, with the median time to tumor progression being 8 months.[53] The toxicity in both of the European trials was thought to be acceptable, making future escalation of the radiation dose possible. Small numbers of patients were also treated at Studsvik Medical AB in Uppsala University[54] and at the Nuclear Research Institute in the Czech Republic.[55] Currently, only the FiR No. 1 reactor is treating patients.

After approximately a 30-year hiatus, the first "modern era" BNCT clinical program in the United States was begun at the Massachusetts Institute of Technology (MIT) research reactor in collaboration with Tufts Medical Center. The first patient was treated in September 1994. This project was under the clinical direction of the New England Deaconess Hospital. Treatments were delivered using an epithermal beam with BPA as the ^{10}B-carrier agent. Between 1996 and 1999, a total of 22 patients with intracranial lesions, either glioblastoma multiforme or metastatic melanoma, were treated.[56] The initial clinical trial was a dose-searching toxicity study with the target dose ranging between 8.8 GyE and 14.2 GyE. At the higher radiation doses, the time required to deliver the dose ranged up to 3 hours. At the higher dose levels, significant skin and mucosal reactions were observed. No adverse effects were noted because of the BPA administration, and no long-term complications relating to the BNCT treatment were noted. Some tumor responses were noted in the patients with metastatic melanoma, but there was no obvious prolongation of survival rates in either group of treated patients. This facility is no longer treating patients.

A second clinical BNCT program focusing on high-grade gliomas of the brain was initiated at Brookhaven National Laboratory. This program differed from the Japanese glioma program in two main respects: (1) a higher-energy epithermal neutron beam was used instead of a thermal neutron beam, and (2) a different ^{10}B-carrier agent (BPA) was used rather than BSH. The epithermal beam meant that patients could be treated without recourse to a craniotomy and intraoperative irradiation and that more deeply located tumors could be given adequate doses. It was expected that BPA would produce higher tumor ^{10}B concentrations than could be achieved with BSH. Based on ^{10}B blood levels, it appeared that tumor ^{10}B concentrations of approximately 35 μg/g to 50 μg/g were achieved. However, unlike BSH, BPA is not excluded from the normal brain by the blood-brain barrier, and tumor enrichment depends on other mechanisms of selective uptake (perhaps relating to an enhanced amino acid transport system). A dose-escalation approach was used. Before June 1996, all patients were treated using a simple appositional field with a single treatment fraction being given. A critique of this early Brookhaven National Laboratory treatment technique indicated significant deficiencies in the basic approach relating to the inability to achieve a tumor dose adequate to sterilize glioblastoma multiforme tumors using a single appositional field.[57]

Between September 1994 and May 1999, 53 patients with primary glioblastoma multiforme received BPA-fructose–mediated BNCT at Brookhaven National Laboratory using one, two, or three irradiation fields on a sequential, dose-searching protocol. The median age for the subjects treated with one field was 56.5 years, with a median tumor volume of 20.5 cm^3 (2 cm^3 to 70 cm^3) and a median Karnofsky Performance Status (KPS) of 80. The volume-weighted average radiation dose to normal brain (ABD) varied from 1.9 GyE to 4.1 GyE for one field, from 4.1 GyE to 6.6 GyE for two fields, and from 6.7 GyE to 9.5 GyE for the three-field group.

Fifty of the 53 subjects have exhibited tumor persistence/recurrence within the treatment volume.[58] The median time to progression was independent of dose. In fact, there was a significant trend toward worse local control in subjects treated using three fields. Survival as an endpoint was found to be more dependent on the aggressiveness of the postrecurrence treatment than the BNCT dose given and, as such, was not a useful indicator of treatment-dependent tumor control. The functional brain tolerance was reached in the three-field group. All except one patient treated with three fields exhibited significant acute or subacute functional neurologic toxicity at average brain doses as low as 6.7 GyE. This may indicate a "volume effect" in that multiple fields generally treat a larger volume of normal brain to a lower dose compared with when a single field is used. The early stopping criterion of a more than 20% incidence of grade 3 or 4 toxicity (RTOG and European Organization for Research and Treatment of Cancer [EORTC] criteria) was reached during this study. However, no significant tumor response was observed in the patients treated to minimum tumor doses above those predicted by Laramore et al to be therapeutic.[57,58] We also note that preclinical studies using a 9-L rat gliosarcoma model showed significant tumor response of the tumor to BPA-fructose–mediated BNCT at comparable doses.[59] Hence, neither the preclinical radiobiologic studies nor the mathematical modeling based on fast neutron data provided an accurate guide to the necessary therapeutic dose. The Brookhaven National Laboratory clinical program is no longer in operation.

In parallel with the BNCT program for malignant gliomas, a second area of major interest is the treatment of malignant melanoma metastatic to the brain. This work was instigated by Mishima et al[60,61] in Japan. They used BPA as the ^{10}B-carrier agent with a single treatment fraction of thermal neutrons. BPA acts as a dopamine analog in the melanin synthetic pathway and concentrates well in pigmented tumors. Initial reports describe good clinical results with this treatment,[62,63] but no randomized trials have been performed. Reports from the MIT/Massachusetts General Hospital program indicate that responses are better in this setting than in the treatment of glioblastoma multiforme, which is consistent with BPA being better suited to the treatment of pigmented tumors. Under the auspices of the Atomic Energy Commission of Argentina, a program for the treatment of metastatic melanoma has been instituted at the RA-6 research reactor in San Carlos de Bariloche, and this program is still clinically active.[64] An updated report showed an overall response rate of 69% in treated skin nodules with an additional 31% of nodules showing stable behavior.[65]

A third area of increasing interest in the BNCT community is the treatment of patients with recurrent head and neck cancers. A report on 26 patients treated at the KURRI and JRR-4 reactors using both BSH and BPA as boron carrier agents

showed an overall response rate of 85% although there were three instances of osteoradionecrosis and one case of brain necrosis.[66] The majority of these patients was treated for tumor recurrence after having received previous standard radiotherapy and therefore represent a high-risk population with respect to complications. Thirty patients with recurrent head and neck cancers were treated in Finland between 2003 and 2008 using the FiR 1 reactor. Like the Japanese work, a combination of BSH and BPA was used to maximize the boron concentration in the tumors. Two portals were irradiated and the mean boron dose was 19.6 μg/g for the first portal and 16.4 μg/g for the second portal.[67] For 29 evaluable patients, 76% had some response and the 2-year locoregional control rate was 27%. There were 3 patients who developed osteoradionecrosis and 1 patient who developed a soft-tissue necrosis.

Kawabata et al recently reported on using BNCT to treat 20 patients with recurrent, high-grade meningomas who had failed surgery followed by one or more courses of radiotherapy.[68] Either BPA alone or combined with BSH was used as the boron carrier agent. The radiation dose to normal brain was restricted to 15 Gy-equivalent or less in the planning process. With a median follow-up duration of 13 months, 6 patients were still alive and only 3 deaths were as a result of in-field failure. The majority of deaths were the result of systemic metastases or cerebrospinal fluid (CSF) dissemination indicating the aggressive nature of the tumors that were treated. The authors noted a rapid tumor shrinkage in many of the treated patients.

An interesting approach to the treatment of liver metastases was begun at the University of Pavia in Italy. The patient is infused with BPA, and the diseased liver is extirpated and irradiated in the reactor and then reimplanted into the patient. Two patients have been treated in this manner, with one long-term survivor at 3 years from the time of the procedure. Model calculations indicate that it may be possible to perform this treatment without first removing the liver.[69] There is continued work on this concept through EORTC 11001. This biodistribution trial showed that BPA is taken up preferentially in liver metastases of colorectal adenocarcinoma to an extent that is high enough for therapeutic BNCT whereas BSH does not preferentially accumulate.[70]

Summary

To date there is no convincing evidence that BNCT offers a therapeutic advantage over conventional treatments for glioblastoma multiforme. Reactor-based treatment centers are sufficient in number to conduct well-designed clinical trials to provide a "proof of concept" but certainly will not be adequate to treat large numbers of patients in the event that a therapeutic advantage is demonstrated. In this event, accelerator-based sources must be designed and placed in hospital settings. The main hurdle at the present time is the lack of tumor-specific ^{10}B-carrier agents. Besides BSH and BPA, only one other boron compound, GB-10 ($Na_2B_{10}H_{10}$), is approved for human trials. GB-10 and BSH are global agents with no specific tumor cell targeting, whereas BPA has some specificity for certain types of tumors. All three are suboptimal for clinical use. Support of research in compound development is key to further development of the field.[71-73]

CALIFORNIUM 252 BRACHYTHERAPY

Californium was the sixth transuranium element that was produced by a team at the Lawrence Berkeley Laboratories in 1950 by bombarding a curium target with α particles. The particular isotope used in radiotherapy, californium-252 (^{252}Cf), is produced in high-neutron flux reactors and is made available for peaceful uses by the U.S. Department of Energy. ^{252}Cf is a neutron-rich isotope that has a half-life of 2.647 years. It decays either by α-particle emission or by spontaneous fission with a branching ratio of 96.9% to 3.1%. It is a highly prolific neutron emitter with a spectrum of energies similar to that produced by nuclear reactors. Although its use in medicine requires significant radiation protection precautions, it is theoretically attractive for brachytherapy applications wherein high-LET radiation is advantageous from a radiobiologic aspect. It has also been proposed as a hospital-based teletherapy source for BNCT applications.

Gynecologic applications of ^{252}Cf brachytherapy were explored by Maruyama et al,[74] who developed appropriate dosing schedules. More recently, Tacev et al[75] reported on long-term results of a randomized trial for patients with advanced cervical cancer (stages IIB and IIIB) that compared ^{252}Cf brachytherapy with a supplementary gamma ray boost of 16 Gy with conventional brachytherapy alone with gamma ray–emitting radium-226 (^{226}Ra) or cesium-137 (^{137}Cs) sources following 40-Gy external beam radiotherapy. Using an RBE of 6 for the ^{252}Cf neutrons, point A doses of 56 GyE were given with the implants. Two hundred seventy-seven patients were entered into the study, and there was an improved 5-year survival rate in the group receiving the ^{252}Cf implant (75.2% vs. 56.3%; $p < 0.001$).

Also of note is a pilot study using ^{252}Cf interstitial brachytherapy in 56 patients with high-grade gliomas of the brain.[76] After surgical debulking, catheters were placed under CT guidance followed by ^{252}Cf placement. A dose of 3 Gy was given over 4 to 6 hours to the residual tumor, and then patients received 60-Gy to 70-Gy doses of conventional external beam radiotherapy. The median survival time was only 10 months, and recurrent tumor was found in all patients who died and were autopsied. Given the dose inhomogeneties and the relatively small amount of neutron radiation given, this outcome is not surprising.

Summary

^{252}Cf sources offer a means of performing brachytherapy with neutrons. Conceptually, this is intriguing for tumors in which hypoxia is thought to be a factor in limiting tumor control with standard treatment and which lend themselves to brachytherapy approaches. There has been one randomized study for advanced cervical cancer showing benefit compared with standard brachytherapy with gamma ray sources, but this field still requires considerable development. Remote afterloading devices allow implementation of this technique without high risk to medical personnel. A recent review shows that there are 21 ^{252}Cf brachytherapy systems being used in China today.[77]

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