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## **Clinical Applications of Proton Radiation Treatment at Loma Linda University: Review of a Fifteen-year Experience**

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Proton radiation therapy has been used at Loma Linda University Medical Center for 15 years, sometimes in combination with photon irradiation, surgery, and chemotherapy, but often as the sole modality. Our initial experience was based on established studies showing the utility of protons for certain management problems, but since then we have engaged in a planned program to exploit the capabilities of proton radiation and expand its applications in accordance with progressively accumulating clinical data. Our cumulative experience has confirmed that protons are a superb tool for delivering conformal radiation treatments, enabling delivery of effective doses of radiation and sparing normal tissues from radiation exposure.

Key words: Cancer therapy, Conformal radiation therapy, Proton, Radiotherapy, Review.

### ***Introduction***

Proton radiation is a heavy-charged-particle radiotherapeutic modality that is perhaps best known for the ability it provides radiation oncologists to design and deliver highly conformal treatments to intended target volumes. This conformability is related to the intrinsic characteristics of accelerated protons: they deposit little radiation as they enter the patient's body and proceed to the target; they deposit the bulk of their ionizing energy in the targeted volume, followed by a sharp fall-off (the Bragg peak); and they do not irradiate tissues distal to the target. These features provide radiation oncologists with the opportunity to deliver higher radiation doses to the target, with the potential of increased tumor control, as well as a significantly reduced integral volume dose to the normal tissues and, consequently, fewer radiation-related side effects.

Protons were first suggested for clinical use in 1946 (1). They were first used clinically but in a laboratory setting in 1954 (2), and subsequently were offered in several physics laboratories around the world. In 1990, the Department of Radiation Medicine at Loma Linda University (LLURM) began clinical investigations using the world's first proton accelerator and facility designed for treating patients in a hospital setting (3). This treatment center features five beam lines serving four treatment rooms, three of which have rotating gantries. A fifth room, containing three beam lines, is used for radiobiological and physics research. The proton

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**Abbreviations:** AVM, Arteriovenous malformation; CT, Computed tomography; CTV, Clinical target volume; GTV, Gross tumor volume; GyE, Gray equivalent (a measure of proton radiation dose based on an RBE ratio of 1.1 with respect to gamma radiation); CNS, Central nervous system; LET, Linear energy transfer; MeV, Million electron volts; MRI, Magnetic resonance imaging; PET, Positron emission tomography; PROG, Proton Radiation Oncology Group; RBE, Radiobiologic effect; RTOG, Radiation Therapy Oncology Group.

synchrotron permits delivery of beam energies ranging from 70 to 250 MeV; the energy employed depends on depth of penetration desired. Treatments are designed on a computer-assisted planning system based on CT data obtained from the patient, with data from other imaging studies, such as MRI and/or PET, added as needed for an individual patient's case.

At present, the proton facility treats between 125 and 150 patients per day. The total number of patients treated with proton beams at Loma Linda as of December 1, 2005, exceeds 10,600, the largest total from any institution and accounting for about 25% of all patients treated with protons since 1954 (4).

Efforts at Loma Linda to exploit the therapeutic potential of protons began when the facility opened in 1990. Initial goals were: i) build on the long experience with photon radiation and previous experience with protons at laboratory facilities by investigating additional clinical sites that might benefit from protons; ii) develop protocols to treat anatomic sites and evaluate outcomes; and iii) improve or develop technology that would allow additional anatomic sites to be investigated. Clinical studies have had two overarching objectives. The first was to employ protons to reduce treatment-related morbidity for patients having conditions for which curative treatment options exist but have been associated with significant morbidity. We pursued this outcome irrespective of whether control rates were increased with the use of protons. The second objective was to use protons to improve control rates for tumors that were not well controlled by other modalities. Investigations proceeded in small, progressive steps. Initial dose-escalation studies for prostate cancer, for example, explored whether total doses only 10% higher than had been used in conventional photon regimens could be administered without affecting treatment-related morbidity. If the desired outcomes were obtained, further escalation studies would be pursued. Proton studies in other anatomic sites sought to determine whether lower morbidity rates could be obtained given the same total dose as had been delivered with photons; dose-escalation studies were pursued if the data showed that morbidity had in fact been reduced.

A fundamental presumption in both forms of studies was that ionizing radiation from any source, heavy-charged-particle or photon, would destroy a targeted tissue volume if the total dose was sufficiently high; the main issue to be investigated was whether such doses could be delivered to patients without causing unacceptable permanent damage to untargeted tissues. We used proton beams because their physical dose distribution could be controlled so as to permit such outcomes; their slightly higher RBE (1.1 relative to gamma radiation from cobalt sources) was not a significant factor in employing them. Accordingly, we further presumed that the proton RBE was essentially the same as that of photons, and that, conse-

quently, such normal cells as were irradiated would have the same repair capacity as cells exposed to photon radiation.

In the early years of the Loma Linda facility, proton beams were used to treat relatively few tumors. More anatomic sites were added as experience accumulated and as technological advances occurred in treatment delivery and control systems. Protons are now used at Loma Linda to treat approximately 50 tumors and other diseases in most regions of the body.

In this document we review the records, data analyses, and published accounts of patients undergoing proton radiation treatment at Loma Linda University Medical Center from October 1990 to October 2005. Data are grouped according to anatomic region. Only patients who completed treatment were included in data analyses and are included in this review.

### *Central Nervous System and Base of Skull (in Adults)*

#### *Stereotactic Radiosurgery*

At Loma Linda, proton radiosurgery currently is used to treat brain metastases and AVMs. As such, it harkens back to one of the original uses of proton radiation. Protons were employed at the University of Uppsala, in Sweden, in the 1950s (5), and at Harvard Cyclotron Laboratory (HCL) – Massachusetts General Hospital (MGH) in the early 1960s (6). Qualitatively similar helium ion beams were used for the same purpose at Lawrence Berkeley Laboratory (7).

MGH/HCL investigators reported long-term success with stereotactic proton radiosurgery for pituitary adenomas. Reporting on patients treated during the period from 1963 to 1990, they observed that 98% of 581 patients with acromegaly had hormone normalization at 20 years post treatment. In a group of 36 patients with Nelson's syndrome and 180 patients with Cushing's disease, 85% achieved hormone normalization at 20 years. Among patients treated to higher doses, 100% remained cured 10 years following treatment (8).

At LLURM, we opted for protons for radiosurgical applications because, by comparison with photon beams from a linear accelerator or a gamma knife, protons produce less normal-tissue radiation, particularly at larger volumes and for peripheral lesions, offer better coverage for irregularly shaped volumes, and yield more uniformity of dose within the target volume (9-11). One radiosurgical application of protons has been in the treatment of AVMs (12), and in the past there has been controversy as to whether proton radiosurgery should be employed to treat large (>3 cm) lesions (13). However, a recent report from Sweden suggests that fractionated proton radiosurgery was effective in managing such lesions (14). At present, investigators from LLURM and the departments of Neurosurgery and Neuroradiology

at Loma Linda University are collaborating with investigators from the departments of Neurosurgery and Neuro-radiology at Stanford University in the evaluation stage of a program for treating large (> 3 cm) AVMs with surgery, embolization, and hypofractionated protons. The program has been pursued since 1994 and offers doses of 20 to 25 GyE in 1 to 5 fractions using stereotactic protons, with the dose based on the volume of the target.

#### *Fractionated Proton Therapy*

We use fractionated proton therapy for the majority of lesions occurring in the CNS and the base of the skull, including chordomas, chondrosarcomas, acoustic neuromas, meningiomas, and pituitary adenomas. Our protocols have built on prior experience at other institutions.

Five-year recurrence-free survival rates following conventional photon radiation for chordomas and chondrosarcomas of the skull base has been reported to be about 30% (15). Overall five-year recurrence-free survival rates for patients treated by heavy charged particles at Lawrence Berkeley Laboratory was reported to be about 60% (16), and investigators at Massachusetts General Hospital obtained a local recurrence-free survival rate of 76% at five years (17). Our experience with these lesions began in 1992. From March of that year through January 1998, we treated 58 patients with protons, with doses ranging from 64.8 GyE to 79.2 GyE; 44 patients (76%) were treated for primary disease, 12 (24%) for recurrent disease. Analysis revealed five-year local control and survival rates of 59% and 79%, respectively, for chordomas, and local control and survival rates of 75% and 100%, respectively, for chondrosarcomas. The control rate was related to tumor size, as has been reported by other investigators: for tumors  $\leq$  25 ml, the local control rate was 100%; for tumor > 25 ml, the local control rate was 55% (18, 19).

At present, we are collaborating with colleagues from Massachusetts General Hospital and Lawrence Berkeley Laboratory on a Phase III dose-escalation trial of proton radiation for chordomas and chondrosarcomas (PROG 85-26). Patients were randomized into one of three treatment arms, to receive total radiation doses of 66, 72, or 79 GyE, stratified according to histology, site, boost volume, and sex. Patient accrual was completed in 1999; data are being analyzed.

Acoustic neuromas are tumors for which complete surgical removal or radiosurgery yields control rates greater than 90%. However, some toxicity is associated with this result: facial nerve dysfunction has been noted to occur in 5-38% of patients treated; postsurgical deaths have been reported in up to 6%; and useful hearing retention has been observed in 30-65% of patients having tumors < 1.5 cm in greatest dimension (20-22). At Loma Linda, we use protons to treat patients

having recurrent or unresectable acoustic neuromas, or for patients who refuse surgery. There is no size limitation. We administer 1.8 GyE per fraction, to total doses of 50.4 or 59.4 GyE, depending on pretreatment analysis of hearing. Of the first 30 patients who had completed treatment through February of 2000, 18 had been followed for periods ranging from 1 to 7 years after treatment (median 3.5 years). All lesions were controlled in that population, and no patient had permanent cranial nerve injury. Audiometric testing continues to evaluate long-term hearing (23).

Patients with meningiomas whom we have treated with proton radiation are those presenting with recurrent or unresectable disease, or who refuse surgery. Treatment consists of protons at 1.8 GyE per fraction; the total dose delivered ranges from 54.0 to 63.0 GyE in six weeks. Ninety-six patients were treated at Loma Linda through February of 2000; follow-up of the first 82 patients ranged from 0.5 to 7 years (median 3.5 years). No local failures had occurred at the time of analysis; two patients had surgery for post-treatment edema.

Analysis of 47 patients whom we treated with protons for pituitary adenoma revealed that 42 of them underwent prior surgical resection and five were treated with primary radiation. Approximately 50% of the tumors were functional. The median dose was 54 GyE. Tumor stabilization occurred in all 41 patients available for follow-up imaging; 10 of these had no residual tumor and three demonstrated greater than 50% reduction in tumor size. Seventeen patients with functional adenomas had normalized or decreased hormone levels; progression occurred in three patients. Six patients died; two of the deaths were attributed to functional progression. Complications included temporal lobe necrosis in one patient, new significant visual deficits in three patients, and incident hypopituitarism in 11 individuals. We concluded that fractionated conformal proton radiation achieved effective radiologic, endocrinological, and symptomatic control. Significant morbidity was uncommon, with the exception of postradiation hypopituitarism, which we attributed in part to concomitant risk factors for hypopituitarism present in our patient population (24).

#### *Diseases of the Eye and Tumors of the Head and Neck*

Proton and helium-ion irradiation have a long-established role in treating patients with ocular melanoma: both modalities are an alternative to enucleation. Ophthalmologists and radiation oncologists in Boston, Massachusetts have long collaborated in offering this alternative. Of 1,006 patients treated there with protons from 1975 to 1986, 96% had tumor controlled in the eye at five years (25); 89% of patients retained their diseased eye, including 97% of those having small lesions (26); and more than 50% of patients retained vision better than 20/100 (27).

We evaluated the efficacy and safety of proton radiation therapy for medium-size and large choroidal melanomas. A retrospective review revealed that the 5-year local control rate was 91% and the 5-year disease-specific survival rate was 76%. Eye preservation was achieved in 75.3% of patients, with useful ( $> 20/200$ ) visual acuity obtained in 49%. The patient's initial visual acuity, the proximity of the tumor to the optic disc, and the total dose received by the optic disc and fovea were all significant prognostic factors for maintaining useful visual acuity following treatment. The diameter of the tumor at its base was related significantly to survival but did not impair local tumor control or visual acuity. Our data suggested that protons were indeed effective and safe for medium and large melanomas, and can preserve the eye and its function in a reasonable percentage of patients with these tumors (28).

We are investigating protons for treating subfoveal neovascularization associated with age-related macular degeneration. Of our first 48 patients, 21 received a single dose of 8 GyE and 27 received a single dose of 14 GyE. Patients were followed for a mean period of 16 months after treatment. The actuarial rate of freedom from recurrence at 21 months for patients receiving 8 CGE was 36%; the corresponding rate for patients receiving 14 CGE was 89%, a significant difference. Seventy-seven percent of patients whose lesions were controlled improved their visual acuity, in contrast to 44% of patients whose lesions were not controlled. At 24 months, actuarial vision loss as measured by lines lost on visual testing for proton-treated maculas was zero. No clinically significant treatment-related morbidity ensued, utilizing RTOG criteria. Preliminary analysis showed that single-fraction proton radiation effectively controlled the process at two years when administered in the higher dose (29). Further trials are planned, comparing protons to newer treatments for the disease.

LLURM reported recently on the use of proton radiation to deliver a dose sufficient to treat locally advanced oropharyngeal cancer. Patients were treated under a Phase I/II study (PROG 92-14) employing proton radiation as a boost treatment for squamous-cell carcinomas of the oropharynx. The PROG protocol was a modification of a previous RTOG protocol (90-03), in which the RTOG investigators studied three altered fractionation schedules, each of which, although yielding significantly greater acute side effects compared to standard fractionation, led to no significant increase of late effects. RTOG investigators concluded that hyperfractionation and accelerated fractionation with concomitant boost were more efficacious than standard fractionation for locally advanced head and neck cancer (30).

PROG 92-14 assessed accelerated fractionation with concomitant boost using photon and proton radiation to improve local control and reduce complications. Twenty-nine patients

received accelerated photon (50.4 GyE to CTV) and proton radiation (25.5 GyE to GTV), yielding a total dose of 75.9 GyE in 45 fractions administered in 5.5 weeks, to the primary disease, involved lymph nodes, and potential areas of sub-clinical spread (three patients were administered a prescribed total dose of 74.4 GyE). Patients were followed for periods ranging from 2 to 96 months. The 5-year actuarial control rate for local disease was 88%, and for neck node disease, 96%, yielding a locoregional control rate of 84% at 5 years. Four patients developed distant metastases. The actuarial 2-year disease-free survival rate was 81%; the rate was 65% at 5 years. We concluded that protons, used as a concomitant boost with photons, effectively delivered an accelerated time-dose schedule to the cancer with a more tolerable schedule to surrounding normal tissues; our preliminary results revealed increased locoregional control without increased toxicity as compared to other radiation techniques delivering lower doses (31). We are planning future studies to evaluate the optimum time-dose schedule; one anticipated trial will utilize protons to treat the CTV and, we hope, decrease morbidity. Another likely avenue of investigation is topical protectors.

LLURM physicians have also used protons to re-treat recurrent cancers of the nasopharynx. We analyzed control, survival, and complication rates of conformal proton radiation for patients with such tumors who were initially treated with 50.0-88.2 Gy of photons with and without chemotherapy. Following evidence of treatment failure, we re-treated these individuals with protons alone to additional doses of 59.4-70.2 GyE. We correlated local-regional control and survival with extent of relapse, recurrence versus persistence, prescribed dose, and dose-volume histogram analyses of target coverage. The mean duration of follow-up was 23.7 months (range, 4-47 months). The rates of 24-month actuarial overall and local-regional progression-free survival were both 50%. Of greater import, we analyzed dose-volume histograms to determine the patients who had received "optimal" coverage of their tumors. In such cases the 24-month actuarial overall survival rate was 83%, a significantly higher rate than obtained for patients whose coverage was not "optimal" (32).

### *Lung Cancer*

Approximately 170,000 new cases of lung cancer are diagnosed every year in the United States. About 20% of patients have clinical Stage I disease at diagnosis; such tumors are associated with a 3-year survival rate of about 55% after surgery. Approximately 15% of clinical Stage I patients are medically inoperable, even though many of them have tumors that are technically resectable; these patients have historically been offered radiation therapy. Although conventional photon radiation therapy can control early-stage inoperable lung cancer, it often results in injury to functional lung tissue. We conducted a prospective Phase II clinical

up to 12 years. Again, outcomes were measured primarily in terms of biochemical relapse and toxicity. The overall 10-year biochemical disease-free survival rate in this series of 1,255 patients was 73%, and was 90% in patients with initial PSA levels of 4.0 or less. The 10-year biochemical disease-free survival rate was 87% in patients with post-treatment prostate-specific antigen (PSA) nadirs of 0.50 or less. Rates dropped with rises in initial and nadir PSA values. Conformal proton radiation therapy at these initial dose levels yielded disease-free survival rates comparable with other forms of local therapy, and was associated with minimal morbidity. These results laid the groundwork for dose-escalation trials (43). In a related report, we examined the common perception that radiotherapy is preferred for "older" prostate-cancer patients and surgery should be indicated for "younger" men. Both radiotherapy and surgery yield similar results in terms of long-term biochemical disease-free survival. We analyzed biochemical disease-free survival results from more than 1,000 patients treated solely with conformal proton radiotherapy to determine whether a difference in outcome supervened for patients younger than 60 years of age versus those older. We found no statistically significant difference; rather, analysis confirmed the well-known statistically significant predictors of outcome: pretreatment PSA level, clinical stage at diagnosis, and Gleason score. We concluded that age should not be used in and of itself to recommend one type of treatment over another for men with prostate cancer (44).

As our experience in treating patients with prostate cancer accumulated, we increasingly reached the conclusion that the precise dose distribution of the proton beam would enable higher doses could be delivered, to increase the probability of controlling the disease, while yet retaining a low rate of radiation-related side effects. Accordingly, we collaborated with investigators from MGH in PROG protocol 95-09, to evaluate the hypothesis that increasing the radiation dose delivered to men with clinically early-stage prostate cancer improves disease outcome. Our institutions conducted a randomized controlled trial of 393 patients with stage T1b through T2b prostate cancer and PSA levels less than 15 ng/mL. The median age of study subjects was 67 years; the median PSA level was 6.3 ng/mL. The median duration of follow-up was 5.5 years (range, 1.2-8.2 years). Patients were randomized to receive external-beam radiation, *via* a combination of conformal photon and proton beams, to a total dose of either 70.2 Gy (defined as the conventional dose) or 79.2 Gy (high dose). The primary outcome measure was PSA level five years after treatment. Sixty-one percent of patients receiving treatment on the conventional dose arm were free from biochemical failure at five years, as opposed to 80% of those receiving treatment on the high-dose arm. The difference was significant, and the advantage obtained for both low-risk and higher-risk subgroups. No significant difference was seen in overall survival rates. Both groups had similarly low rates of

acute urinary or rectal morbidity, and of severe late morbidity (RTOG Grade 3 or greater). The study participants concluded that men with clinically localized prostate cancer have a lower risk of biochemical failure if they receive high-dose rather than conventional-dose conformal radiation, and that this advantage obtained without an associated increase in RTOG Grade 3 acute or late urinary or rectal morbidity (45).

Dose-response curves for early prostate cancer are still relatively steep, *i.e.*, a 12% increase in dose yields an 18% increase in disease-free survival at five years for low-risk patients, and a 34% increase in disease-free survival at five years for those at higher risk. Findings such as these suggest that the utility of protons for prostate cancer, and most probably for other diseases, has not yet reached its ultimate application.

### *Pediatric Neoplasms*

Tumors in children comprise a variegated mixture of neoplasms that share their loci in growing tissues. This fact has always presented a special problem for radiation treatment of pediatric tumors, as normal-tissue damage can lead to a progressive series of side effects that persist throughout the patient's lifetime. We have explored proton radiation for many pediatric treatment problems, in hopes of exploiting its physical dose distribution so as to spare these growing tissues as much as possible. In treating children, avoiding even moderate amounts of irradiation to normal tissues is paramount; we have proceeded on the assumption that conformal 3-D planned proton irradiation can contribute to this goal. It is reasonable to expect that reduced dose and volume irradiated will reduce radiation effects, but full expression of late effects may occur in children five to ten or more years after treatment (46).

Protons have been used to limit treatment-related morbidity in children with tumors in or near the developing brain. In an early study, our analysis indicated that instances of early treatment-related morbidity associated with proton therapy were infrequent, albeit tumor progression remained a problem, particularly for histologies such as high-grade glioma (47). In a study of patients having progressive or recurrent low-grade astrocytoma, proton radiation therapy was generally well tolerated and all children who achieved local control maintained their performance status (48). This outcome also prevailed in a study of children treated by protons for optic-pathway glioma, a neoplasm for which adequate therapy offers excellent long-term survival rates, making it especially important to avoid treatment-related functional long-term sequelae. A comparison of proton, 3D photon, and lateral photon treatment plans revealed that the proton plans offered a high degree of conformity to target volumes, with steep dose gradients, leading to substantial normal-tissue sparing. Notably, we observed that even in small tumors, conformity

shown that a reasonable density resolution for imaging can be achieved with a relatively small dose of protons, one that is comparable to or even lower than that of x-ray CT (55).

It has been noted that "modern photon delivery techniques permit high dose isodose conformality similar to protons in many cases." The same author goes on to note, however, that proton radiation has an advantage for treating target volumes of "higher degrees of complexity and concavity," and has established a "gold standard" for treatment of some tumors. He comments further that the "advantage of protons and disadvantage for photons constitutes an 'inherent physical gap' that will likely be long lasting" (56). It should be noted that while conformity to the target has improved with photons using such techniques as intensity modulation, it comes at the expense of exposure of a significantly greater volume of non-target tissues. It remains to be seen whether the potential benefits of increasing the conformity to the target with photons outweighs the potential risk of an increased integral dose to such tissues.

At LLURM, we believe that the potential of protons is only beginning to be appreciated. Technological advances, such as those alluded to above, and collaborative trials will reveal more applications for protons as the years go on. Our experience at LLURM, we believe, is but the prologue to even more progress.

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