CURRENT AND POTENTIAL CLINICAL INDICATIONS OF PROTON IRRADIATION

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ABSTRACT

Over the past 2 decades of clinical development, proton irradiation has become the standard of care for selected tumor sites, e.g. ocular melanoma and skull base sarcomas (chordomas/chondrosarcomas). Proton therapy has made possible tumor dose escalation with maintenance of normal tissue dose constraints, increasing local control rates by over 30% in these tumors. The 3-dimensional planning tools developed specifically for proton treatment design have recently been emulated in several advanced 3-D photon planning algorithms, narrowing the dosimetric advantage afforded by proton therapy. However, the precise beam range modulation has been demonstrated to be of continued potential advantage in other clinical sites - specifically, advanced nasopharynx, paranasal sinus, oropharyngeal, nervous system, and prostate neoplasia. Reviews of the current tumor indications and control rates, Proton Radiation Oncology Group (PROG) clinical trials, and future applications are presented.

INTRODUCTION

Radiation oncology represents a discipline of medicine with the mandate of maximizing the local control of malignant disease. Although the spectrum of human neoplasia is broad and includes tumors whose natural behavior may be so aggressive as to be metastatic at first clinical presentation, many tumors remain locally confined for a significant period before dissemination. Such tumors range from slow-growing sarcomas of the skull base and ocular melanomas, to more histologically aggressive prostate carcinoma and squamous cell tumors of the head and neck. Recent statistical analyses of patterns of failure suggest that the ability to obtain local control of a tumor does, indeed, translate into decreased rates of metastases and, ultimately, into increased survivals.[1)]

Proton therapy represents one therapeutic modality within the armamentarium of irradiation possessing unique dosimetric qualities.[2)] The particle nature of proton irradiation results in extremely rapid dose fall-off at the distal range of the absorption - a phenomenon recognized as the "Bragg Peak". Unlike photon irradiation, the positive charge of protons results in slowing of the particles by attraction of electrons in tissue, as well as deflection and repulsion from nuclei. These magnetic characteristics result in a finite range of the proton as it traverses through tissue medium. Furthermore, this range is energy dependent and may be controlled by "range modulation". Additionally, dose profiles of protons in tissue equivalent phantom materials suggest a constant loss of energy across a range, resulting in a "flat" dose distribution across a useful depth of tissue. However, such a distribution comes at the expense of the well-recognized "skin-sparing" provided by higher energy photon beams. Because entrance doses for proton beams may vary as high as 70-100%, clinical therapy dictates either multiple entrance sites (i.e., multiple proton portals) or some mixture of photon and proton irradiation in order to lessen skin toxicity. The effective absence of exit dose beyond the range of proton irradiation also results in a lack of useful energy with which to image treatment volumes; therefore, diagnostic photon energy must be used to generate treatment portal verification films.

The sharp distal edge to the proton beam, combined with the ability to contour its width profile through the use of tissue compensation designed, not only to replace missing tissue, but also to correct for tissue inhomogeneities, both result in a facile method for tightly conformal therapy design. Such conformal therapy results in significant savings to "normal" non-target tissues during the irradiation of adjacent tumors. It is this ability to shape, or contour, the dose profile about the target volume that distinguishes proton irradiation - no radiobiological advantage is recognized for proton radiation per se. Relative Biologic Effectiveness (RBE) values have been repeatedly measured for proton therapy and are recognized to approximate 1.1; that is a coefficient multiplier of 1.1 will translate proton absorbed dose into photon, "Cobalt Gray Equivalent = CGE", dose. Therefore, only through target dose escalation made possible by conformal proton irradiation will local control of tumors be increased.

Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) curves both assume sigmoidal shapes, paralleling each other. Over the dose range resulting in significant incremental increases in tumor kill, i.e., over the range of the sigmoidal curve with the greatest slope, there exists a relatively small dose difference between curves reflecting damage to tumor and normal tissue. Scattered and "exit" radiation, such as exists in conventional photon therapy, results in dose to normal tissues, reducing the dose available to treat tumorous tissues. Partial organ tolerances, for the most part, have been poorly described in conventional photon literature. Proton therapy makes restriction of treated volumes possible and also allows treatment of only partial volumes of normal structures. One important result of proton therapy trials is the recognition of partial organ tolerances, some of which are currently being reported.[3)]

Three-dimensional treatment planning is a requirement of proton radiotherapy. Accurate predictions of scatter from surrounding tissue in all planes can only be made with the use of dose algorithms capable of 3-dimensional calculations. Equally important is the ability to represent the tumor and surrounding normal structures in such a fashion as to allow arbitrary viewing from any projection angle. The capacity to generate isodose surfaces, correlate these surfaces with CT and MR-defined anatomy, and to view the relationships of these surfaces and anatomy from any "Beam's Eye View" angle brings interactive 3-dimensional treatment planning to reality. Such software was originally developed for proton therapy and has been emulated by several photon algorithms.[4)] The volumetrics associated with the 3-dimensional surfacing implicit in this software makes it now possible to quantitatively compare volumes irradiated, patterns of recurrence relative to volumes irradiated, and normal tissue complications relative to volumes of normal tissues treated.

The development of powerful software tools capable of 3-dimensional treatment planning for both proton and now, photon, therapy has narrowed the dosimetric advantage gap between proton and photon treatments. Conformal photon irradiation is now possible for a number of disease sites, significantly improving the potential therapeutic ratio. However, the presence of a photon exit dose dictates the use of many beams in order to average the integral dose to normal tissue over as great a volume as possible. The ultimate expression of this integral dose averaging lies in dynamic therapy - conformal shaping of photon fields dynamically changing with rotation about the patient. Dynamic therapy has yet to become a practical reality, thwarted by the practicality of dose and conformal shielding verification. Proton therapy does not require such dose averaging to normal tissues - precise modulation of the distal edge depth and effective compensation across field dimensions obviate the need for more than a few static beams to achieve conformal therapy distributions. Nonetheless, optimal radiation planning may ultimately require both modalities: proton therapy for restricted, conformal boost irradiation and dynamic photon therapy for irradiation of surrounding tissues at risk for subclinical disease.

CURRENT CLINICAL EFFORTS

Proton therapy commenced at the Lawrence Berkeley Laboratory in 1955 for patients with benign arteriovenous malformations and pituitary neoplasia. Since that inception, worldwide interest has increased markedly, most recently due to the availability of practical software planning tools and to the decreased cost of cyclotron construction. It is estimated that over 12,000 patients have received proton irradiation, the majority for small intracranial lesions and for tumors of the eye. The recent formation of the ACR (American College of Radiology) sponsored Proton Radiation Oncology Group (PROG) represents a significant clinical focus designed to test the relative efficacy of proton therapy in well-designed trials. Several on-going Phase III trials, as well as recently commenced Phase I-II efforts, will be described.

Phase III trials

Uveal melanoma

As of June, 1992, 1764 patients have received radical irradiation therapy for choroidal melanomas utilizing protons delivered by the Harvard Cyclotron Laboratory (HCL). It is estimated that over 3000 melanoma patients have been treated worldwide.

Alternative therapies for choroidal melanoma include either enucleation or radioactive plaque therapy. Survival rates have been demonstrated to be fully comparable to those realized with enucleation, suggesting that dissemination of tumor cells during treatment localization, delivery, or follow-up is not occurring.[5] Plaque therapy is also being tested in a nationwide randomized trial against enucleation and appears to offer another alternative.[6]

Analysis of greater than 1000 proton patients at the HCL suggests local control rates within the globe to exceed 96% with control within the high-dose region exceeding 99%.[7] Ten-year survivals have remained in excess of 80% across all participating centers. With the excellent local control and equivalent survival rates to enucleation and plaque therapy, proton therapy for uveal melanoma appears to be most suited for 1) Posterior lesions close to the fovea where plaque placement is difficult and 2) Larger lesions with ultrasound measured height >/= 8mm which are not homogeneously treated with plaque therapy. Anterior lesions are more readily suited to plaque therapy due to facile placement.

We are currently testing the hypothesis that lower proton dose levels are possible while maintaining control rates and decreasing toxicity to the disc and fovea. The current Phase III dose trial randomly compares 5 x 10 CGE to our historical 5 x 14 CGE dose level for patients with tumors proximal to the disc and fovea. Eligibility criteria have remained constant throughout this trial and include tumors of </=15 mm diameter and </= 5mm height + located within 4 disc diameters of the optic disc/fovea + no evidence of distant disease + vision of counting fingers or better. Clinical results thus far have remained excellent, with no evidence of local failures. Therefore, the trial will continue with current acceptance parameters. An anticipated 176 patients are expected to be entered into the trial.

An additional phase III trial is underway testing the efficacy of DTIC chemotherapy and BCG immunotherapy in preventing the spread of disease for patients with larger choroidal melanomas and higher risks of metastatic spread. These established agents for the treatment of cutaneous melanomas are tested for patients with ocular melanomas >/= 15 mm in diameter and >/= 8 mm in height with no evidence of metastases. The radiation therapy will remain at the higher level (our historical control) of 70 CGE over 5 treatments.

Skull base sarcomas

Sarcomas of the skull base represent rare, difficult neoplasms to treat with conventional means of surgery and photon irradiation. Consisting primarily of chordomas and

chondrosarcomas, these tumors are usually not accessible to complete surgical removal, manifest relentless local invasive behavior, and are juxtaposed to critical structures (brainstem and chiasm) that effectively prevent the delivery of photon doses greater than 55.8 Gy. Austin-Seymour reviewed the historical control rates for this site with conventional treatment and reported local control rates at 3.5 years not to exceed 36%.[8)]

Proton therapy results have been previously reviewed and found to offer clear advantages over conventional photon treatment.[9-10)] Since 1974, over 200 patients with chordomas or low-grade chondrosarcomas of the base of skull have been treated with combined, fractionated proton and photon irradiation at the MGH/HCL facility. Greater than 70% of the dose was given with proton radiation, allowing significantly increased doses to be delivered, while respecting tolerance doses to adjacent critical structures (brainstem, chiasm). All planning has been performed with the aid of 3-dimensional planning techniques, optimizing the delivery of irradiation. Median dose delivered was 68 CGE. Outcome has been assessed in terms of local recurrence-free survival (LRFS) and overall survival. Local failure, defined as a definite increase on CT or MR imaging, occurred in 18% of patients, while metastases was documented in 4%. Median follow-up at time of last analysis is 37 months. LRFS at 36 and 84 months is 84% and 65% respectively, while overall survival is 94% and 77%. Significant prognostic variables include sex (males significantly better than females); histology (chondrosarcoma better than chordoma); location (base of skull better than cervical spine); and age (younger better). Currently, RTOG 86-25, a randomized dose protocol between 66.6 and 72 CGE for skull base sarcomas employing combined proton and photon irradiation, is being examined.

Advanced prostatic carcinoma

As of June, 1992, 192 patients have been entered onto a MGH/HCL study of dose escalation for advanced carcinoma of the prostate.[11)] Designed for T3-4 disease with N0-2 nodal status, the trial randomly compares 68.4 G to 75.6 CGE using conformal proton therapy. A total of 200 patients are planned to be treated before conclusion of the study. The acceptable tolerances of the rectum and bladder to the higher dose of irradiation suggests that proton beam therapy may realize significant increases in local control. Results from the trial will only be available after accrual completion and adequate follow-up time has occurred; however, toxicity results suggest the higher proton dose to be well-tolerated.

Phase II Clinical Trials

Recently, expanding clinical focus has resulted in the development and implementation of new protocols for the treatment of tumors of the paranasal sinus, oropharynx, benign intracranial meningioma, and astrocytomas at the HCL. These new efforts have required renewed attention to the details of facile, precise immobilization, as well as the incorporation of permanently implanted fiducial markers.[12)] Used in concert with repositioning software, these markers allow corrections of cranial position to be made to the sub-millimeter level in a reasonable treatment period of time, usually 20-30 minutes per patient.

It is noteworthy to indicate a change in emphasis in clinical trials towards the therapy of more rapidly growing, locally aggressive tumors. Whereas the period from surgical resection to irradiation for skull base sarcomas often exceeds several months, every effort is made to follow surgery with post-operative irradiation within 3-6 weeks for the squamous cell tumors of the paranasal sinus and oropharynx. Additionally, the astrocytoma treatment regimens demand a similar time schedule, including aggressive steroid management during therapy for intracranial swelling. Such new time constraints dictate close coordination with referring surgeons, rapid and interactive treatment planning, and close follow-up of these tumors.

Paranasal sinus

A hyperfractionated, accelerated combined photon and proton trial is currently in progress for patients with advanced malignancies of the paranasal sinuses. This aggressive regimen builds on the MGH experience of hyperfractionation to include the increased targeting accuracy of proton therapy, hoping to spare patients morbid, extensive surgical resections of the orbital contents and premaxillary area.[13] Tumors of this anatomical area have a relatively sparse lymphatic drainage pattern; therefore, they represent a category of head and neck tumors for whom increased local control may translate into increased survival.[14] Statistical predictions based upon dose-response data from pharyngeal wall tumors (similar in metastatic rate and growth patterns) suggest that a dose increase from current standards of 65 Gy to 75 Gy may result in as much as a 35% increase in local control.[15]

This program has accrued 10 patients thus far, including 2 currently under treatment. Despite the complexity of treatment planning involved, we have been able to maintain the same timetable for post-operative treatment as for conventional planning, i.e., commencing irradiation within 4 weeks following limited surgery. Permanently implanted cranial fiducials, in concert with improved cranial immobilization, have resulted in daily positioning inaccuracies of less than 0.5 mm. Because of this patient set-up accuracy, we have been able to treat tumors in close approximation to the visual system (optic nerves and chiasm) to radical (curative) doses.

Astrocytoma

Treatment of patients with high-grade astrocytomas of the brain has seen little improvement in local control over the past two decades, despite increasingly aggressive surgery and sophisticated imaging. Irradiation techniques have previously been constrained from delivering higher doses due to dose-volume tolerances of the brain. However, restricted volumes of the brain seem to be able to tolerate high levels of radiation from stereotactic interstitial techniques.[16]

A protocol has been developed, and is presently accruing the third patient, designed to deliver 90 CGE to restricted volumes of brain for patients with glioblastoma multiforme, totally resected. Fields are designed to conformally irradiate MR and CT-planned volumes, sparing the maximal amount of "normal" brain surrounding enhancing target volumes. Fractionation involves twice-daily irradiation - 1.8 Gy photon in the morning followed by 1.8 CGE proton treatment in the afternoon, at least 7 hours later. 50.4 CGE is delivered to the CT enhancing volume + 3 cm; 60 CGE to the CT enhancing volume + 2 cm; and 90 CGE to the enhancing volume alone. In such a manner, a dose gradient is delivered to the tumor isocenter that parallels the tumor cell densities at radial distances about the center of the tumor.

Maximal surgical extirpation will be required prior to irradiation in order to relieve edema effects of radiotherapy. Our previous pilot study of 9 patients indicated that edema resulting either from tumor expansion or acute radiation cerebral swelling is a major untoward effect of high dose irradiation and must be relieved by maximal resection when possible. The patients in the previous pilot study who received maximal resection are the only patients still alive and free of evidence of tumor.

Future protocols for low and intermediate-high grade astrocytomas (Grades II and III) are planned, building on our current study. These efforts will maintain the tightly conformal therapy possible with proton therapy, although total dose will be reduced, reflecting the earlier tumor stage.

Benign intracranial meningioma

A randomized, prospective, trial is currently underway to examine the additional efficacy afforded by 63.0 CGE versus conventional 55.8 CGE for recurrent, or

incompletely excised, benign intracranial meningiomas. These tumors account for 20% of intracranial neoplasms and, although histologically benign, account for significant morbidity due to their frequent proximity to the visual system. Tumors of the sphenoid ridge, parasellar area, and posterior fossa represent particularly difficult areas where detection is often late and complete surgical resection rates are low. Although a dose response relationship has not been established, data from University of California at San Francisco would suggest that 5 and 10 year local control is significantly improved when post-operative radiotherapy is delivered.[17] Nonetheless, 10-year local control rates remain as low as 50% following combined therapy with conventional irradiation doses of 55.8 Gy.

This trial employs the precise dose delivery of proton irradiation to ensure marginal coverage of resected meningiomas - marginal coverage which is difficult to ensure with conventional therapy because of close proximity to eyes, chiasm, and brainstem. Additionally, the dose escalation arm will seek to establish a dose response relationship for the treatment of benign meningiomas. To demonstrate an increase in local control rate of 13% at 5-years (80% to 93%) in this group of patients, 110 patients will be needed. Prior experience at MGH, LBL, and Loma Linda suggest that combined accrual rates dictate 5 year completion dates for the study. Thus far at the MGH, 6 patients have been randomized to the study this year. No acute complications have been realized from the treatment of this initial patient group.

Carcinoma of oropharynx

The Loma Linda proton facility has introduced to PROG a phase II protocol for oropharyngeal squamous carcinoma involving the delivery of concomitant proton boost irradiation during the last 3 weeks of photon treatment. This focussed "field-in-field" proton irradiation is intended to deliver a total of 3.3 CGE of daily treatment to sites of gross disease during the final, most radioresistant phase of a conventional course of therapy. Intended for tumors of the tonsil and base of tongue, both sites where local control is poor (<40%) and morbidity of surgical resection is high (total glossectomy/laryngectomy), this application of proton therapy seeks to emulate a non-invasive brachytherapeutic boost to sites of palpable, gross disease. However, unlike implant therapy, no requisite interval will be needed after conventional photon therapy for mucositis to heal. M.D. Anderson experience suggests that concomitant boost therapy results in superior local control for photon therapy, and should be delivered at the conclusion of the course of irradiation.[18] This protocol seeks to improve on the results of the M.D. Anderson group by targeting the tumor more precisely during this boost period, reducing morbidity and allowing an increased dose to be delivered.

Accordingly, 75.6 CGE will be prescribed to all sites of visible tumor at the time of initial endoscopic evaluation. This volume will not include nodal disease - such residual disease following irradiation to 50.4 CGE will be resected with modified neck dissection. All effort will be made to confine the proton boost most effectively in order to spare contralateral parotid and preserve pharyngeal wall constrictor function. Two patients have been entered on this protocol thus far - one each at the Loma Linda and MGH facilities. It is expected that this effort will be a major clinical endeavor due to the large numbers of patients with suitable tumors.

FUTURE CLINICAL EFFORTS

Extrasellar and recurrent pituitary neoplasia

Patients with recurrent (after transphenoidal surgery) pituitary disease, as well as those patients presenting with bulky, suprasellar and extrasellar disease not manageable with surgery, will be offered a tightly conformal, MRI-planned, fractionated irradiation course to elevated doses of 55.8 CGE. Normal tissue constraints to the hypothalamus and optic chiasm will be

maintained, if possible. This protocol will examine if the precise dose localization of proton therapy may offer these patients improved marginal control of pituitary adenomas, while minimizing untoward effects to the hypothalamus and medial temporal lobes.

Acoustic neuromas

Patients with unresectable or incompletely resected acoustic neuromas, for whom observation alone is inappropriate, either because of aggressive growth rates or critical tumor location, will be offered a fractionated, conformal proton therapy designed to deliver 35 CGE to the tumor + 0.5 cm while maintaining normal tissue constraints to the brain stem and temporal lobes. Developed in concert with the Department of Neurosurgery at MGH, this protocol will offer distinct dosimetric advantages over conventional photon "wedged-pair" therapy or "gamma-knife" stereotactic treatments in the reduction of dose inhomogeneities to surrounding structures. Larger fraction sizes will be employed in order to effect a greater therapeutic ratio, taking advantage of the dosimetry of proton therapy.

Advanced nasopharynx

Patients with advanced nasopharyngeal tumors (T3 and T4) will be offered a proton boost designed to ensure uniform delivery of 72 CGE to the base of skull. The cranial foramen are common routes of direct extension of these larger nasopharyngeal tumors, accounting for a significant proportion of the local failure rate (>40%) for advanced disease. Conventional therapy is constrained from uniform delivery of dose through the base of skull because of adjacent brainstem and cerebral tolerances. Proton therapy experience with skull base sarcomas will be applied directly to these tumors and should result in an increased cure rate as a result of improved local control.

SUMMARY

Although proton therapy is well-established for the treatment of ocular melanomas and skull base sarcomas, the dosimetric advantages of this particle therapy should also be of benefit to patients with other malignancies, specifically those of the paranasal sinuses, nasopharynx, brain, and prostate. However, in order to statistically demonstrate the advantages of proton therapy in local control of these tumors, cooperative trials must be completed with consistent protocol guidelines. The Proton Radiation Oncology Group represents an important collaboration towards achieving this protocol cooperation. Even within the short period since its inception, PROG has designed and implemented a number of challenging, new clinical efforts in order to test proton therapy. This next period of protocol accrual and completion will be an important one in the effort to make proton therapy a practical reality to the radiation oncology community at large.

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