

Proton Therapy in Clinical Practice: Current Clinical Evidence

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INTRODUCTION

Radiation therapy (RT), as primarily a localized form of treatment, strives for improved local tumor control and cure with few adverse effects. The physical characteristics of protons offer the theoretical benefit of more localized delivery of RT than can be achieved with photons produced by a linear accelerator. The improved dose distribution can potentially be exploited either by allowing higher RT doses to the tumor without increased RT-induced normal tissue toxicity or by reducing adverse effects at equally effective doses. Either of the two approaches is appealing, particularly when a critical normal structure is in close proximity to the tumor.

Proton therapy has been in clinical use since the 1970s. It was initially used in two US centers (Boston, MA, and Loma Linda, CA) and subsequently in Europe (d'Orsay, France) and Japan (Tsukuba, Japan); these centers reported most of the initial clinical results. The principal sites chosen for the evaluation of protons were uveal melanomas and tumors at the skull base. Other disease sites were subsequently treated including head and neck and liver tumors; tumors in the brain, upper abdomen, and pelvis; lung cancer; and tumors in the vicinity of the spinal cord. The main rationale had been poor local disease control with conventional therapy, and the proximity of critical dose-limiting normal tissue, which is a bar to safe dose escalation using conventional photon RT. The introduction had frequently been underpinned by planning studies demonstrating, in selected cases, improved dose distribution of protons compared with photons.¹⁻¹¹ The perception of physical and clinical advantage has led to the establishment of new clinical facilities, and some tens of thousands of patients are claimed to have been treated to date.

The necessary prerequisite for introduction of such technologically complex treatment into the clinical arena is enthusiasm for particle therapy, a belief in its benefit, and considerable financial outlay. The investment in clinical facilities offering proton therapy should not simply follow enthusiasm and belief in the new technology but should be

firmly based on objective outcome data demonstrating the real additional value of protons over photons using the criteria of evidence-based medicine. This article attempts to review the currently available clinical evidence.

METHODOLOGY OF THE ANALYSIS OF PUBLISHED DATA

A systematic review was performed and presented in part¹² and in full,¹³ and we provide an update with additional analysis. Briefly, all publications of clinical applications of protons were searched on Biologic Abstracts (1993 to 2004); CINAHL (1982 to September 2006); The Cochrane Library (Issue 1 2006); Database of Abstracts of Reviews of Effects; EMBASE (1980 to September 2006); Health Technology Assessment database; ISI Science and Technology Proceedings; MEDLINE (1966 to September 2006); National Health Service Economic Evaluation Database; Office of Health Economics Health Economic Evaluations Database; and System for Information on Grey Literature in Europe. The subsequent analysis included only studies with at least 20 patients and with a follow-up period of at least 2 years. The studies identified are listed in Table 1. There were only two phase III trials, both in prostate cancer, and neither of the trials is a straight comparison of photons with protons.

In the absence of randomized trials, we performed a systematic analysis of the identified proton articles. The principal proton centers published sequential results at different times. Only the latest publication containing outcome data was used, assuming this superseded previous data. The individual actuarial outcome was obtained from the published text and graphs. In case of discrepancy, the value was taken from the published graph. The summary figure was expressed as a weighted mean (weighted for initial number of patients in the study) of the available data.

Most publications were in the form of retrospective, quasi-phase II studies. Although the design is not appropriate for outcome comparison with conventional therapy, weighted means provide the

Table 1. Clinical Studies of Proton Therapy With at Least 20 Patients and With a Follow-Up Period of at Least 2 Years

Tumor Site	No. of Studies	No of Patients
Head and neck tumors ^{15,75}	2	62
Prostate cancer ^{14,16,17}	3	1,642
Ocular tumors ¹⁸⁻²⁶	9	9,522
Gastrointestinal cancer ²⁷⁻³¹	5	375
Lung cancer ³²⁻³⁴	3	125
CNS tumors ^{28-35,54,55}	10	753
Sarcomas ⁴³	1	47
Other sites ⁴⁴⁻⁴⁶	3	80
Total	36	12,606

most objective information on a reasonably large group of patients, and these were compared with published outcome of the best available conventional treatment. Such comparisons are fraught with difficulty because of patient selection and the consequent bias. Nevertheless, in the absence of prospective comparative studies, this is likely to provide the most objective assessment.

RESULTS BY TUMOR SITE AND TYPE

Chordomas and Chondrosarcomas of the Skull Base

Chordomas and chondrosarcomas are rare tumors arising in the skull base. Chordomas also present in the axial skeleton, particularly in the cervical region and the sacrum. Most proton therapy data are available for skull-based tumors.

The difficulty in achieving complete removal of skull-based tumors, frequently affecting the brainstem and cranial nerves, led to the introduction of RT. There is little prospective data to demonstrate that, in chordomas and chondrosarcomas, RT offers benefit in tumor control and survival over surgery alone, and a dose-response relationship for photon therapy has also not been prospectively documented.⁴⁷

Because of the progressive nature of residual/unresectable chordomas, RT is recommended in patients with unresectable and/or residual tumors after surgery. The reported local progression-free survival (PFS) rate after conventional therapy ranges from 17% to 65% at 5 years,⁴⁸⁻⁵³ and this wide range is at least in part a result of bias of patient selection and changing surgical techniques. The principal rationale for the use of protons has been to reduce the dose to the

brainstem and allow for safe dose escalation to the primary tumor with the hope of improving tumor control and survival.

Actuarial local tumor control (local PFS) is the most appropriate measure to assess the efficacy of surgery and RT. The most recent surgical series representing modern skull base surgery (only 20% of patients had conventional RT), reports a 5-year PFS rate of 65% in patients with chordoma.⁴⁸ Surgery followed by fractionated stereotactic RT for skull base chordoma resulted in a 5-year PFS rate of 50%.⁴⁹ The published results of proton therapy for chordoma, generally administered as part protons and part photons, are listed in Table 2. The largest series reports the outcome in 169 of 290 treated patients (reasons for not reporting 42% of the treated patients are not specified) at a median follow-up time of only 3.4 years.⁵⁴ The summary statistic of selected patients treated with protons is a 5-year PFS rate of 60% (Table 2). On the basis of the available literature, no clear superiority in terms of local tumor control of protons over photons in the treatment of skull base chordoma has been demonstrated.

Chondrosarcomas are usually low-grade tumors. Published series are generally small, and the outcome after surgery, which is usually followed by photon external-beam RT, is reported as 90% to 100% actuarial local control at 5 years.^{48,49} The summary of tumor control in published proton therapy studies is a 5-year local PFS of 95% (Table 3),^{35,54,55} which is no different than the results of conventional therapy.

There is insufficient data available to be able to formally compare RT-induced toxicity after proton therapy and conventional treatment for both chordoma and chondrosarcoma. Nevertheless, the use of protons for tumors involving the brainstem can result in brainstem damage, and the risk is related to the volume of brainstem irradiated to doses more than 60 Gray equivalents (GyE).⁵⁶

Ocular Tumors

The treatment options in patients with uveal melanomas include local resection, enucleation, transpupillary thermotherapy, photodynamic therapy, ruthenium-106 and iodine-125 brachytherapy, stereotactic photon RT, and proton therapy. In patients with early tumors, local tumor control and survival for different treatment modalities seem equivalent.⁵⁷

Two prospective phase I to II dose-escalation studies, with a total of 594 patients,^{20,21} and seven retrospective studies (six case series and one comparison study of proton v iodine-125), with a total of 8,928 patients,^{18,19,22-26} have been identified. Tumors where the posterior margin extends close to the optic disc or close to the fovea or where the height exceeds 5.5 mm cannot be treated with plaque brachytherapy

Table 2. Actuarial Local Control in Adult Patients With Skull Base Chordoma Treated With Protons

Publication	Year of Publication	No. of Patients	Median Follow-Up Time (years)	5-Year Local Progression-Free Survival Rate (%)
Noel et al ⁵⁵	2005	100	2.3	54*
Hug et al ³⁵	1999	33	2.8	59
Munzenrider and Liesch ⁵⁴	1999	169	3.4	64
Total, † weighted mean	—	302	3.0	60

* Only 4-year results given. Estimate for 5-year progression-free survival rate is approximately 50%.

†Based on extrapolation of 4-year progression-free survival rates of 54% to 50% at 5 years.

Table 3. Actuarial Local Control in Adult Patients With Skull Base Chondrosarcoma Treated With Protons

Publication	Year of Publication	No. of Patients	Median Follow-Up Time (years)	5-Year Local Progression-Free Survival (%)
Hug et al ³⁵	1999	25	2.8	75
Munzenrider and Liebsch ⁵⁴	1999	165	3.4	98
Total, weighted mean	—	190	3.3	95

without causing optic neuropathy, and thus, proton RT has been considered the appropriate option.

Studies with 5-year survival data are listed in Table 4. In selected patients, the 5-year local tumor control after proton RT is in excess of 95%, with a 10% risk of needing subsequent enucleation both for local recurrence and severe adverse effects.⁵⁷ The summary statistic is a 5-year cause-specific survival rate of 85%, a local tumor control rate of 97%, and an eye preservation rate of 90% (Table 4). Only 40% of patients had preservation of vision of 20/40 or better. Ten percent of patients died from metastatic melanoma.⁵⁷

Patients with ocular melanoma not suitable for plaque therapy have also been treated with fractionated stereotactic RT using photons. The results both for local tumor control and complications are similar to protons,⁶⁴⁻⁷¹ with local tumor control achieved in 98% of patients and subsequent enucleation needed in 10% to 15% of patients.⁶⁵ Less than 10% of patients developed metastases. In conclusion, there is currently no clear evidence that proton therapy is superior to photon irradiation in patients with ocular melanomas.

Prostate Cancer

RT remains one of the principal treatment options in the management of localized prostate cancer. The aim of modern photon RT techniques, which include three-dimensional conformal RT, intensity-modulated RT (IMRT), and brachytherapy, is to increase RT dose without additional RT toxicity, particularly to the rectum. Five completed randomized dose-escalation studies^{16,17,72-74} show improved tumor control in patients receiving higher RT dose, although this is generally at the cost of increased rectal toxicity.

Protons have been evaluated with the aim of allowing higher RT dose without increased toxicity. The largest published phase II study of 1,255 patients with stages IA, II, and III prostate cancer using a combination of photon and proton therapy does not provide useful infor-

mation on the comparative efficacy of protons versus photons, and the results are not dissimilar to other forms of local therapy.¹⁴

Proton therapy has been used in two randomized dose-escalation studies.^{16,17} Both studies used protons for RT boost after initial photon irradiation. The earlier study compared a lower dose photon boost with a higher dose proton boost,¹⁶ and the more recent study compared two dose levels of proton boost.^{16,17} The study design does not attempt to compare the efficacy of protons versus photons. Nevertheless, the studies confirm improved tumor control with higher RT dose but not without increase in late GI toxicity.^{16,17}

In summary, there are currently no studies demonstrating improved tumor control or survival in the treatment of localized prostate cancer with protons compared with best available photon RT. In addition, there is no clear evidence that high-dose proton boost is associated with less toxicity than the toxicity expected with photons.

Head and Neck Cancer

Two studies of proton therapy have been identified.^{15,75} The local tumor control rate varied between 74% and 84%, the 5-year survival rate ranged from 44% to 65%, and the severe late complication rate ranged from 10% to 18% for a mixture of tumor types and stages. The results in such a phase II trial are largely not assessable, and in any case, the results are similar to those achieved with photon RT.⁷⁶

Other Tumors

Protons have been used and reported in a variety of tumors. In esophageal cancer, one prospective study of 30 patients²⁷ and one retrospective study of 46 patients²⁸ have been reported. Tumor control rates in the region of 50%, with 5-year survival rates of 10% to 15%,^{27,28} after proton doses of 76 to 86 GyE seem superior to the results in historical controls treated with RT alone to doses of approximately 60 Gy. However, the apparently favorable results may be

Table 4. Eye Preservation Rate and 5-Year Cause-Specific Survival in Patients With Ocular Melanoma Treated With Protons

Institution and/or Location	No. of Patients	Eye Preservation Rate (%)	Local Control Rate (%)	5-Year Cause-Specific Survival Rate (%)	Reference	Year of Publication
Nice, France	538	88	89	86	Courdi et al ²²	1999
D'Orsay, France	1,406	92	96	81	Dendale et al ¹⁹	2006
Loma Linda, United States	78	75	91	76	Fuss et al ²³	2001
Boston, United States	2,069	91	97	87	Gragoudas et al ⁵⁸	2002
London, United Kingdom	267	89	95	91	Wilson and Hungerford ²⁵	1999
PSI Villingen, Switzerland	2,648	89	99	85	Egger et al ¹⁸	2003
Clatterbridge, United Kingdom	349	91	97	90	Damato et al ²⁶	2005
Total, weighted mean	7,355	90	97	85	—	—

NOTE. Only studies with 5-year results are shown.

accounted for by patient selection and are not dissimilar to modern multimodality therapy. Therefore, the value of proton therapy in esophageal cancer remains unclear.

One retrospective (235 patients) and two prospective studies (64 patients) of protons in patients with hepatocellular carcinoma²⁹⁻³¹ report results similar to those achieved with stereotactic photon RT.⁷⁷ One retrospective study reported the outcome in 15 patients with osteogenic sarcoma and 12 patients with giant-cell tumors, osteoblastomas, and chondroblastomas⁴³; the benefit over conventional treatment is not clear.

A single prospective study of 37 patients with non-small-cell lung cancer³² and two retrospective case studies in 88 patients with non-small-cell lung cancer^{33,34} lead to similar conclusions that equivalent outcome can be achieved in such selected patients using modern photon therapy.⁷⁸ In conclusion, although none of the studies have been designed to provide useful information about comparative efficacy with best conventional therapy, the available data do not demonstrate superiority over modern photon RT.

Protons have been evaluated in a number of other intracranial tumors, including a prospective study in glioblastoma multiforme (23 patients) and low-grade glioma (33 patients).^{36,37} As seen in photon dose-escalation studies using brachytherapy, conformal RT, IMRT, and stereotactic RT,⁷⁹⁻⁸² dose escalation with protons has not demonstrated convincing survival benefit in malignant glioma other than the benefit that would be expected as a result of patient selection. Further retrospective studies reporting the results in patients with acoustic neuroma (30 patients), low-grade astrocytoma (27 patients), and cavernous arteriovenous malformation (85 patients)³⁸⁻⁴¹ do not allow for conclusion about superiority over photons. The reported results in patients with benign meningioma (46 patients)⁴² show no better tumor control and possibly greater toxicity compared with best conventional therapy.

Among pelvic tumors, the results in 25 patients with cervical cancer have been reported in one study,⁴⁴ and results in 55 patients with bladder cancer have been reported in two retrospective studies.^{44,45} Selected patients with bladder cancer treated with protons after transurethral resection followed by chemotherapy had a 5-year survival rate of 60% and local tumor control rate of 73%, with nearly one third of patients developing severe late adverse effects.^{45,46} The results are no different to the reported outcomes after combined-modality therapy including photon RT.⁸³

DISCUSSION

The clinical implementation of high-energy proton therapy is fueled by the combination of the apparent advantage of dose distribution, early clinical results, and the availability of equipment supported by commercial interest. As is the case for any innovative technology, proton therapy requires considerable expertise, effort, and investment, and the introduction into clinical practice is initially without grade 1 and high-level grade 2 evidence.

Before rolling out proton therapy into daily practice, it is necessary to establish its real additional value. This requires well-designed phase II trials and adequately powered phase III trials to provide objective information on the efficacy and toxicity compared with best conventional therapy. The early implementation of protons in the treatment of skull base tumors provides an example of how the sug-

gested improved outcome in early studies of selected patients with chordoma and chondrosarcoma has not stood up to comparison with best conventional therapy and, as in other tumor types, may be explained by patient selection. The claim by proton therapy supporters that protons are the treatment of choice for chordoma and chondrosarcoma is no longer tenable based on the currently available evidence.

Despite many years of clinical studies of proton therapy, there are no adequately powered prospective studies in ocular tumors and a range of other intracranial and systemic tumors tested that would provide robust evidence of benefit in efficacy and toxicity compared with best photon therapy. Again, any potential differences in outcome may be explained by selection bias.

The lack of available evidence in favor of protons does not mean that protons may not be useful in selected tumors. It should be a stimulus for more research, particularly in the form of appropriately designed and powered prospective studies. The promising sites where protons may offer the potential advantage of more localized treatment are similar to the tumor sites where IMRT is being explored. The likely requirements are a tumor lying in close proximity to critical structures and reliable data showing that dose escalation is likely to improve tumor control and survival. These tumor sites initially include some head and neck tumors and pelvic tumors, particularly prostate cancer. There is also increasing interest in offering protons for pediatric tumors requiring RT where a reduction in normal tissue dose is of particular importance, although there is concern about the effects of neutron contribution.⁸⁴ However, prospective outcome data from appropriately designed studies in children should be available before protons become an accepted alternative to conventional therapy in pediatric tumors.

Proton and other particle therapies need to be explored as potentially more effective and less toxic RT techniques. A passionate belief in the superiority of particle therapy and commercially driven acquisition and running of proton centers provide little confidence that appropriate information will become available. Objective outcome data from prospective studies is only likely to come from fully supported academic activity away from commercial influence. An uncontrolled expansion of clinical units offering as yet unproven and expensive proton therapy is unlikely to advance the field of radiation oncology or be of benefit to cancer patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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