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Technology Review

PROTON THERAPY FOR CANCER TREATMENT

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TECHNOLOGY REVIEW: PROTON THERAPY FOR CANCER TREATMENT

1.0 INTRODUCTION

Proton therapy is a painless, non-surgical radiation treatment at the atomic and molecular levels. It is currently the most precise and advanced form of radiation therapy available.

Proton therapy provides the radiation oncologist with a highly precise method of placing radiation within a patient, when compared with conventional radiation therapy using X rays or electrons. Improved conformation of the high-dose region to the targeted volume minimizes normal-tissue injury, thereby reducing treatment-related side effects and complications. The reduced dose received by normal tissues allows the physician to increase the dose of radiation to the tumor beyond that which is possible with conventional radiation. Increasing the dose of radiation to a tumor has proved to increase the potential for tumor control; this translates to an increased cure rate when treating localized tumors[1].

Currently, there are 23 proton therapy centres worldwide, and there is an increasing demand for this facility. However, this technology is very expensive and to date, no proton centre worldwide accepts and treats enough patients to be a profitable business except for one hospital-based centre, the Loma Linda University Medical Centre, USA.

2.0 NATURE OF TECHNOLOGY

Conventional radiation uses x-rays; whereas proton therapy uses protons which are positively charged particles taken from hydrogen gas atoms. Proton therapy works using the principle of ionization.

Ionization occurs when the energized proton particles come in contact with orbiting electrons and the positively charged protons attract the negatively charged electrons. This process pulls the electrons out of their orbit and changes the characteristics of the atom, which consequently alters the character of the entire molecule. Ionization, which occurs during radiation, damages the DNA of a cell and hampers its ability to grow and reproduce.

There are several techniques used when giving proton radiation therapy, which includes spot scanning, passive scattering, intensity modulated, fractionated conformal beam or accelerated beam.

Proton therapy is considered superior because it is more ‘site-specific’ and primarily radiates the tumour site, compared to the conventional x-ray radiation which radiates healthy tissues in its path and those surrounding the cancerous cells. The technology allows for a more selective destruction of cells because the radiation can be controlled to focus on a specific depth within the body and form an exact three-dimensional shape of the tumor. This process minimizes radiation deposits in the areas along the beam’s path and in surrounding tissues, thus preventing unnecessary damage to the healthy tissues. Proton therapy causes minimal side effects compared to those associated with conventional x-ray radiation.

The marketing for proton therapy systems for the treatment of cancer has been approved by the FDA[54].

3.0 METHODOLOGY

Retrieval of evidence-

1. Literature search was done using the MEDLINE and COCHRANE database. The search includes studies in all languages, and limited to studies on human subjects in the last 10 years of publication.

The keywords used in the search were:
- ("proton therapy" OR "proton radiation" OR "proton beam" OR "proton radiation therapy") AND (effectiveness OR effective OR efficacy) AND (cancer OR carcinoma)
- ("proton therapy" OR "proton radiation" OR "proton beam" OR "proton radiation therapy") AND (cost OR cost effectiveness OR budget) AND (cancer OR carcinoma)
- ("proton therapy" OR "proton radiation" OR "proton beam" OR "proton radiation therapy") AND (safe* OR "adverse effects") AND (cancer OR carcinoma)

2. HTA databases were also searched- AHFMR, AHRQ, HTA database
3. Related links were also searched-ECRI, UHMS, TRIP database, Journal websites
4. General search using Google.

4.0 DISCUSSION OF RESULTS

4.1 Safety

There are many literatures available on the safety aspect of proton therapy. Most of the clinical studies either it be cohort, cross-sectional or comparative treatment planning studies reported that proton therapy is safe. This is particularly in reduction of radiation dose to normal tissues, thus minimizing the side effects of radiation.

A retrospective study by Tsina et al [2005] found that in patients with choroidal metastases treated with proton beam therapy, complications occurred in 56% of cases. These include madarosis, keratitis, dry eye syndrome, cataract, neovascular glaucoma, chorioretinal atrophy, radiation papillopathy, and radiation maculopathy[4]. However, none of the treated eyes required enucleation. These papers also reported that although complications occur in most cases, many of these are minor and were not associated with a change in function. In another study, proton beam therapy in the treatment of iris melanoma was also well tolerated[3].

In the treatment of skull base chordomas and chondrosarcomas, 10% of patients developed temporal lobe damage. The cumulative temporal lobe damage incidence at 2 and 5 years were 7.6% and 13.2% respectively[48]. Damien C et al [2005] also reported that spot-scanning proton therapy for treating skull base chordomas and chondrosarcomas caused radiation-induced pituitary dysfunction in 14% of patients. However, no patient presented with post-proton therapy brainstem or optic pathways necrosis or dysfunction[12].

Wenkel E et al [2000] reported that among 46 patients with partially resected, biopsied, or recurrent meningiomas who were treated with combined photon and 160-MeV proton beam therapy, eight patients developed severe long-term toxicity from radiotherapy, including ophthalmologic (4 patients), neurologic (4 patients), and otologic (2 patients) complications. However, the observed toxicity appears to be dose-related[14]. Damien C et al [2004] also reported a similar finding, of which ophthalmologic complications which

occurred after the treatment of intracranial meningiomas with proton beam was dose-related[16].

In lung cancers treated with proton radiation therapy, complications such as symptomatic radiation pneumonitis, esophageal or cardiac toxicity were minimal or none [21,22].

Proton radiation therapy caused minimal toxicity in cases of prostate cancer. In a non-randomized prospective study of 643 patients treated with proton beam, minimal radiation proctitis was seen in 21% of patients[23].

Proton radiation therapy can be safely administered in acoustic neuromas. Besides providing good tumour control, it also preserve the functions of surrounding cranial nerves[40,41]. Harsh et al [2002] similarly reported that cranial neuropathies were infrequent, which include persistent facial hyperesthesia, persistent facial weakness, transient facial weakness and synkinesis[42].

In paediatric patients, proton therapy is a promising technology to be used in treating paediatric malignancies, particularly its ability to achieve the therapeutic target dose without causing harm to the surrounding normal tissues. A comparative treatment planning study by Miralbell R et al [1997] demonstrated a potential role of proton therapy in decreasing the dose (and toxicity) to the critical structures in the irradiation of the spinal neuraxis in medulloblastoma. The potential bone marrow and growth arrest sparing effects make proton therapy especially attractive for intensive chemotherapy protocols and for very young children. Sparing the thyroid gland, the posterior heart wall, and the gonads may be additional advantages in assuring a long-term post-treatment morbidity-free survival[49].

Another comparative treatment planning study [Miralbell R et al, 2002] found that proton beams reduced the expected incidence of radiation-induced secondary cancers for the rhabdomyosarcoma patients by a factor of >2 and for the medulloblastoma case by a factor of 8 to 15 when compared with either IM or conventional X-ray plans[50]. The potential for a significant reduction in secondary cancers with pediatric cancers after using proton beams (forward planned or IM) in the treatment of rhabdomyosarcoma and medulloblastoma in children and adolescents represents an additional argument supporting the development of proton therapy for most radiotherapy indications in pediatric oncology.

Lee C et al [2005] reported that in retinoblastoma, protons resulted in the best target coverage combined with the most orbital bone sparing, while in medulloblastoma, for posterior fossa and craniospinal irradiation, protons resulted in the least dose to the cochlea and hypothalamus-pituitary axis. With pelvic sarcoma, protons were superior in eliminating any dose to the ovaries and to some extent, the pelvic bones and vertebrae[46].

4.2 Evidence of Effectiveness of Proton Therapy are described for the following cancers:

A. Ocular (Uveal) Melanoma

Choroidal melanoma is the most common form of ocular melanoma which represents as focal accumulation of melanocytes at the level of the uvea. It could be benign or malignant. For many years, the standard form of therapy was enucleation, but this has been replaced whenever possible by a variety of therapies aimed at destroying the primary tumor while conserving the eye, ideally with useful vision.

There is sufficient evidence to conclude that proton radiation therapy is effective in ocular (uveal) melanoma. A systematic review done by CEDIT in 2003 acknowledged the effectiveness of proton therapy in melanomas of the eye. However, this report commented that the role of this form of treatment in comparison with radio surgery remains uncertain[2].

There are a few cohort studies which showed that in the treatment of choroidal melanoma with proton beam therapy; there is a higher rate of local tumor control and ocular conservation[3,5]. Tsina [2005] reported in a retrospective study that proton radiation therapy is a useful therapeutic approach for choroidal metastases, of which it allows retention of the globe, achieves a higher probability of local tumor control and helps to avoid pain and visual loss[4].

B. Sarcomas Of The Skull Base And Spine

Chordomas of the base of the skull are rare. They are locally infiltrative and frequently arise close to radiosensitive structures, which limit the ability to deliver a high dose of radiotherapy.

There is sufficient evidence to conclude that proton radiation therapy is effective in the treatment of skull base cancer. A systematic review done by CEDIT in 2003 acknowledged the effectiveness of proton therapy in skull base chordomas and chondrosarcomas[2]. A review by the Proton Therapy Working Party reported that in the treatment of skull base chordoma, the outcome after proton radiation therapy is superior to conventional photon radiation[11].

There are several cohort studies done to evaluate the effectiveness of proton therapy in the treatment of skull base chordomas or chondrosarcomas. Igaki H et al [2004] reported that proton beam therapy is effective for patients with skull base chordoma, especially for those with small tumours. This study also found that the 5-year local control rate was 46.0%, and the cause-specific, overall, and disease-free survival rates at 5 years were 72.2%, 66.7% and 42.2% respectively[10]. Another study found that spot-scanning proton therapy offers high tumour control rates of skull base chordomas and chondrosarcomas[12]. However, the result compared favorably to other combined proton-photon or carbon ion radiation series. In a prospective study by Noël G et al [2001] the combination of photons with a proton boost offers an excellent chance of cure for skull-base chordomas and chondrosarcomas[8].

Vernimmen FJ et al [2001] reported from a retrospective study of 27 patients that proton radiation therapy is effective in controlling large and complex-shaped skull base meningiomas[13].

C. Intracranial Tumour

There is fair evidence to say that proton therapy is effective in treating benign meningioma. A cohort study found that the combination of proton and photon radiation therapy is effective to treat patients with recurrent or incompletely resected benign intracranial meningiomas. This study reported that the overall survival at 5 and 10 year was 93 and 77% respectively, and the recurrence-free rate at 5 and 10 years was 100% and 88% respectively[14]. Another study by Noel et al [2005] also supported that there is clinical efficacy of combined photon-proton radiation therapy in the treatment of meningiomas, especially on cranial nerve palsies[15].

There is also a study done on the effectiveness of proton radiation therapy alone in this cancer. Webera et al [2004] reported from a cohort study of 14 patients that spot-scanning proton radiation therapy is effective for patient with untreated, recurrent or incompletely resected intracranial meningiomas. This technology offers highly conformal irradiation for complex-shaped intracranial meningiomas, while delivering minimal non-target dose[16].

A treatment planning study found that proton irradiation should be irradiation technique of choice in treating small intracranial tumours, when available[17]. In this study, proton techniques were shown to be superior in treating meningiomas, neurinomas and pituitary adenomas, when compared to 3D conformal radiotherapy (3DCRT), stereotactic arc therapy or intensity modulated radiotherapy with photons (IMRT). This is particularly after taking into account the long life expectancy of the patients suffering from this type of cancers, toxicity and the possibility of secondary tumour induction[17].

Ronson et al [2006] reported from a prospective study of 47 patients with pituitary adenomas treated with proton radiation therapy that this technology achieved effective radiologic, endocrinological and symptomatic control of pituitary adenomas[18].

D. Paranasal Sinus, Nasal, And Nasopharyngeal Tumours

There is no evidence to support the use of proton therapy in these types of cancers.

E. Lung Cancer

There are a few studies done to evaluate the effectiveness of proton radiation therapy in the treatment of lung cancer. In a non-randomized prospective study conducted on 51 non-small cell lung carcinoma (NSCLC) patients treated with proton beams at the University of Tsukuba found that the 5-year overall survival rate was 29% for all patients, 70% for 9 Stage IA patients, and 16% for 19 Stage IB patients, respectively[21]. This author concluded that proton therapy is an effective treatment for patients with NSCLC, especially for those with early stages.

Another study found that proton radiation therapy is a promising treatment modality for stage I NSCLC. After a median follow up of 2 years, the 2 year local progression-free and overall survival rates were 80% and 84% respectively[22].

Lee CH et al [1999] reported in a comparison study that proton therapy is capable to deliver an escalated high dose to target volume in NSCLC whilst maintaining the normal tissue doses within tolerance, when compared to conformal x-ray therapy[19].

F. Prostate Cancer

There are a few cohort studies which support the use of proton radiation therapy in prostate cancer. Most of these studies analyzed the biochemical disease-free survival rate as the outcome. Slater et al [2004] reported in a retrospective study that by using proton radiation therapy, the overall biochemical disease-free survival rate was 73%, and was 90% in patients with initial PSA level <4.0, and 87% in patients with post treatment PSA nadirs < 0.50 [26]. There was also another study which reported a similar result, in which the overall 7 year actuarial biochemical disease-free survival rate was 79% and this outcome was strongly influenced by pre-treatment PSA levels[24].

There is also one study which found an even better result. Slater et al [1999] found in their prospective study that the overall 5 year clinical and biochemical disease-free survival rates were 97% and 88% respectively. This was comparable to those who underwent radical prostatectomy[23].

G. Liver Cancer

There are not many evidence available to support the role of proton radiation therapy in liver cancer. Two retrospective studies reported the effectiveness of this technology in this type of cancer. Hata et al [2005] reported that proton beam therapy for patients with hepatocellular carcinoma (HCC) was feasible and effective. It appeared to significantly improve survival and local tumour control, with progression-free survival rates reported at 67% at 2 years and 24% at 5 years[28].

One case study reported that in a 54-year old man with HCC Stage III had achieved local tumor control and maintained for 9 months following proton therapy, thus enabling him to gain time for a liver transplantation[30]. In another case of a 76-year old lady with a secondary liver tumor originated from gastric tumor was cured after she received both proton radiation therapy and chemotherapy, and no recurrence was detected for 2 years after termination of the treatment[29].

H. Gastrointestinal Tract Cancers

There are a few literatures available regarding the use of proton radiation therapy in different types of gastrointestinal tract cancers.

Sugahara S et al [2005] reported in a cohort study of 65 esophageal cancer patients who were irradiated with protons, with or without x-rays[34]. This study found that proton radiation therapy is an effective modality for patients with locally confined esophageal cancer. It was also found that the local control rates for patients radiated with accelerated fractionation might be better than that for those irradiated with conventional fractionation. A treatment planning study also found that protons appear to have clear therapeutic advantages over conventional external radiotherapy when treating patients with esophageal carcinoma[33].

There is only one comparison planning study available regarding the use of proton therapy in pancreatic cancer. However, the findings only stated the superiority of proton therapy compared to other conventional radiation with respect to dose distribution, but did no analyze the effectiveness of the technology for the treatment of this type of cancer[35].

In rectal cancer, a comparative treatment planning study found that proton radiation therapy has potential advantages when treating medically inoperable large rectal cancers when compared with conventional x-ray therapy[37].

I. Breast Cancer

There are limited studies available regarding the role of proton radiation therapy in breast cancer. Two treatment planning studies were available, but the findings only stated the superiority of proton therapy compared to other conventional radiation with respect to dose distribution, and did not analyze the effectiveness of this technology on the treatment of breast cancer.[38,39].

J. Acoustic Neuroma

An acoustic neuroma (sometimes termed a neurolemmoma or schwannoma) is a benign (non-cancerous) tissue growth that arises on the eighth cranial nerve leading from the brain to the inner ear.

There are only a few studies found regarding the use of proton radiation therapy in acoustic neuroma. Three cross-sectional studies found that proton radiation therapy resulted in good tumour control in acoustic neuromas, with preservation of function of the surrounding cranial nerves[40,41,42].

K. Paediatric Malignancies

There are limited studies available regarding the effectiveness of proton radiation therapy in the treatment of various paediatric malignancies. In a retrospective study by Mcallister et al [1997], there is no strong proof that proton therapy is effective for the treatment of paediatric cranial tumours. However, this study was also methodologically poor[43].

Another prospective study by Yock T [2005] found that in the treatment of orbital rhabdomyosarcoma, proton therapy is superior to 3D conformal photon radiation therapy[44].

A comparative treatment planning study found that protons are most optimal in treating retinoblastomas, medulloblastomas and pelvic sarcomas in children when compared to 3-dimensional conformal radiation therapy, electron therapy or intensity-modulated radiation therapy[46]. However, this result would be more justified if done on real-time patients.

4.3 Cost-effectiveness

There is limited evidence available regarding the cost or cost-effectiveness of proton radiation therapy in the treatment of cancers. Goitein M [2003] reported that sophisticated proton therapy is more expensive than sophisticated x-ray radiation therapy; the ratio of cost is about 2.4:1. However, it could come down in the next 5 to 10 years by 2.1 or even 1.7 [51].

In a hypothetical cohort study to assess the cost effectiveness of proton therapy in the treatment of 55 year old women with breast cancer, it was found that a cost per QALY

gained of €67,000 for the base case analysis of an average breast cancer patient. This study also found that proton therapy for breast cancer can be cost-effective if appropriate risk groups are chosen as targets for the therapy[52].

The Proton therapy Working Party reported that in the year 2000 the treatment costs at Boston are likely to be approximately $60–70 000. Patients from United Kingdom who have been referred for proton therapy to the Orsay cyclotron, situated at the Southeast periphery of Paris had to bear a cost of approximately FFr240 000, excluding hostel accommodation[11].

4.4 ORGANISATION

Technology Development

NanoLife Holdings (NanoLife) which was established in February of 1999 is a nanotechnology company that owns several proprietary of proton radiation and antiproton technologies. NanoLife Sciences was formed in June 2004 by NanoLife Holdings to develop its cancer treatment strategy[53].

Currently, NanoLife is focusing on the research and development of the antiproton cancer surgery (ACS). Anti-protons are negatively charged protons that are produced in a special purpose particle accelerator complex. Antiprotons are considered superior to proton therapy because it increases cell lethality in a tumor by several multiples than what can be delivered with protons and with the same sub-millimeter level of precision. This means a tumor can be terminated by far fewer visits and with a less collateral damage and fewer side effects[53].

At present, there are no proton therapy centers that can be converted into antiproton systems. NanoLife has entered into a Cooperative Research and Development Agreement (CRADA) with the Brookhaven National Laboratory (Brookhaven), assisted by Bechtel, and Advanced Energy Systems (AES) to develop a proprietary design to manufacture a proton therapy system that can be converted to antiprotons. NanoLife has selected Ion Beam Applications as the projected exclusive manufacturer of this proton-to-antiproton system[53].

NanoLife is currently planning to develop a worldwide network of proton therapy centers (12 in North America and 12 additional centers in Asia) that are convertible to anti-protons. These centers will be linked by an international marketing and cancer awareness organization. NanoLife projected that ACS will be available to the public within 6 to 8 years[53].

5.0 CONCLUSION

5.1 Safety

There is fair evidence to indicate that proton radiation therapy is safe for the treatment of most cancers discussed in this report, including paediatric malignancies.

5.2 Effectiveness

i. There is good evidence to support the use of proton radiation therapy for the following conditions:
- ocular (uveal) melanoma

ii. There is fair evidence to support the use of proton radiation therapy for the following conditions:
- skull base chordomas and chondrosarcomas
- intracranial tumours, particularly benign meningioma and pituitary adenoma
- lung cancer, particularly the small non-cell carcinoma
- prostate cancer
- acoustic neuroma

iii. There is poor evidence to support the use of proton radiation therapy for the following conditions:
- liver cancer
- gastrointestinal cancers
- paediatric malignancies

iv. There is no evidence to support the use of proton radiation therapy for the following condition:
- paranasal sinus, nasal and nasopharyngeal tumors

5.3 Cost-effectiveness

There is insufficient evidence to conclude whether proton radiation therapy is cost-effective in the treatment of cancers.

6.0 APPENDIX

LEVELS OF EVIDENCE SCALE

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Fair	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT (CAHTA), SPAIN

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8.0 EVIDENCE TABLE

No	Author, title, Journal, Year, Volume, Page Number	Study Design, Sample Size, Follow up	Outcomes & Characteristics	Grade	Comment
Effectiveness					
Ocular (Uveal) Melanoma					
	Proton therapy. CEDIT Report (in French) No.o1.10/ Ra1/01/ Recommendation 01.10/Re-1/ 02. INAHTA briefs issue 2003/19 CEDIT, Committee for Evaluation and Diffusion of Innovative Technologies	Systematic review of 3 databases- MEDLINE, EMBASE, Pascal	CEDIT acknowledges the effectiveness of proton therapy in melanomas of the eye and skull-base chordomas and chondrosarcomas. However, the role of this form of treatment in comparison with radio surgery remains uncertain. CEDIT proposed a fundamental reorganization, perhaps creating a new centre with its administration being more national in character to maintain performance and patient growth level.	Good	Abstract
	Bertil Damato, Andrzej Kacperek, Mona Chopra. Proton Beam Radiotherapy Of Choroidal Melanoma: The Liverpool-Clatterbridge Experience. Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 5, Pp. 1405–1411, 2005	Retrospective, non-randomized study. 349 patients. Between January 1993 and December 2003. Outcomes measured were local tumor recurrence; ocular conservation; vision; and metastatic death according to age, gender, eye, visual acuity,location of anterior and posterior tumor margins, quadrant, longest basal tumor dimension, tumor height, extraocular extension, and retinal invasion.	5-year actuarial rates were 3.5% for local tumor recurrence, 9.4% for enucleation, 79.1% for conservation of vision of counting fingers or better, 61.1% for conservation of vision of 20/200 or better, 44.8% for conservation of vision of 20/40 or better, and 10.0% for death from metastasis. Conclusion: Proton beam radiotherapy with a 62 MeV cyclotron achieves high rates of local tumor control and ocular conservation, with visual outcome depending on tumor size and location.		Methodology of this study was clearly described. Appropriate statistical analysis were done to verify the results.

	Efthymia K. Tsina, Anne Marie Lane, David N. Zacks. Treatment of Metastatic Tumors of the Choroid with Proton Beam Irradiation. Ophthalmology 2005;112:337–343	Non-comparative case series. A retrospective chart review was performed on a series of 63 patients (76 eyes) with Choroidal metastases treated with proton beam therapy between December 1989 and September 2000.	Eighty-four percent of treated tumors regressed completely within 5 months of treatment, and none of these recurred. Retinal detachment resolved in 82% of patients within 3.8 months after treatment, and visual acuity was preserved or improved in 47% of the patients. Proton beam irradiation is a useful therapeutic approach for choroidal metastases; it allows retention of the globe, achieves a high probability of local tumor control, and helps to avoid pain and visual loss.		
	Emmanuel Egger, Leonidas Zografos, Ann Schalenbourg et al. Eye Retention After Proton Beam Radiotherapy For Uveal Melanoma. Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 4, Pp. 867–880, 2003	Prospective, non-comparative, interventional, consecutive case series. A total of 2645 patients (2648 eyes) with uveal melanoma were treated between 1984 and 1999 with proton beam radiotherapy. Data were analyzed as of February 2001. Patients' age ranged from 9 to 90 years, 1284 were men, and 1361 were women. Largest tumor diameter ranged from 4 to 27.5 mm, and tumor height from 0.9 to 15.6 mm. Median follow-up time was 44 months.	-The overall eye retention rate at 5, 10, and 15 years after treatment was 88.9%, 86.2%, and 83.7%, respectively. -In total, 218 eyes had to be enucleated. -After optimization of the treatment technique, the eye retention rate at 5 years was increased from 97.1% to 100% for small tumors, from 86.7% to 99.7% for medium, and from 71.1% to 89.5% for large tumors. Conclusions: The treatment technique as used today results in excellent eye retention rates, even in less favorable cases such as large tumors and tumors located close to the optic disc. The experience and a continuous quality control program allowed the authors to improve the 5-year eye retention rate for all tumor sizes. These findings demonstrate the positive impact of experience and quality control–based efforts for treatment technique optimization.		
	Adel Courdi, Jean-Pierre Caujolle, Jean-Daniel Grange et al. Results Of Proton Therapy Of Uveal Melanomas Treated In Nice. Int. J. Radiation Oncology Biol. Phys., Vol. 45, No. 1, pp. 5–11, 1999	538 patients treated with the Medicyc Cyclotron proton beam facility in Nice	The cause-specific survival (CSS), was 77.4% at 78 months, the overall survival was 73.8% and the local control was 89.0%. The CSS was not influenced by the patient age or the site of the tumor. It was 81.5% for T1 and T2 tumors, versus 75% for T3 and T4 tumors (*P* 5 0.035). Conclusion: The outcome of patients suffering from uveal melanoma and treated with high-energy protons compares favorably with other techniques of treatment.		

	Matthew W. Wilson, John L. Hungerford. Comparison of Episcleral Plaque and Proton Beam Radiation Therapy for the Treatment of Choroidal Melanoma. Ophthalmology August 1999; 106 (8):1579-1588	A retrospective, nonrandomized comparative study. Compared the efficacy of iodine-125 and ruthenium-106 episcleral plaque radiation therapy and proton beam radiation therapy (PBRT) in the treatment of choroidal melanoma. A total of 597 patients were identified (^{125}I = 190, ^{106}Ru = 140, PBRT = 267)	Patients treated with106Ru had a significantly greater risk of local tumor recurrence than did patients treated with either ^{125}I (*P* =0.0133; confidence interval [CI], 1.26–7.02; risk ratio, 2.97) or PBRT (*P* = 0.0097; CI, 1.30–6.66; risk ratio, 2.94). A stepwise Cox proportional hazard model found maximal basal diameter to be a significant covariate (*P* = 0.0033). Conclusion: Patients treated with ^{106}Ru had a significantly greater risk of local tumor recurrence than did those patients treated with either ^{125}I or PBRT.	Fair	Disparities in total apical radiation dose, significant differences in dose rates, lack of standardization of treatment margins, and no uniform definition of what in fact constitutes continued tumor growth or regrowth.
Cancer Of The Skull Base And Spine					
	Proton therapy. CEDIT Report (in French) No.o1.10/ Ra1/01/ Recommendation 01.10/Re-1/ 02. INAHTA briefs issue 2003/19. CEDIT, Committee for Evaluation and Diffusion of Innovative Technologies	Systematic review of 3 databases- MEDLINE, EMBASE, Pascal	CEDIT acknowledges the effectiveness of proton therapy in melanomas of the eye and skull-base chordomas and chondrosarcomas.		
	Georges No¨El, Jean-Louis Habrand, Hamid Mammar et al. Combination Of Photon And Proton Radiation Therapy For Chordomas And Chondrosarcomas Of The Skull Base: The Centre De Protonthe´ Rapie D'orsay Experience. Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 2, Pp. 392–398, 2001	Prospective (non-randomized) study. 44 consecutive patients treated with fractionated photon and proton radiation for a chordoma or chondrosarcoma of the skull base. Mean follow-up of 30.5 months (range: 2–56)	-The 3-year local control rates for chordomas and chondrosarcomas were 83.1% and 90%, respectively, and 3-year overall survival rates were 91% and 90%, respectively. -Eight patients (18%) failed locally (7 within the clinical tumor volume and 1 unknown). -Four patients died of tumor and 2 others of intercurrent disease. -In univariate analysis, young age at time of radiotherapy influenced local control positively ($p < 0.03$), but not in multivariate analysis. -Only 2 patients presented Grade 3 or 4 complications. Conclusion: In skull-base chordomas and chondrosarcomas, the combination of photons with a proton boost of one-third the total dose offers an excellent chance of cure at the price of an acceptable toxicity.	Fair	These results should be confirmed with a longer follow-up

	Damien C. Weber, Alexei V. Trofimov et al. A Treatment Planning Comparison Of Intensity Modulated Photon And Proton Therapy For Paraspinal Sarcomas. Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 5, Pp. 1596–1606, 2004	Comparative treatment planning study between intensity modulated (IM) photon therapy and IM proton therapy (IMPT) in paraspinal sarcomas. Plans for 5 patients were computed for IM photons (7 coplanar fields) and protons (3 coplanar beams)	-Gross tumor volume coverage was optimal and equally homogeneous with both IM photon and IM proton plans. – -Compared to the IM photon plans, the use of IM proton beam therapy leads to a substantial reduction of the organ at risk (OAR) total integral dose in the low-level to mid-dose level. -Median heart, lung, kidney, stomach, and liver mean dose and dose at the 50% volume level were consistently reduced by a factor of 1.3 to 25. Conclusion: The use of IM photon therapy, when compared to IM protons, can result in similar levels of tumor conformation. IM proton therapy, however, reduces the OAR integral dose substantially, compared to IM photon radiation therapy. As a result, tumor dose escalation was always possible with IM proton planning, within the maximal OAR dose constraints.	Fair.	
	Hiroshi Igaki, Koichi Tokuuye, Toshiyuki Okumura et al. Clinical Results Of Proton Beam Therapy For Skull Base Chordoma. Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 4, pp. 1120–1126, 2004	Retrospective study. 13 patients with skull base chordoma who were treated with proton beams with or without X-rays at the University of Tsukuba between 1989 and 2000 were reviewed.	-The 5-year local control rate was 46.0%. -Cause-specific, overall, and disease-free survival rates at 5 years were 72.2%, 66.7%, and 42.2%, respectively. -The local control rate was higher, without statistical significance, for those with preoperative tumors <30 mL. Partial or subtotal tumor removal did not yield better local control rates than for patients who underwent biopsy only as the latest surgery. Conclusion: Proton beam therapy is effective for patients with skull base chordoma, especially for those with small tumors. For a patient with a tumor of <30 mL with no prior treatment, biopsy without tumor removal seems to be appropriate before proton beam therapy.	Fair	

	The Proton Therapy Working Party. Proton Therapy for Base of Skull Chordoma: A Report for the Royal College of Radiologists. Clinical Oncology (2000)12:75–79	Review article	Outcome after proton irradiation is superior to that reported for conventional photon irradiation. Radiotherapy schedules involving a mixed schedule of protons and photons have achieved an approximately 60% local control rate at 5 years. Proton therapy has the potential for improved dose distribution compared with conformal photon radiotherapy.	Fair	The report did not explain whether it is a systematic or a narrative review.
	Damien C. Weberhans Peter Rutz, Eros S. Pedroni et al. Results Of Spot-Scanning Proton Radiation Therapy For Chordoma And Chondrosarcoma Of The Skull Base: The Paul Scherrer Institut Experience. Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 2, pp. 401–409, 2005	Prospective study. Between October 1998 and October 2003, 29 patients (median age, 39 years) with chordomas (n= 18) and CS (n= 11) were treated at the Paul Scherrer Institut (PSI) with protons. Tumor conformal application of proton beams was realized by spot scanning technology.	-Actuarial 3-year local control rates were 87.5% and 100% for chordoma and CS, respectively. -No regional failure or distant metastasis was observed. -At 3 years, actuarial PFS and OS for the entire cohort was 90% and 93.8%, respectively. -Actuarial 3-year complication-free survival was 82.2%. Conclusion: Spot-scanning PT offers high tumor control rates of skull base chordoma and CS. These results compare favorably to other combined proton-photon or carbon ion irradiation series.		
	Stereotactic Proton Beam Therapy Of Skull Base Meningiomas. Frederik J. Vernimmen, Jill K. Harris, Jennifer A. Wilson et al. Int. J. Radiation Oncology Biol. Phys., Vol. 49, No. 1, pp. 99–105, 2001	Prospective study. 27 patients with intracranial meningiomas: 18 patients underwent proton hypofractionated stereotactic radiotherapy (HSRT, 3 fractions), 5 patients were treated with stereotactic radiotherapy (SRT, 16 or more fractions).	-In the HSRT group, 16/18 (89%) of patients remained clinically stable or improved, while 2/18 (11%) deteriorated. -Radiologic control was achieved in 88% of patients, while 2 patients had a marginal failure. -Among the 5 SRT patients, 2 were clinically better, and 3 remained stable. -All SRT patients achieved radiologic control. Conclusion: Proton irradiation is effective and safe in controlling large and complex-shaped skull base meningiomas.	Fair	Inclusion criteria were explained. Patient character, methodology, follow up on treatment were described well. Kaplan-Meier analysis was done to justify the results.
Intracranial tumour					
	Evelyn Wenkel, Allan F. Thornton, Dianne Finkelstein, Judy Adams. Benign Meningioma: Partially Resected, Biopsied, And Recurrent Intracranial Tumors Treated With Combined Proton And Photon Radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol. 48, No. 5, pp. 1363–1370, 2000	Retrospective cross sectional study. 46 patients with partially resected, biopsied, or recurrent meningiomas (median age of 50 years; range 11–74 years) were treated with combined photon and 160-MeV proton beam therapy	Overall survival at 5 and 10 years was 93 and 77%, respectively, and the recurrence-free rate at 5 and 10 years was 100% and 88%, respectively. Survival without severe toxicity was 80% at 5 and 10 years. Three patients presented with local tumor recurrence at 61, 95, and 125 months Conclusion: Combined proton and photon radiotherapy is an effective treatment for patients with recurrent or incompletely resected benign intracranial meningiomas.	Fair	

	Georges Noël, Marc A. Bollet, Valentin Calugaru et al. Functional Outcome Of Patients With Benign Meningioma Treated By 3d Conformal Irradiation With A Combination Of Photons And Protons. Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 5, Pp. 1412–1422, 2005	Non-randomized prospective study. Evaluated efficacy and tolerance of external fractionated combination of photon and proton radiation therapy (RT) for intracranial benign meningiomas. Between 1994 and 2002, 51 patients with intracranial meningiomas of the base of the skull were treated with a combination of photon and proton RT. Mean follow-up was 25.4 months.	-Out of the 108 eye-related symptoms, 106 (96%) were evaluated. – -Improvements were reported in 54 cases (67%). -Median time to improvement ranged from 1 to 24 months after completion of the radiotherapy, depending on the symptom. -No worsening of primary clinical signs. -Four-year local control and overall survival rates were, respectively, 98% and 100%. -Stabilization of the tumor was observed in 38 cases (72%), volume reduction in 10 cases (20%), and intratumor necrosis in 3 cases. Conclusion: These results stressed the clinical efficacy of fractionated-associated photon-proton RT in the treatment of meningiomas, especially on cranial nerve palsies, without severe toxicity in almost all patients.	Fair	
	Damien C. Webera, Antony J. Lomaxa, Hans Peter Rutz et al. Spot-scanning proton radiation therapy for recurrent, residual or untreated intracranial meningiomas. Radiotherapy and Oncology 71 (2004) 251–258	Sixteen patients with intracranial meningioma were treated with PRT between July 1997 and July 2002. Eight patients had skull base lesions. Thirteen patients received PRT after surgery either as adjuvant therapy for incomplete resection (eight patients) or for recurrence (five patients). The median follow-up time was 34.1 months (range, 6.5–67.8).	-Cumulative 3-year local control, progression-free survival and overall survival were 91.7, 91.7 and 92.7%, respectively. -Cumulative 3-year toxicity free survival was 76.2%. -One patient presented with radiation induced optic neuropathy (SOMA Grade 3) and retinopathy (SOMA Grade 2) 8.8 and 30.4 months after treatment, respectively. These patients with ophthalmologic toxicity received doses higher than those allowed for the optic/ocular structures. Another patient developed a symptomatic brain necrosis (CTCAE Grade 4) 7.2 months after treatment. No radiation-induced hypothalamic/pituitary dysfunction was observed. Conclusions: Spot-scanning PRT is an effective treatment for patient with untreated, recurrent or incompletely resected intracranial meningiomas. It offers highly conformal irradiation for complex-shaped intracranial meningiomas, while delivering minimal non-target dose. Observed ophthalmologic toxicity is dose-related.		

	Alessandra Bolsia, Antonella Fogliata, Luca Cozzi. Radiotherapy of small intracranial tumours with different advanced techniques using photon and proton beams: a treatment planning study.	Treatment planning study. Plans for five acoustic neurinomas, five meningiomas, and two pituitary adenomas were computed using five different radiation techniques- 3D conformal radiotherapy (3DCRT), stereotactic arc therapy (SRS/T), intensity modulated radiotherapy with photons (IMRT), and radiotherapy with protons (spot scanning (SSp) or passive scattering (PSp).	-Proton techniques were shown to be superior to all photon approaches for the irradiation of small brain lesions in terms of target dose uniformity and conformity and in terms of sparing organs at risk (OARs). -No major differences were observed between the results of the photon techniques, which were generally good for target coverage. -Maximum brain stem irradiation ranged from 60% with IMRT to 26% with protons and the conformity index from 4.4 with IMRT to 2.5 with protons. Considering the rather long life expectancy of the patients suffering from meningiomas, neurinomas, and pituitary adenomas, toxicity and the possibility of secondary tumour induction, proton irradiation should be the irradiation technique of choice, when available. If not, IMRT, or even 3DCRT, techniques can provide an acceptable compromise.		
	Brian B. Ronson , Reinhard W. Schulte, Khanh P. Han et al. Fractionated proton beam irradiation of pituitary adenomas. International Journal of Radiation Oncology*Biology*Physics Volume 64, Issue 2 , 1 February 2006, Pages 425-434	Forty-seven patients with pituitary adenomas treated with protons, who had at least 6 months of follow-up, were included in this analysis. Forty-two patients underwent a prior surgical resection; 5 were treated with primary radiation	-Tumor stabilization occurred in all 41 patients available for follow-up imaging; 10 patients had no residual tumor, and 3 had greater than 50% reduction in tumor size. -17 patients with functional adenomas had normalized or decreased hormone levels; progression occurred in 3 patients. -6 patients have died; 2 deaths were attributed to functional progression. -Complications included temporal lobe necrosis in 1 patient, new significant visual deficits in 3 patients, and incident hypopituitarism in 11 patients. Coclusion: Fractionated conformal proton-beam irradiation achieved effective radiologic, endocrinological, and symptomatic control of pituitary adenomas. Significant morbidity was uncommon, with the exception of postradiation hypopituitarism, which we attribute in part to concomitant risk factors for hypopituitarism present in our patient population.		

Lung Cancer					
	C H M Lee, D Tait, A E Hanum, S Webb. Comparison of proton therapy and conformal x-ray therapy in non-small cell lung cancer (NSCLC). The British Journal of Radiology, 72 (1999): 1078-1084.	Study compares performance of one proton and four conformal x-ray planning techniques in treating NSCLC. 13 patients.	-proton therapy is capable to deliver an escalated high dose to target volume in NSCLC whilst maintaining the normal tissue doses within tolerance. -without dose escalation, the performance of x-ray therapy and proton therapy does not differ much.	Poor	-The abstract is not comprehensive and misleading. -Study type not mentioned. -no comparison between subjects -no statistical analysis to verify the results
	Bush D A et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. American College of Chest Physicians.	Prospective phase 2 trial. To determine the efficacy and toxicity of high-dose hypofractionated proton beam therapy. 68 patients, medically inoperable or refused surgery	-3 year local control and disease-specific survival rates were74% and 72% respectively. -significant improvement in local tumor control in T1 vs. T2 (87% vs. 49%) with a trend toward improved survival.		Abstract
	Yoshiyuki Shioyama, Koichi Tokuuye, Toshiyuki Okumura et al. Clinical Evaluation Of Proton Radiotherapy For Non–Small-Cell Lung Cancer. Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 1, Pp. 7–13, 2003	Non- randomized prospective study. Between 1983 and 2000, 51 NSCLC patients were treated with proton beams at the University of Tsukuba. There were 28 patients in Stage I, 9 in Stage II, 8 in Stage III, 1 in Stage IV, and 5 with recurrent disease.	-The 5-year overall survival rate was 29% for all patients, 70% for 9 Stage IA patients, and 16% for 19 Stage IB patients, respectively (IA vs. IB: $p < 0.05$). -The 5-year in-field local control rate was higher in patients with Stage IA (89%) when compared with those with Stage IB (39%). Conclusion: Proton therapy is a very safe and effective treatment for patients with NSCLC, especially for those with early stages. The relative merit of proton therapy in comparison with stereotactic photon radiotherapy or three-dimensional conformal photon radiotherapy remains to be defined through future clinical trials.		

	Keiji Nihei M.D., Takashi Ogino, Satoshi Ishikura and Hideki Nishimura. High-dose proton beam therapy for Stage I non–small-cell lung cancer. Presented at the 41st Annual Meeting of the American Society of Clinical Oncology, Orlando, Florida, May 13–17, 2005.	Between 1999 and 2003, 37 patients were treated in Radiation Oncology Division, National Cancer Center Hospital East, Kashiwa, Chiba, Japan The indications for PBT were pathologically proven NSCLC, clinical Stage I, tumor size ≤5 cm, medically inoperable or refusal of surgery, and written informed consent.	-With a median follow-up period of 24 months, the 2-year local progression-free and overall survival rates were 80% and 84%, respectively. -The 2-year loco-regional relapse-free survival rates in Stage IA and Stage IB were 79% and 60%, respectively. Conclusions: Proton beam therapy is a promising treatment modality for Stage I NSCLC, though loco-regional relapse and late pulmonary toxicities in Stage IB patients were substantial. Further investigation of PBT for Stage I NSCLC is warranted.		
Prostate Cancer					
	Jerry D. Slater, Carl J. Rossi, Jr, Leslie T. Yonemoto Et Al. Conformal Proton Therapy For Early-Stage Prostate Cancer. Urology *53 (5), 1999*	Non-randomized prospective study. 319 patients with T1-T2b prostate cancer and initial prostate-specific antigen (PSA) levels 15.0 ng/mL or less received conformal radiation doses of 74 to 75 cobalt gray equivalent with protons alone or combined with photons.	Overall 5-year clinical and biochemical disease-free survival rates were 97% and 88%, respectively. **Conclusions.** It appears that patients treated with conformal protons have 5-year biochemical disease-free survival rates comparable to those who undergo radical prostatectomy, and display no significant toxicity.	Fair	
	C. .J. Rossi. Jr., J. D. Slater, J. M. Slater. Proton beam therapy of prostate cancer-report of long- term PSA-based outcomes in over twelve hundred patients. Loma Linda Universivity Med. Centre, Loma Linda, CA. Proceedings of the 42nd Annual ASTRO Meeting	The median follow up is forty-two months (range l-l 15 months).	-Overall seven year actuarial Biochemical Disease-Free Survival (BNED) was 79%. -BNED survival was strongly influenced by pretreatment PSA levels. -PSA nadir also correlated with BNED survival. -Treatment was extremely well tolerated with a 0.3% incidence of RTOG > Grade 3 late complications. -BNED survival rates compare favorably with other modalities (surgery, 3-D CRT), while treatment-related morbidity is less than that which has been reported in large conformal x-ray therapy series **Conclusions:** Long-term follow up continues to demonstrate the safety and efficacy of conformal proton beam radiotherapy of prostate cancer.		Abstract only

	Laura Cella, Antony Lomax & Raymond Miralbell. Potential Role Of Intensity Modulated Proton Beams In Prostate Cancer Radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol. 49, No. 1, Pp. 217–223, 2001	Four treatment plans were compared in a prostate cancer patient aiming to deliver 81 Gy to the target: 1) conformal 18 MV X-rays, 6-fields; 2) 214 MeV protons, 2-fields; 3) IM 15 MV X-rays, 5-fields; and 4) 177–200 Mev IM protons, 5-fields as in Plan 3.	-Both IM X-ray and proton beams were able to optimize the dose distribution and comply with the goal of delivering the highest dose to the target while reducing the risk of severe morbidity to acceptable levels. -The main advantage compared to IM X-rays was that IM protons succeeded in significantly reducing the low-to-medium dose to the non-target tissues and achieved a small improvement in planning target volume (PTV) dose heterogeneity.	Fair	
	Jerry D. Slater, Carl J. Rossi, Jr., Les T. Yonemoto et al. Proton Therapy For Prostate Cancer: The Initial Loma Linda University Experience.Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 2, Pp. 348–352, 2004	Prospective study. Results of conformal proton radiation therapy for localized prostate cancer for 1255 patients treated between October 1991 and December 1997. Outcomes were measured on primarily in terms of biochemical relapse and toxicity.	-The overall biochemical disease-free survival rate was 73%, and was 90% in patients with initial PSA <4.0; it was 87%, in patients with post-treatment PSA nadirs <0.50. -Long-term survival outcomes were comparable with those reported for other modalities intended for cure. Conclusions: Conformal proton radiation therapy at the reported dose levels yielded disease-free survival rates comparable with other forms of local therapy, and with minimal morbidity.	Fair	Patient inclusion criteria were described, but no exclusion criteria mentioned. The explanation regarding treatment planning was explained in detail.
	Jerry D. Slater, Les T. Yonemoto, Carl J. Rossi, Jr. et al. Conformal Proton Therapy For Prostate Carcinoma. Int. J. Radiation Oncology Biol. Phys., Vol. 42, No. 2, Pp. 299–304, 1998	Non-randomized prospective study. 643 patients with localized prostate cancer were treated with protons, with or without photons.	-The overall clinical disease-free survival rate was 89% at 5 years. -When post-treatment prostate-specific antigen (PSA) was used as an endpoint for disease control, the 4.5-year disease-free survival rate was 100% for patients with an initial PSA of < 4.0 ng/ml, and 89%, 72%, and 53% for patients with initial PSA levels of 4.1–10.0, 10.1–20.0, and > 20.0, respectively. Conclusion: Proton therapy to 74–75 CGE produced minimal treatment-related toxicity and excellent PSA normalization and disease-free survival in patients with low initial PSA levels.	Fair	Good explanation of methodology, patient characteristics, use of statistical analysis to verify the results.

Liver Cancer					
	Hata M et. Al. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. Cancer, 2005; 104(4): 794-801	Retrospective study 12 patients with HCC with PVTT(clinical T3- T4N0M0), age 42-80 years. Total dose 50-72 Gy in 10-22 fractions given.	- All tumors treated with proton beam therapy remained controlled at median follow up of 2.3 years (0.3- 7.3 years) - 10 of 12 patients had new liver tumors outside the irradiated volume 0.1-2.4 years after proton beam therapy, and 3 patients had distant metastases. 8 died of disease, 2 salvaged by further therapies. - The remaining 2 patients were alive, no evidence of disease 4.3 years and 6.4 years. Progression-free survival rates were 67% at 2 years, 24% at 5 years. Conclusion: proton beam therapy for patients with HCC who had PVTT was feasible and effective. It appeared to significantly improve survival and local control of the tumor.	Poor	Abstract
	Takeshi Gohongi et al. Concurrent proton beam therapy and systemic chemotherapy for metastatic liver tumor of gastric carcinoma: a case report. Jpn J Clin Oncol 2005: 35(1) :40-44	Case report. 76 year old woman with a metastatic liver tumor from gastric carcinoma.	Concurrent proton beam therapy and systemic chemotherapy was given. The tumor disappeared 3 months after the treatment and no recurrence detected for 2 years after termination of the treatment. This treatment was well tolerated. Liver failure related to proton irradiation has not been observed.	Poor.	Abstract. The result could have been due to other confounding effect i.e. systemic chemotherapy
	Hillebrand Donald J et al. Local control of hepatocellular carcinoma with proton beam therapy followed by curative liver transplantation. AJG; Vol. 95, No. 9, 2000	Case report. A 54 years old male with HCC Stage III (T3N0M0). Proton beam therapy was performed with 63 Gy delivered to the radiographic extent of the tumor and a surrounding 1.0 –2.0 cm of non-cancerous liver (15 daily 4.2 Gy sessions).	Proton beam therapy of a large localized hepatocellular carcinoma in the setting of advanced decompensated cirrhosis was well tolerated and achieved local tumor control maintained over the 9 months on the UNOS waiting list. Curative liver transplantation was then performed in this patient without adjuvant chemotherapy which may accelerate recurrent post-transplant vital hepatitis. This is the first report of the curative combination of proton beam therapy and liver transplantation for hepatocellular carcinoma.	Poor	Abstract
	Tanaka N, Matsuzakki Y, Chuganji Y et al. Proton irradiation for hepatocellular carcinoma {letter}. Lancet 1992; 340(8831): 1358	11 HCC patients with pre-existing cirrhosis. 5 patients received proton irradiation alone, 6 patients received chemotherapy plus proton beam therapy.	Tumor size was reduced in 80% in proton therapy alone group, 71% in combination group. Complete tumor control could be sustained in all cases for at least 1 year.	Poor	Abstract

	Takayuki Hashimoto, Koichi Tokuuye, Nobuyoshi Fukumitsu et al. Repeated proton beam therapy for hepatocellular carcinoma. Presented in part at Forty Seventh Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), October 16–20, 2005, Denver, CO.	Retrospective study. From June 1989 through July 2000, 225 patients with HCC underwent their first course of proton beam therapy at the University of Tsukuba. Of them, 27 with 68 lesions who had undergone two or more courses were retrospectively reviewed in this study. Median interval between the first and second course was 24.5 months (range 3.3–79.8 months).	The 5-year survival rate and median survival period from the beginning of the first course for the 27 patients were 55.6% and 62.2 months, respectively. Five-year local control rate for the 68 lesions was 87.8%. Of the patients, 1 with Child-Pugh class B and another with class C before the last course suffered from acute hepatic failure. Repeated proton beam therapy for HCC is safe when the patient has a target in the peripheral region of the liver and liver function is Child-Pugh class A.		
Gastrointestinal Tumors					
	Ulf Isacsson, Bo Lennern¨As, Erik Grusell et al. Comparative Treatment Planning Between Proton And X-Ray Therapy In Esophageal Cancer. Int. J. Radiation Oncology Biol. Phys., Vol. 41, No. 2, Pp. 441–450, 1998	Conformal treatment planning with megavoltage x-rays and protons for five patients with esophageal cancer. For each of the five patients, two different proton plans, one x-ray plan, and one mixed plan with x-rays and protons were made. A three-dimensional treatment planning system, TMSy, was used.	-The comparison shows advantages of using protons instead of x-rays for all five patients. The dose limiting organs at risk are the spinal cord, the lungs, and the heart, but the proton plans also spare the kidneys better than the x-ray plan does. -At 5% normal tissue complication (NTCP) in any risk organ, the calculated mean tumour control probability (TCP) value for the five patients is increased by an average of 20%-units (from 2 to 23%-units) with the best proton plan compared with x-rays only. Conclusions: Protons appear to have clear therapeutic advantages over conventional external radiotherapy when treating esophageal carcinoma.		

	S. Sugahara, K. Tokuuye, A. Nakahara et al. Clinical Results of Proton Beam Therapy for Esophageal Cancer at the University of Tsukuba. I. J. Radiation Oncology – Biology- Physics. 2005; 63(2): Proceedings of the 47th Annual ASTRO Meeting	65 esophageal cancer patients who were irradiated with protons with or without x-rays between 1985 and 2003 were reviewed. Of the 65 patients, 32 had T1 tumors and 33 T2/3/4. 10 patients received combined irradiation with x-rays and protons using accelerated fractionation. 41 patients received combined irradiation with x-rays and protons using conventional fractionation.	-57 (88%) patients showed complete response within 4 months after completion of treatment. -The overall 5-year actuarial survival rates for all 65 patients, the 32 with clinical T1, and the 33 with clinical T2/3/4 were 34%, 50%, and 18%, respectively. -The corresponding 5-year cause-specific survival rates were 65%, 87%, and 39%, respectively. -The 5-year local control rates for all 65 patients, the 32 with T1, and the 33 with T2/3/4 were 59%, 83%, and 35%, respectively. -The 5-year local control rates for 10 patients irradiated using accelerated fractionation and 55 irradiated using conventional fractionation were 77% and 56%, respectively. **Conclusions:** The results suggest that proton radiation therapy is an effective modality for patients with locally confined esophageal cancer. Local control rate for patients irradiated with accelerated fractionation might be better than that for those irradiated with conventional fractionation.		No statistical analysis done for any of the results.
	Diana C. Hsiung-Stripp, James McDonough et al. Comparative Treatment Planning Between Proton And X-Ray Therapy In Pancreatic Cancer. Medical Dosimetry, Vol. 26, No. 3, Pp. 255–259, 2001	Treatment comparative study. Compared proton therapy to conventional 3-dimensional conformal radiation, by minimizing the dose to normal tissues. Model: 4 patients with unresectable pancreatic adenocarcinoma.	With the clinical target volume (CTV) and gross target volume (GTV) receiving the same dose from the proton and photon plans, all individual proton plans were superior to the photon plans in reduction of normal tissue dose. For the 4 patients, the average dose reduction to 50% of the organ at risk was 78% to spinal cord ($p < 0.003$), 73% to left kidney ($p < 0.025$), 43% to right kidney ($p < 0.059$), and 55% to liver ($p < 0.061$). These comparative treatment plans show proton therapy results in significant reductions of dose to normal tissue compared to conventional photons while treating the same target volumes. This allows for the design of dose-escalation protocols using protons in combination with new biologic therapies and chemotherapy.	Fair	

	Hata M et al. Proton beam therapy for invasive bladder cancer: A prospective study of bladder-preserving therapy with combined radiotherapy and intra-arterial chemotherapy. International Journal of Radiation Oncology *Biology*Physics 2006; 64(5): 1371-1379	Cross-sectional study. 25 patients with transitional cell carcinoma of the urinary bladder, cT2-3N0M0, underwent transurethral resection of bladder tumor(s), followed by pelvic X-ray irradiation combined with intra-arterial chemotherapy. Then patients were evaluated by transurethral resection biopsy. Patients with no residual tumor received proton irradiation boost to the primary sites, whereas patients demonstrating residual tumors underwent radical cystectomy.	Of 25 patients, 23 (92%) were free of residual tumor at the time of re-evaluation; consequently, proton beam therapy was applied. Of the 23 patients treated with proton beam therapy, 9 experienced recurrence at the median follow-up time of 4.8 years: local recurrences and distant metastases in 6 and 2 patients, respectively, and both situations in 1. The 5-year overall, disease-free, and cause-specific survival rates were 60%, 50%, and 80%, respectively. The 5-year local control and bladder-preservation rates were 73% and 96%, respectively, in the patients treated with proton beam therapy.	Fair	Abstract only
	Ulf Isacsson, Anders Montelius, Bo Jung, Bengt Glimelius. Comparative treatment planning between proton and X-ray therapy in locally advanced rectal cancer. Radiotherapy and Oncology 41 (1996) 263-272	Comparative treatment planning study. Comparative dose planning was performed for six patients (2 women and 4 men, median age 60 years, range 47-79) with a primary rectal adenocarcinoma. Three dose plans were made for each patient: one proton plan, one X-ray plan, and one mixed plan with 4 X-ray beams and a boost with 3 proton beams.	-The comparison shows advantages of using protons instead of X-rays for all six patients, but in three of them, the advantage is only marginal. -The dose-limiting organ at risk is the small bowel, but the proton plan and the mixed plan also spare the bladder and the femoral heads better. Conclusions: Proton beam therapy has potential advantages when treating medically inoperable patients with a large rectal cancer over conventional X-ray therapy. Since the benefits are comparatively small, although clinically worthwhile, large randomised studies are needed.	Fair	
Breast Cancer					
	Antony J. LomaxLaura Cella, Damien Weber. Potential Role Of Intensity-Modulated Photons And ProtonsIn The Treatment Of The Breast And Regional Nodes. Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 3, Pp. 785–792, 2003	Comparative treatment planning study. Treatment plans were computed using “standard” photon/ electron, IMRT, and forward-planned proton techniques using CT data from a breast cancer patient	In comparison with the standard plan, IMRT photons have the potential to greatly improve the target dose homogeneity with only a small increase in the doses delivered to the neighboring critical structures. However, when attempting to further reduce doses to the critical structures, substantial loss of target dose homogeneity was found. In conclusion, only the two-field, energy-modulated proton plan had the potential to preserve target dose homogeneity while simultaneously minimizing the dose delivered to lungs, heart, and the contralateral breast	Fair	

	Antonella Fogliataa, Alessandra Bolsia, Luca Cozzia. Critical appraisal of treatment techniques based on conventional photon beams, intensity modulated photon beams and proton beams for therapy of intact breast. Radiotherapy and Oncology 62 (2002) 137–145	Five breast cancer patients with highly concave breast tissue volume around the lung were considered at planning level in order to assess the suitability of different irradiation techniques. Three-dimensional dose distributions for conventional two-field tangential photon treatment, two-field intensity modulated radiotherapy (IMRT), three-field non-IMRT, three-field IMRT, and single-field proton treatment were investigated.	-Planned target volume (PTV) coverage was comparable for non-IMRT and IMRT techniques (EUD from 47.1 to 49.4 Gy), and improved with single-field proton treatment (EUD ¼ 49:8 Gy). -Lung irradiation was reduced, in terms of mean dose, with three-field (9.5 Gy) and proton technique (3.5 Gy), with respect to the conventional two-field treatment (12.9 Gy); also a reduction of the lung volume irradiated at high doses was observed. Better results could be achieved with protons. In addition, cardiac irradiation was also reduced with those techniques.		
Acoustic Neuroma (Vestibular Schwannoma)					
	F.J. Vernimmen, Z. Mohamed, J. Slabbert. Stereotactic Proton Beam Radiotherapy for Acoustic Neuromas. Proceedings of the 47th Annual ASTRO Meeting	A retrospective study evaluating control rate, hearing preservation, facial and trigeminal nerve complications of proton radiotherapy for acoustic neuromas. 35 acoustic neuromas (mean follow up time 68.3 months) were analyzed.	Stereotactic proton beam radiotherapy for predominantly large acoustic neuromas achieves good tumor control with preservation of function in the surrounding cranial nerves. Hearing preservation appears to be worse than in the gamma knife and linac-based radio surgery and radiotherapy series reviewed, but is comparable to other proton series.		Abstract only
	C. J. McAllister, D. A. Bush, L. N. Loredo, J. M. Slater, J. D. Slater. Acoustic neuromas treated with fractionated conformal proton beam irradiation. Loma Linda University Medical Center, Loma Linda, CA. Proceedings of the 47th Annual ASTRO Meeting	Cross-sectional study.31 acoustic neuromas in 30 patients were treated with fractionated proton beam therapy from March 1991 to June 1999. Age: 21-80 years old. 15 males and 14 females. Radiographic follow-up ranges from seven to 98 months with a mean of 34 months.	Fractionated conformal proton beam therapy provides excellent local control for acoustic neuromas. The 42% rate of useful hearing preservation appears similar to published data from stereotactic radio surgery as well as microsurgical series.		Abstract only

	Griffith R. Harsh, Allan F. Thornton, Paul H. Chapman et al. Proton Beam Stereotactic Radiosurgery Of Vestibular Schwannomas. Int. J. Radiation Oncology Biol. Phys., Vol. 54, No. 1, pp. 35–44, 2002	Sixty-eight patients (mean age 67 years) were treated between 1992 and 1998. The mean tumor volume was 2.49 cm3. The prospectively specified follow-up consisted of neurologic evaluation and MRI at 6, 12, 24, and 36 months	-Mean clinical follow-up of 44 months and imaging follow-up of 34 months in 64 patients -35 tumors (54.7%) were smaller and 25 (39.1%) were unchanged (tumor control rate 94%; actuarial control rate 94% at 2 years and 84% at 5 years). -97% of tumors required no additional treatment. -Of 6 patients with functional hearing ipsilaterally, 1 improved, 1 was unchanged, and 4 progressively lost hearing. Conclusion: Proton beam stereotactic radiosurgery of vestibular schwannomas at the doses used in this study controls tumor growth with relatively few complications.		
Paediatric Malignancies					
	Bruce Mcallister, John 0. Archambeau, M. Connie Nguyen. Proton Therapy For Pediatric Cranial Tumors: Preliminary Report On Treatment And Disease-Related Morbidities. Int. J. Radiation Oncology Biol. Phys. Vol. 39, No. 1. Pp. 455-460. 1997	Retrospective study. Cbildren treated with protons at Loma Linda University Medical Center between August 1991 and December 1994 were analyzed. 28 children, aged 1 to 18 years were identified as at risk for brain injury from treatment. -Follow up:7 – 49 months (median 25 months)	-4 instances of treatment related morbidity were identified -41 instances of site-specific, disease-related morbidity were identified: 15 improved or resolved and 26 remained unchanged after treatment. -Four patients had radiographic evidence of local failure.3 of these patients, including two with high-grade glioma, have died. Conclusion: Early treatment-related morbidity associated with proton therapy is low. Tumor progression remains a problem when treating certain histology such as high-grade glioma. Escalating the dose delivered to target volumes may benefit children with tumors associated with poor rates of local control.	Fair	No inclusion or exclusion criteria mentioned. The treatments were also not the same- some received proton only, others received x-rays and proton boost.
	Torunn Yock, Robert Schneider, Alison Friedmann et al. Proton Radiotherapy For Orbital Rhabdomyosarcoma: Clinical Outcome And A Dosimetric Comparison With Photons. Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 4, Pp. 1161–1168, 2005	Prospective study. Conformal 3D photon and proton radiotherapy plans were generated for children treated with proton irradiation for orbital RMS at Massachusetts General Hospital. 7 children were treated for orbital rhabdomyo-sarcoma with proton irradiation and standard chemotherapy. The median follow-up is 6.3 years (range 3.5–9.7 years).	Fractionated proton radiotherapy is superior to 3D conformal photon radiation in the treatment of orbital RMS. Proton therapy maintains excellent tumor coverage while reducing the radiation dose to adjacent normal structures.		

	Marco Krengli, Eugen B. Hug, Judy A. Adams et al. Proton Radiation Therapy For Retinoblastoma: Comparison Of Various Intraocular Tumor Locations And Beam Arrangements. Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 2, pp. 583–593, 2005	Comparative treatment study. To study the optimization of proton beam arrangements for various intraocular tumor locations: posterior– central, nasal, and temporal tumor locations, with straight, intrarotated, or extrarotated eye positions.	Proton therapy achieved homogeneous target coverage with true lens sparing. Doses to orbit structures, including bony growth centers, were minimized with different beam arrangements and eye positions. Proton therapy could reduce the risks of second malignancy and cosmetic and functional sequelae as no appreciable dose was delivered to the contralateral eye, brain tissue, or pituitary gland.	Fair.	
	Treatment Planning With Protons For Pediatric Retinoblastoma, Medulloblastoma, And Pelvic Sarcoma: How Do Protons Compare With Other Conformal Techniques? Catherine T. Lee, Stephen D. Bilton, Robin M. Famiglietti et al. Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 2, pp. 362–372, 2005	Treatment planning study. Tumor volumes from 8 patients (3 retinoblastomas, 2 medulloblastomas, and 3pelvic sarcomas) were studied retrospectively to compare DVHs from proton therapy with three-dimensional conformal radiation therapy (3D-CRT), electron therapy, and intensity-modulated radiation therapy (IMRT)	-In retinoblastoma, protons resulted in the best target coverage combined with the most orbital bone sparing (10% was the mean orbital bone volume irradiated at >5 Gy for protons vs. 25% for 3D-CRT electrons, 69% for IMRT, 41% for a single 3D lateral beam, 51% for a 3D anterolateral beam with a lens block, and 65% for a 3D anterolateral beam without a lens block). -In medulloblastoma, for posterior fossa and craniospinal irradiation, protons resulted in the least dose to the cochlea and hypothalamus-pituitary axis -With pelvic sarcoma, protons were superior in eliminating any dose to the ovaries (0% of mean ovarian volume was irradiated at >2 Gy with protons) and to some extent, the pelvic bones and vertebrae. Conclusion: Protons are most optimal in treating retinoblastomas, medulloblastomas (posterior fossa and craniospinal), and pelvic sarcomas in children `when compared with 3D-CRT, electrons, IMRT	Fair.	

Safety					
Ocular (uveal) melanoma					
	Bowyer J et al. Visual complications of proton beam therapy for clival chordoma. Eye 2003;17:318-323	Case report. 4 consecutive patients with clival chordoma were referred for postoperative proton beam therapy.	High complication rate (50%) of delayed radiation optic neuropathy, which resulted in profound bilateral visual loss at 1 and 2 years post-proton beam therapy.		

	Efthymia K. Tsina, Anne Marie Lane, David N. Zacks. Treatment of Metastatic Tumors of the Choroid with Proton Beam Irradiation. Ophthalmology 2005;112:337–343	Non-comparative case series. A retrospective chart review was performed on a series of 63 patients (76 eyes) with Choroidal metastases treated with proton beam therapy between December 1989 and September 2000.	Complications occurred in 56% of cases and included madarosis, keratitis, dry eye syndrome, cataract, neovascular glaucoma, chorioretinal atrophy, radiation papillopathy, and radiation maculopathy. None of the treated eyes required enucleation. Although complications occur in most cases, many of these are minor and are not associated with a change in function. This modality is accurate and efficient,		
	Bertil Damato, Andrzej Kacperek, Mona Chopra Et Al. Proton Beam Radiotherapy Of Iris Melanoma. Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 1, Pp. 109–115, 2005	Between 1993 and 2004, 88 patients with iris melanoma received proton beam radiotherapy, with 53.1 Gy in 4 fractions.	Proton beam radiotherapy of iris melanoma is well tolerated, the main problems being radiation cataract, which was treatable and preexisting glaucoma, which in several patients was difficult to control.		
Cancer of the Skull Base and Spine					
	Riccardo Santoni, Norbert Liebsch, Dianne M. Finkelstein et al. Temporal Lobe (TI) Damage Following Surgery And High-Dose Photon And Proton Irradiation In 96 Patients Affected By Chordomas And Chondrosarcomas Of The Base Of The Skull. Int. J. Radiation Oncology Biol. Phys., Vol. 41, No. 1, pp. 59–68, 1998	96 consecutive patients treated with high-dose proton and photon irradiation at Massachusetts General Hospital (MGH) and Harvard Cyclotron Laboratory (HCL) between June 1984 and 1993, for chordomas and chondrosarcomas of the base of the skull were reviewed.	Of the patients, 10 developed TL damage, with bilateral injury in 2 and unilateral injury in 8. The cumulative TL damage incidence at 2 and 5 years was 7.6 and 13.2%, respectively. Symptoms were severe to moderate in 8 patients.		

	Damien C. Weberhans Peter Rutz, Eros S. Pedroni et al. Results Of Spot-Scanning Proton Radiation Therapy For Chordoma And Chondrosarcoma Of The Skull Base: The Paul Scherrer Institut Experience. Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 2, pp. 401–409, 2005	Prospective study. Between October 1998 and October 2003, 29 patients (median age, 39 years) with chordomas (n= 18) and CS (n= 11) were treated at the Paul Scherrer Institut (PSI) with protons. Tumor conformal application of proton beams was realized by spot scanning technology.	-Actuarial 3-year local control rates were 87.5% and 100% for chordoma and CS, respectively. -No regional failure or distant metastasis was observed. -At 3 years, actuarial PFS and OS for the entire cohort was 90% and 93.8%, respectively. -Actuarial 3-year complication-free survival was 82.2%. -Radiation-induced pituitary dysfunction was observed in 4 (14%) patients (CTCAE Grade 2). No patient presented with post-PT brainstem or optic pathways necrosis or dysfunction. Conclusion: Spot-scanning PT offers high tumor control rates of skull base chordoma and CS. These results compare favorably to other combined proton-photon or carbon ion irradiation series.		
	Frederik J. Vernimmen, Jill K. Harris, Jennifer A. Wilson et al. Stereotactic Proton Beam Therapy Of Skull Base Meningiomas. Int. J. Radiation Oncology Biol. Phys., Vol. 49, No. 1, pp. 99–105, 2001	Prospective study. 27 patients with intracranial meningiomas: 18 patients underwent proton hypofractionated stereotactic radiotherapy (HSRT, 3 fractions), 5 patients were treated with stereotactic radiotherapy (SRT, 16 or more fractions).	-In the HSRT group, 16/18 (89%) of patients remained clinically stable or improved, while 2/18 (11%) deteriorated. -Radiologic control was achieved in 88% of patients, while 2 patients had a marginal failure. -Among the 5 SRT patients, 2 were clinically better, and 3 remained stable. -All SRT patients achieved radiologic control. -Three patients (13%), 2 of them in the HSRT group, suffered permanent neurologic deficits. Conclusion: Proton irradiation is effective and safe in controlling large and complex-shaped skull base meningiomas.	Fair	Inclusion criteria were explained. Patient character, methodology, follow up on treatment were described well. Kaplan-Meier analysis was done to justify the results.
Intracranial tumour					
	Evelyn Wenkel, Allan F. Thornton, Dianne Finkelstein, Judy Adams. Benign Meningioma: Partially Resected, Biopsied, And Recurrent Intracranial Tumors Treated With Combined Proton And Photon Radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol. 48, No. 5, pp. 1363–1370, 2000	Retrospective cross sectional study 46 patients with partially resected, biopsied, or recurrent meningiomas (median age of 50 years; range 11–74 years) were treated with combined photon and 160-MeV proton beam therapy	Eight patients developed severe long-term toxicity from radiotherapy, including ophthalmologic (4 patients), neurologic (4 patients), and otologic (2 patients) complications. Conclusion: Observed toxicity appears to be dose-related; with currently employed dose constraints, toxicity should not exceed that seen in patients treated with conformal fractionated supervoltage photon radiotherapy.	Fair	

	Georges Noël, Marc A. Bollet, Valentin Calugaru et al. Functional Outcome Of Patients With Benign Meningioma Treated By 3d Conformal Irradiation With A Combination Of Photons And Protons. Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 5, Pp. 1412–1422, 2005	Non-randomized prospective study. Evaluated efficacy and tolerance of external fractionated combination of photon and proton radiation therapy (RT) for intracranial benign meningiomas. Between 1994 and 2002, 51 patients with intracranial meningiomas of the base of the skull were treated with a combination of photon and proton RT. Mean follow-up was 25.4 months.	-Two patients complained of Grade 3 side effects: 1 unilateral hearing loss requiring aid and 1 case of complete pituitary deficiency. Conclusion: These results stressed the clinical efficacy of fractionated-associated photon-proton RT in the treatment of meningiomas, especially on cranial nerve palsies, without severe toxicity in almost all patients.	Fair	
	Damien C. Webera, Antony J. Lomaxa, Hans Peter Rutz et al. Spot-scanning proton radiation therapy for recurrent, residual or untreated intracranial meningiomas. Radiotherapy and Oncology 71 (2004) 251–258	Sixteen patients with intracranial meningioma were treated with PRT between July 1997 and July 2002. Eight patients had skull base lesions. Thirteen patients received PRT after surgery either as adjuvant therapy for incomplete resection (eight patients) or for recurrence (five patients). The median follow-up time was 34.1 months (range, 6.5–67.8).	-One patient presented with radiation induced optic neuropathy (SOMA Grade 3) and retinopathy (SOMA Grade 2) 8.8 and 30.4 months after treatment, respectively. These patients with ophthalmologic toxicity received doses higher than those allowed for the optic/ocular structures. Another patient developed a symptomatic brain necrosis (CTCAE Grade 4) 7.2 months after treatment. No radiation-induced hypothalamic/pituitary dysfunction was observed. Conclusions: Spot-scanning PRT offers highly conformal irradiation for complex-shaped intracranial meningiomas, while delivering minimal non-target dose. Observed ophthalmologic toxicity is dose-related.		
Lung Cancer					
	C H M Lee, D Tait, A E Hanum, S Webb. Comparison of proton therapy and conformal x-ray therapy in non-small cell lung cancer (NSCLC). The British Journal of Radiology, 72 (1999): 1078-1084.	Study compares performance of one proton and four conformal x-ray planning techniques in treating NSCLC. 13 patients.	-proton therapy is capable to deliver an escalated high dose to target volume in NSCLC whilst maintaining the normal tissue doses within tolerance. -without dose escalation, the performance of x-ray therapy and proton therapy does not differ much.	Poor	-The abstract is not comprehensive and misleading. -Study type not mentioned. -no comparison between subjects -no statistical analysis to verify the results

	Yoshiyuki Shioyama, Koichi Tokuuye, Toshiyuki Okumura et al. Clinical Evaluation Of Proton Radiotherapy For Non–Small-Cell Lung Cancer. Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 1, Pp. 7–13, 2003	Non- randomized prospective study. Between 1983 and 2000, 51 NSCLC patients were treated with proton beams at the University of Tsukuba. There were 28 patients in Stage I, 9 in Stage II, 8 in Stage III, 1 in Stage IV, and 5 with recurrent disease.	-Forty-seven patients (92%) experienced acute lung toxicity of Grade 1 or less; 3 had Grade 2, 1 had Grade 3, and none experienced Grade 4 or higher. Patients in the present series showed very little late toxicity. Conclusion: Proton therapy is a very safe treatment for patients with NSCLC, especially for those with early stages. The relative merit of proton therapy in comparison with stereotactic photon radiotherapy or three- dimensional conformal photon radiotherapy remains to be defined through future clinical trials.		
	Keiji Nihei M.D., Takashi Ogino, Satoshi Ishikura and Hideki Nishimura. High-dose proton beam therapy for Stage I non–small-cell lung cancer. Presented at the 41st Annual Meeting of the American Society of Clinical Oncology, Orlando, Florida, May 13–17, 2005.	Between 1999 and 2003, 37 patients were treated in Radiation Oncology Division, National Cancer Center Hospital East, Kashiwa, Chiba, Japan	-Late Grades 2 and 3 pulmonary toxicities were observed in 3 patients each. Of these 6 patients, 5 had Stage IB disease. Conclusions: Proton beam therapy is a promising treatment modality for Stage I NSCLC, though loco-regional relapse and late pulmonary toxicities in Stage IB patients were substantial. Further investigation of PBT for Stage I NSCLC is warranted.		
	Bush D A et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. American College of Chest Physicians.	Prospective phase 2 trial. To determine the efficacy and toxicity of high-dose hypofractionated proton beam therapy. 68 patients, medically inoperable or refused surgery	No cases of symptomatic radiation pneumonitis or late esophageal or cardiac toxicity seen.		Abstract
Prostate Cancer					
	Jerry D. Slater, Carl J. Rossi, Jr, Leslie T. Yonemoto Et Al. Conformal Proton Therapy For Early-Stage Prostate Cancer. Urology *53 (5), 1999*	Non-randomized prospective study. 319 patients with T1-T2b prostate cancer and initial prostate-specific antigen (PSA) levels 15.0 ng/mL or less received conformal radiation doses of 74 to 75 cobalt gray equivalent with protons alone or combined with photons.	No severe treatment-related morbidity was seen. **Conclusions.** It appears that patients treated with conformal protons have 5-year biochemical disease-free survival rates comparable to those who undergo radical prostatectomy, and display no significant toxicity.	Fair	

	Jerry D. Slater, Les T. Yonemoto, Carl J. Rossi, Jr. et al. Conformal Proton Therapy For Prostate Carcinoma. Int. J. Radiation Oncology Biol. Phys., Vol. 42, No. 2, Pp. 299–304, 1998	Non-randomized prospective study. 643 patients with localized prostate cancer were treated with protons, with or without photons.	-Minimal radiation proctitis was seen in 21% of patients; toxicity of greater severity was seen in less than 1%. Conclusion: Proton therapy to 74–75 CGE produced minimal treatment-related toxicity and excellent PSA normalization and disease-free survival in patients with low initial PSA levels.	Fair	Good explanation of methodology, patient characteristics, use of statistical analysis to verify the results.
Liver Cancer					
	Tanaka N, Matsuzakki Y, Chuganji Y et al. Proton irradiation for hepatocellular carcinoma {letter}. Lancet 1992; 340(8831): 1358	11 HCC patients with pre-existing cirrhosis. 5 patients received proton irradiation alone, 6 patients received chemotherapy plus proton beam therapy.	Large quantity of protons can be safely administered to HCC patient with pre-existing cirrhosis.	Poor	Abstract
	Takayuki Hashimoto, Koichi Tokuuye, Nobuyoshi Fukumitsu et al. Repeated proton beam therapy for hepatocellular carcinoma. Presented in part at Forty Seventh Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), October 16–20, 2005, Denver, CO.	Retrospective study. From June 1989 through July 2000, 225 patients with HCC underwent their first course of proton beam therapy at the University of Tsukuba.	Repeated proton beam therapy for HCC is safe when the patient has a target in the peripheral region of the liver and liver function is Child-Pugh class A.		
Gastrointestinal l Tumors					
	Hata M et al. Proton beam therapy for invasive bladder cancer: A prospective study of bladder-preserving therapy with combined radiotherapy and intra-arterial chemotherapy. International Journal of Radiation Oncology *Biology*Physics 2006; 64(5): 1371-1379	Cross-sectional study. 25 patients with transitional cell carcinoma of the urinary bladder, cT2-3N0M0.	. Therapy-related toxicities of Grade 3–4 were observed in 9 patients: hematologic toxicities in 6, pulmonary thrombosis in 1, and hemorrhagic cystitis in 2.	Fair	Abstract only
Breast Cancer					
	Antony J. Lomax, Laura Cella, Damien Weber. Potential Role Of Intensity-Modulated Photons And ProtonsIn The Treatment Of The Breast And Regional Nodes. Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 3, Pp. 785–792, 2003	Comparative treatment planning study. Treatment plans were computed using “standard” photon/ electron, IMRT, and forward-planned proton techniques using CT data from a breast cancer patient	Only the two-field, energy-modulated proton plan had the potential to preserve target dose homogeneity while simultaneously minimizing the dose delivered to both lungs, heart, and the contralateral breast.	Fair	

Acoustic Neuroma (Vestibular Schwannoma)					
	F.J. Vernimmen, Z. Mohamed, J. Slabbert. Stereotactic Proton Beam Radiotherapy for Acoustic Neuromas. Proceedings of the 47th Annual ASTRO Meeting	A retrospective study evaluating control rate, hearing preservation, facial and trigeminal nerve complications of proton radiotherapy for acoustic neuromas. 35 acoustic neuromas (mean follow up time 68.3 months) were analyzed.	Stereotactic proton beam radiotherapy for predominantly large acoustic neuromas achieves good tumor control with preservation of function in the surrounding cranial nerves.		Abstract only
	C. J. McAllister, D. A. Bush, L. N. Loredo, J. M. Slater, J. D. Slater. Acoustic neuromas treated with fractionated conformal proton beam irradiation. Loma Linda University Medical Center, Loma Linda, CA. Proceedings of the 47th Annual ASTRO Meeting	Cross-sectional study.31 acoustic neuromas in 30 patients were treated with fractionated proton beam therapy from March 1991 to June 1999. Age: 21-80 years old. 15 males and 14 females.	No fifth or seventh cranial nerve injuries were observed. Other treatment related morbidities were minimal.		Abstract only
	Griffith R. Harsh, Allan F. Thornton, Paul H. Chapman et al. Proton Beam Stereotactic Radiosurgery Of Vestibular Schwannomas. Int. J. Radiation Oncology Biol. Phys., Vol. 54, No. 1, pp. 35–44, 2002	Sixty-eight patients (mean age 67 years) were treated between 1992 and 1998. The mean tumor volume was 2.49 cm3. The prospectively specified follow-up consisted of neurologic evaluation and MRI at 6, 12, 24, and 36 months	-Cranial neuropathies were infrequent, which include persistent facial hypesthesia, persistent facial weakness, transient partial facial weakness and synkinesis Conclusion: Proton beam stereotactic radiosurgery of vestibular schwannomas at the doses used in this study controls tumor growth with relatively few complications.		
Paediatric Malignancies					
	Raymond Miralbell, Anthony Lomax, Mariateresa Russo. Potential Role Of Proton Therapy In The Treatment Of Pediatric Medulloblastoma/ Primitive Neuro-Ectodermal Tumors: Spinal Theca Irradiation. Int. J. Radiation Oncology Biol. Phys., Vol. 38, No. 4, Pp. 805-S I I, 1997	Comparative dosimetric study Compared Plan 1 (Standard plan): a single posterior 6 MV x-ray beam vs. Plan 2 (Proton beam plan) : a single posterior, 100 MeV proton field delivered by spot scanning (18, 23, 32). Both plans aimed to deliver 30 Gy to the target volume.	This study demonstrates a potential role of proton therapy in decreasing the dose (and toxicity) to the critical structures in the irradiation of the spinal neuraxis in medulloblastoma/PNET. The potential bone marrow and growth arrest sparing effects make this approach especially attractive for intensive chemotherapy protocols and for very young children. Sparing the thyroid gland, the posterior heart wall, and the gonads may be additional advantages in assuring a long-term post-treatment morbidity-free survival.	Fair	This is only a comparative planning study, of which no actual experimental or cross sectional study was done to multiple subjects.

	Torunn Yock, Robert Schneider, Alison Friedmann et al. Proton Radiotherapy For Orbital Rhabdomyosarcoma: Clinical Outcome And A Dosimetric Comparison With Photons. Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 4, Pp. 1161–1168, 2005	Prospective study. 7 children were treated for orbital rhabdomyo-sarcoma with proton irradiation and standard chemotherapy. The median follow-up is 6.3 years (range, 3.5–9.7 years).	Fractionated proton radiotherapy is superior to 3D conformal photon radiation in the treatment of orbital RMS. Proton therapy maintains excellent tumor coverage while reducing the radiation dose to adjacent normal structures. Proton radiation therapy minimizes long-term side effects.		
	Raymond Miralbell, Antony Lomax, Laura Cella & Uwe Schneider. Potential Reduction Of The Incidence Of Radiation-Induced Second Cancers By Using Proton Beams In The Treatment Of Pediatric Tumors. Int. J. Radiation Oncology Biol. Phys., Vol. 54, No. 3, Pp. 824–829, 2002	Comparative treatment planning study. Model: Two children, one with a parameningeal rhabdomyosarcoma (RMS) and a second with a medulloblastoma Treatment plans were calculated and optimized. RMS case: conventional X-ray, IM X-rays, protons, and IM protons. Medulloblastoma: irradiation of the spinal axis using conventional X-ray, IM X-rays, protons.	Proton beams reduced the expected incidence of radiation-induced secondary cancers for the RMS patient by a factor of >2 and for the medulloblastoma case by a factor of 8 to 15 when compared with either IM or conventional X-ray plans. Conclusions: The potential for a significant reduction in secondary cancers with pediatric cancers after using proton beams (forward planned or IM) in the treatment of RMS and MBD in children and adolescents represents an additional argument supporting the development of proton therapy for most radiotherapy indications in pediatric oncology.		
	Marco Krengli, Eugen B. Hug, Judy A. Adams et al. Proton Radiation Therapy For Retinoblastoma: Comparison Of Various Intraocular Tumor Locations And Beam Arrangements. Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 2, pp. 583–593, 2005	Comparative treatment study. To study the optimization of proton beam arrangements for various intraocular tumor locations: posterior– central, nasal, and temporal tumor locations, with straight, intrarotated, or extrarotated eye positions.	Proton therapy achieved homogeneous target coverage with true lens sparing. Doses to orbit structures, including bony growth centers, were minimized with different beam arrangements and eye positions. Proton therapy could reduce the risks of second malignancy and cosmetic and functional sequelae as no appreciable dose was delivered to the contralateral eye, brain tissue, or pituitary gland.	Fair.	

	Catherine T. Lee, Stephen D. Bilton, Robin M. Famiglietti et al. Treatment Planning With Protons For Pediatric Retinoblastoma, Medulloblastoma, And Pelvic Sarcoma: How Do Protons Compare With Other Conformal Techniques? Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 2, pp. 362–372, 2005	Treatment planning study. Tumor volumes from 8 patients (3 retinoblastomas, 2 medulloblastomas, and 3pelvic sarcomas) were studied retrospectively to compare DVHs from proton therapy with three-dimensional conformal radiation therapy (3D-CRT), electron therapy, and intensity-modulated radiation therapy (IMRT)	-In retinoblastoma, protons resulted in the best target coverage combined with the most orbital bone sparing (10% was the mean orbital bone volume irradiated at >5 Gy for protons vs. 25% for 3D-CRT electrons, 69% for IMRT, 41% for a single 3D lateral beam, 51% for a 3D anterolateral beam with a lens block, and 65% for a 3D anterolateral beam without a lens block). -In medulloblastoma, for posterior fossa and craniospinal irradiation, protons resulted in the least dose to the cochlea and hypothalamus-pituitary axis -With pelvic sarcoma, protons were superior in eliminating any dose to the ovaries (0% of mean ovarian volume was irradiated at >2 Gy with protons) and to some extent, the pelvic bones and vertebrae. Conclusion: Protons are most optimal in treating retinoblastomas, medulloblastomas (posterior fossa and craniospinal), and pelvic sarcomas in children `when compared with 3D-CRT, electrons, IMRT	Fair.	

Cost-effectiveness					
	Goitein M. The relative costs of proton and x-ray radiation therapy. Clin Oncol 2003;15(1): S37-50	The costs of sub-systems, the entire facility, running costs and cost per fraction.	Sophisticated proton therapy is more expensive than sophisticated x-ray radiation therapy; the ratio of cost is about 2.4. It could come down in the next 5 to 10 years by 2.1 or even 1.7.		Abstract
	Jonas Lundkvista, Mattias Ekmanb, Suzanne Rehn Ericssonc et al. Economic evaluation of proton radiation therapy in the treatment of breast cancer. Radiotherapy and Oncology 75 (2005) 179–185.	Hypothetical cohort study. The cost-effectiveness of proton therapy in the treatment of 55-year old women with left-sided breast cancer was assessed. A Markov cohort simulation model was used to simulate the life of patients diagnosed with breast cancers and treated with radiation.	-A cost per QALY gained of €67,000 for the base case analysis of an average breast cancer patient. The cost per QALY gained would, however, be considerably lower if a population with high-risk of developing cardiac disease was treated. -Sensitivity analyses showed that the results were stable and that the risk of cardiac disease was the most important parameter. Conclusions: The results indicate that proton therapy for breast cancer can be cost-effective if appropriate risk groups are chosen as targets for the therapy.		

	The Proton Therapy Working Party. Proton Therapy for Base of Skull Chordoma: A Report for the Royal College of Radiologists. Clinical Oncology (2000)12:75–79	Review article	-At present (2005) the treatment costs at Boston are likely to be approximately $60–70 000. -Patients from UK have also been referred for proton therapy to the Orsay cyclotron, situated at the Southeast periphery of Paris had to bear cost approximately FFr240 000, excluding hostel accommodation.		