Clinical Proton Therapy at Loma Linda University Medical Center

Jerry D. Slater, M.D.
Chairman, Department of Radiation Medicine
Loma Linda University

Introduction

As this is written (summer 2012), the proton treatment facility at Loma Linda University Medical Center (LLUMC) has operated for more than two decades. When the facility, now named the James M. Slater, M.D., Proton Treatment and Research Center, opened in October 1990, it was the world's first hospital-based proton treatment facility. Today, eleven clinical proton centers operate in the United States (1).

Sparing normal tissue was the fundamental reason to study alternatives to X-ray-based radiation therapy. The key concerns were reducing doses to such tissues and conforming—and often increasing—the total dose to clinical targets. The clinical history and present practice at LLUMC are based on those fundamental concerns.

Developing Clinical Strategies for Proton Radiation Therapy

By 1990, when the LLUMC center opened, proton therapy was known to be excellent for difficult-to-treat conditions such as ocular melanomas and lesions located close to vital structures. When the LLUMC facility was being planned, however, physicians in the Department of Radiation Medicine (LLURM) intended to use protons for virtually any localized solid tumor. Patients ordinarily treated with X rays would benefit from increased ability to deliver conformal treatments while avoiding normal tissue and, thus, minimizing side effects.

To evaluate outcomes, it was essential to treat not only more sites but also to admit many more patients than was possible in non-hospital proton centers. This was necessary to develop a significant body of clinical data and thus demonstrate that proton therapy was meeting anticipated goals. At this writing, up to 150 patients are treated daily, and more than 16,600 patients have completed treatment since the center opened. This large clinical experience results partly from efficiencies designed into the facility in terms of placement of clinics, simulation rooms, dressing rooms, physician offices, and control rooms. It also results from a reliable treatment system, which has operated at more than 98% uptime since it was built. Finally, high throughput results from designed-in capacity, with several beam lines and treatment rooms, permitting staff to accumulate a sufficient body of patient data (Fig. 1).

The facility has generated a large patient flow and has remained in consistent operation owing to regular upgrades and exploiting technological advances. For example, power supplies have been upgraded often; new devices have been installed, such as hardware modifying the manner in which beam exits the gantry; and beam control and treatment planning systems have been upgraded as needed (the present planning system, Odyssey, is a third-generation system developed by PerMedics, Inc., a subsidiary of Optivus Proton Therapy, Inc.). Two major advances are a computer-assisted digital alignment system and a computer-controlled, robotic patient positioner (Fig. 2). In addition, engineers implemented a new accelerator control system, enabling further future upgrades such as beam scanning and intensity-modulated proton therapy. Such upgrades, designed to maintain optimal operating efficiency, permit high patient throughput, maintain safety to patients and personnel, and maintain individualized treatments.

Exploiting the therapeutic potential of protons has been ongoing since 1990. First goals were to build on prior experience with photon and proton irradiation by investigating additional anatomic sites; to develop therapy protocols and evaluate outcomes; and to improve or develop technology to investigate still more anatomic sites. Proton treatment protocols were designed to reduce treatment-related morbidity for patients having conditions for which curative treatments existed but were associated with significant morbidity, and to improve control rates for tumors not well controlled by other means.

Studies proceeded in small steps, keeping patient safety in mind. Initial dose-escalation studies for prostate cancer, for example, investigated whether total doses only 10% higher than used in conventional photon treatment could be given without increasing morbidity. If desired and expected outcomes occurred, further dose escalation was pursued. Other studies investigated whether lower morbidity rates occurred when using the same total doses as with photons.

Investigations proceeded on the premise that ionizing radiation from any source will destroy targeted tissue if the total dose is high enough. The main consideration was to determine whether necessary total doses could be delivered without causing unacceptable permanent damage to normal tissues. Given that protons permit the radiation oncologist to control the physical dose distribution and avoid much normal tissue, the slightly higher proton radiobiologic effect was considered insignificant but was account for in prescribing total doses.

Clinical Applications

The clinical program has changed significantly over the past two decades. LLURM physicians typically divide the program's history into phases, as defined by technological, operative, and clinical developments. The first phase began with the center's opening in 1990 and was primarily focused on quality assurance and integration. Clinical programs attempted to reproduce outcomes other proton facilities had achieved. During this phase only a few anatomic sites were treated, and prescribed doses were those previously reported at other institutions.

The second phase began in 1994, when the second and third gantries opened, a new treatment planning system was developed, and a Memorandum of Agreement was signed between LLUMC and NASA to conduct proton research of mutual interest. The latter began a robust program in which NASA investigators used the LLUMC proton facility for research on the effects of cosmic radiation on space travelers and equipment, and LLURM investigators studied ways to further exploit protons for therapy. In this phase, the clinical emphasis was on expanding treatments to other anatomic sites and modifying fractionation schedules; the latter concentrated primarily in the direction of hypofractionation and accelerated fractionation in different anatomic sites. These studies continue today: priority is given to patients on clinical trials, and patients are accepted outside of clinical trials only when beam time permits.

The third phase, now underway, emphasizes more-difficult therapeutic problems. Among these are the use of protons for more-advanced cancers, or cancers in which photon radiation traditionally has been little used, as well as studies combining protons with other modalities.

Table 1 shows an overview of some of the sites treated at LLUMC. For many anatomic sites, treatment strategies and sites evolved over time, as experience and technology accumulated. Discussions of some of these evolutions follow; Table 2 summarizes many of them.

Stereotactic Radiosurgery of the Central Nervous System and Base of Skull: Radiosurgery is used to treat brain metastases and arteriovenous malformations (AVMs). Compared to photon beams from a linear accelerator or gamma knife, protons produce less normal-tissue radiation, especially for larger volumes and peripheral lesions. Protons also offer better coverage for irregularly shaped volumes and yield more uniform doses within clinical target volumes. Investigators from LLURM and the departments of neurosurgery and neuroradiology collaborate with Stanford investigators to evaluate a program for treating large (> 3 cm) AVMs with surgery, embolization, and hypofractionated protons. The program has been pursued since 1994; doses of 20 to 25 GyE in 1 to 5 fractions are given, based on target volume.

Fractionated Proton Treatment for Tumors of the Central Nervous System. LLURM clinicians use fractionated protons for most CNS and base-of-skull lesions, including chordomas and chondrosarcomas (2, 3); acoustic neuromas (4); pituitary adenomas (5), and meningiomas. In the latter, most of which are benign, fractionated protons provide excellent tumor control rates with minimal morbidity, even for larger lesions, and can be used as definitive treatment. In

patients without symptoms of brainstem compression, imaging diagnosis may be sufficient to use fractionated protons as primary treatment (6). Proton therapy offers potential for treating CNS glial tumors (7), and is used as primary treatment or in combination with other modalities. Although stereotactic approaches, featuring one or a few treatments, are often used for these lesions, the precision of protons and modern methods of positioning patients in effect make fractionated proton therapy as precise as stereotactic methods (8).

Diseases of the Eye. Historically, proton irradiation yields control rates of more than 95% for small ocular melanomas; rates of eye retention typically reach 90%. LLURM clinicians evaluated the efficacy and safety of protons for medium-size and large melanomas (9); results are consistent with other institutions' outcomes and indicate that protons are effective and safe for melanomas of all sizes, and often can preserve the eye and its function.

Tumors of the Head and Neck. Protons are used to treat locally advanced oropharyngeal cancer. Studies show that protons, used as a concomitant boost, effectively deliver an accelerated time-dose schedule to the cancer with a more tolerable schedule to surrounding normal tissues. Results thus far have shown increased locoregional control rates without increased toxicity, as compared to other radiation techniques delivering lower doses. Studies are ongoing to optimize the time-dose schedule (10). LLURM physicians also use protons for nasopharyngeal cancers, including retreatment following photon radiation (11).

Medically Inoperable Non-small-cell Lung Cancer. Conventional irradiation can control early-stage disease but also can result in irreversible injury to lung tissue. LLURM physicians studied hypofractionated protons as a means of controlling disease, sparing adjacent lung tissue, and minimizing side effects. Integral volume doses were reduced when compared with photon plans (12). A prospective phase II trial delivered doses as high as 60 GyE in ten fractions. No symptomatic radiation pneumonitis or late esophageal or cardiac toxicities supervened; hypofractionated proton therapy was administered safely and with minimal toxicity, and local tumor control appeared to be improved when compared to conventional radiotherapy. These outcomes persisted in later evaluations (13-15). Studies are now underway at LLUMC to use protons for locally advanced tumors, using altered fractionation and concurrent chemotherapy.

Breast Cancer. Hypofractionated proton therapy is used for early-stage breast cancer. LLURM radiation oncologists deliver protons to a circumscribed volume around the postoperative site (Fig. 3) (16). Two clinical trials have been conducted: each delivered 40 GyE in 10 fractions; treatment typically was given with 3 or 4 beams, with several fields treated daily. A recent report on the first trial shows excellent local control with no treatment-related effects seen subsequently (17). The second trial has finished accrual; preliminary results in that trial have been good in terms of patients' ability to complete the program with minimal side effects.

Hepatocellular Carcinoma. A phase II clinical trial using hypofractionated protons, done to determine efficacy and toxicity patients with locally unresectable carcinoma, revealed local tumor control rates superior to conventional radiation therapy and comparable overall survival rates. Most patients demonstrated markedly reduced post-treatment alpha-fetoprotein levels, and some, given protons to prepare for liver transplantation, demonstrated no evidence of residual carcinoma in the explanted liver. Post-treatment toxicity has been minimal (18). An updated report, based on extensive follow-up, shows that proton therapy is safe and effective for inoperable disease (19). A randomized controlled trial is underway, comparing proton therapy to transarterial chemoembolization.

Prostate Cancer. Current treatment programs, which feature high total doses and hypofractionated schedules, were developed cautiously and conservatively, seeking to optimize proton radiotherapy while being strictly mindful of patients' safety. The initial treatment scheme was not very different from standard photon protocols (total dose was increased by only 10%.). Preliminary results showed that conformal proton therapy at that dose level yielded disease-free survival rates comparable to other forms of local therapy, with only minimal morbidity (20).

Results were even more favorable when patients with early-stage disease were evaluated (21). There was no significant difference when groups were divided by age (22).

With time it became clear that the proton dose distribution enabled higher total doses, to increase the probability of disease control while retaining low rates of side effects. A phase III randomized trial demonstrated that men with clinically localized, early-stage prostate cancer had a significantly increased likelihood of biochemical disease control if they received high-dose conformal radiation, without increasing grade 3 acute or late urinary or rectal morbidity (23, 24).

At present, most patients at LLUMC receive 81 GyE. Two clinical trials of hypofractionated proton therapy are underway. In patients with early prostate cancer, LLURM physicians deliver the total dose of 60 GyE (biologically equivalent to 81 GyE in that time frame, in fractions of 3.0 GyE) in four weeks rather than eight to nine. Patients with intermediate risk prostate cancer receive a biologically higher dose of 66 GyE delivered in 3.2 GyE fractions over four weeks. LLURM experience with hypofractionated regimens for other disease sites underlies the prostate trials, as well as the repeated demonstration from dose-escalation studies that high total doses can be delivered with protons without increasing side effects. The same proton dose distribution that enables dose-escalation studies makes hypofractionation possible.

Pediatric Tumors. Tumors in children have always presented a special problem for radiation treatment. Damage to growing normal tissues can lead to a progressive series of side effects that persist throughout the patient's lifetime.

When treating children with ionizing radiation, avoiding even moderate doses to normal tissues is essential. At LLUMC, the physical dose distribution of protons is exploited to spare growing tissues as much as possible for a variety of pediatric treatment problems (25-32).

Protons limit treatment-related morbidity in children with tumors in or near the developing brain and spinal cord. An example can be seen in the case of a very young child treated with proton therapy for medulloblastoma: craniospinal protons reduced the dose to the cochlea and vertebral bodies and essentially eliminated the exit dose through the thorax, abdomen, and pelvis. Radiation-related acute and late effects were minimal; the technique may be especially advantageous in children having a history of myelosuppression (Fig. 4) (31).

More-difficult Therapeutic Problems. Proton radiation therapy is being applied to other clinical situations at LLUMC. Many of these involve sites wherein radiation therapy has been little used in the past. Among the latter are cancers of the pancreas, esophagus, and esophagogastric junction: protocols are underway to evaluate proton therapy as part of a comprehensive tri-modality program; protons are being used to deliver radiation while sparing thereapy-sensitive adjacent normal tissues and structures. Protons are also being evaluated in a Phase I/II study as stereotactic treatment for liver metastases. The aims are to determine maximum tolerable fraction sizes and whether a few proton radiation treatments are effective in controlling metastatic disease, thus promoting survival and quality of life.

Clinical Perspective

The fundamental objective is sparing normal tissue. The greater the extent to which dose to normal tissues can be reduced, the lesser is the likelihood of compromising radiotherapy because of unacceptable side effects. Reducing or eliminating radiation dose to normal tissues not only allows the physician to deliver the total dose; it also fosters opportunities to deliver that dose in fewer fractions without increasing side effects. This has been borne out in dosimetry studies and clinical trials. LLURM radiation oncologists are examining hypofractionation as a way to reduce treatment time and costs, provided that control rates are maintained and side effects do not increase. Given that costs such as beam time are a fixed part of each treatment fraction delivered, hypofractionated regimens should lead to cost reductions. These reductions, however, will not be permitted to compromise patient safety.

Minimizing the volume integral dose to normal tissues is a salient goal. Radiation oncologists at LLUMC presume that there is no such thing as a "safe" radiation dose. Studies dating back more than 40 years support this. The body's tissues have varying ranges of

radiation tolerance; some express radiation injury soon after relatively low doses; others may not express clinical injury till much time has passed after larger doses are given. With passage of sufficient time, however, any irradiated tissue will demonstrate chronic radiation-related injury (33, 34).

Accordingly, LLURM radiation oncologists have always proceeded cautiously with dose escalation and hypofractionation. Protons have been proven to be an effective way to accomplish both approaches because of the superior ability they give the physician to spare uninvolved tissues. Given the ongoing need to control medical costs, the ability to deliver a total radiation dose in fewer treatments becomes increasingly important.

Hypofractionation is not new. Early treatments with ionizing radiation, done not long after the discovery of X rays, consisted of delivering a single dose. Severe side effects resulted. In the 1920s and 1930s, work pioneered in France showed that fractionating the total dose allowed many normal cells to recover, while cancer cells, which have poorer repair capabilities, were destroyed. Fractionated treatments became common. Radiation oncologists learned that fractions of 2 Gray or less generally provided good opportunities for disease control while minimizing side effects as much as possible with photons. Assuming treatments given five days a week, this meant delivering 10 Gray or less per week, requiring several weeks to deliver the full dose.

Even so, the therapeutic value of larger fractions was never forgotten. Over the years, hypofractionation studies were done with photon radiation, especially for aggressive cancers. However, normal tissues also received higher doses, often leading to undesirable sequelae. Hypofractionation with standard photon radiation generally was not pursued.

Nonetheless, hypofractionation can be a valuable therapeutic tool if it can be administered safely. Two desirable outcomes can be accomplished: besides the greater cell-killing effect in tumors, hypofractionation can reduce costs associated with each treatment session and the time patients must spend undergoing treatments.

Proton therapy offers a way to deliver hypofractionated treatments safely and accomplish both objectives. As always, the key is sparing normal tissues. The physical properties of accelerated protons enable the physician to conform the dose precisely to a target volume while at the same time sparing normal tissues to a greater extent, and while using fewer treatment fields, than can be accomplished with photons. Dose comparison studies consistently show protons eliminating dose in normal tissues that are exposed to some dose of radiation with photon beams. This ability to spare normal tissues, in turn, permits higher doses in the target volume, both in terms of total doses and doses per fraction.

This capability is not merely theoretical. Hypofractionation studies for cancers of the lung, liver, and breast show that LLURM physicians have been able to deliver needed therapeutic doses while not increasing side effects. Studies are being done now for cancer of the prostate. The total dose is being given in four weeks instead of eight, thus almost halving the cost of the entire treatment. Long-term evaluation must be done to determine whether side effects remain low, as with standard proton fractionation, but LLURM investigators anticipate that outcome.

The ability to deliver large fractions with few side effects offers other potential benefits. One is the use of protons for palliation: controlling metastases can extend survival and improve quality of life. At LLURM, studies are being done of using protons to deliver palliative doses in a few fractions, in hopes of offering substantial symptom relief at substantially reduced cost.

Delivering the needed therapeutic dose of radiation in a shorter time has many potential advantages for patients and for society. Maximizing the potential of this technique is, therefore, a high priority at LLURM.

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Table 1. Initial treatment of tumors at various anatomic sites, LLUMC, 1990 to present

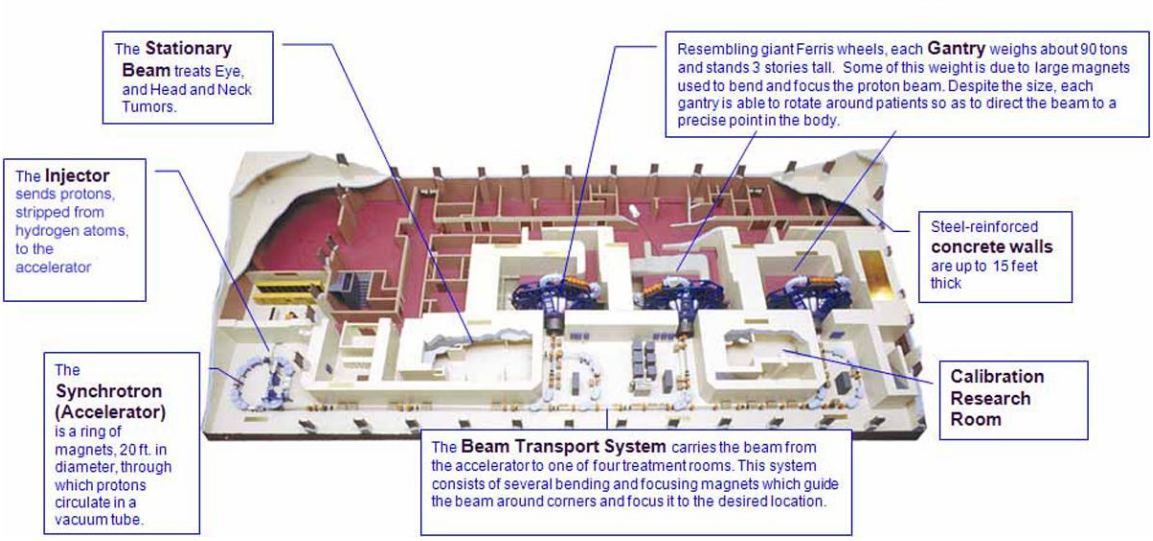
Phase in Facility Development	Sites Initially Treated in Indicated Phase
Phase I (1990 – 1994)	Ocular Melanomas Orbital Tumors Chordomas Chondrosarcomas Meningiomas Acoustic Neuromas Pituitary Adenomas Craniopharyngiomas Radiosurgery (AVM) Locally Advanced Prostate Cancer
Phase II (1995 – 2008)	Pediatric CNS Oropharyngeal Cancer Recurrent Nasopharyngeal Cancer Early Lung Cancer (Medically Inoperable) Locally Advanced Lung Cancer Prostate Cancer (dose-escalation trials) Radiosurgery (Brain Metastasis) Macular Degeneration Pediatrics (Non CNS) Hepatocellular Cancer Early Breast Cancer (node negative)
Phase II (2009 – Present)	Early Prostate Cancer (Hypofractionated) Intermediate Prostate Cancer (Hypofractionated) Early Breast Cancer (incl. nodal involvement) Pancreatic Cancer Esophageal Cancer Liver Metastases Sarcomas

Table 2. Summary of results of proton therapy at LLUMC

Reference	Site	Salient Findings
6	CNS (benign meningioma)	Follow-up: 74 mo (mean & median). Overall 5-year actuarial control rate, 96%; 99% in pts w/ grade 1 or absent histologic findings and 50% for 4 grade 2 pts. Pts w/o histologic verification and 46 of 47 w/ histologic grade 1 tumor had disease control at 5 yr.
5	CNS (pituitary adenoma)	Tumor stabilization occurred in all. Ten pts had no residual tumor; 3 had >50% reduction in tumor size. Seventeen pts with functional tumor had normalized or decreased hormone levels; progression occurred in 3 pts. Two of 6 deaths attributed to functional progression. Complications included temporal lobe necrosis (1 pt), new significant visual deficits (3 pts), and incident hypopituitarism (11 pts).
4	CNS (acoustic neuroma)	Mean follow-up: 34 mo. No pts had disease progression on MRI; 11 showed radiographic regression. Of 13 pts with pretreatment Grade I or II hearing, 4 maintained useful hearing. No treatment-related trigeminal or facial nerve dysfunction. Tumor dose subsequently reduced to increase hearing preservation rate.
30	CNS (pediatric low-grade astrocytoma)	Mean follow-up: 3.3 yr. Rates of local control and survival, central tumors, 87% and 93%; hemispheric tumors, 71% and 86%; brain stem, 60% and 60%. Therapy generally well tolerated; all children with local control maintained performance status. All pts with optic pathway tumors and useful vision maintained or improved visual status.
2, 29	Skull-base mesenchymal tumors (adult, pediatric)	In children (ref 29), mean follow-up: 40 mo. Actuarial 5-year local control and overall survival for pediatric malignant tumors: 72%, 56% (males significantly higher); for benign tumors, 89%, 100%. Severe late effects observed in 7% of children. In adults (ref 2), mean follow-up: 33 mo. Actuarial 5-yr survival: 100% for pts with chondrosarcoma, 79% for pts with chordoma. Grade 3 and 4 late toxicities observed in 7%.
9	Eye melanoma (medium and large size)	Five-year data: local control, 90%; metastasis-free survival, 75%; disease-specific survival, 75%. Eye preservation achieved in 75% of pts; useful vision preserved in 49%.
10	Head and neck (stage II-IV oropharynx)	Follow-up range: 2-96 mo. Five-year actuarial locoregional control rate: 84%. Actuarial 2-year disease-free survival rate, 81%; at 5 years, 65%. All pts completed prescribed treatment; late Grade 3 toxicity in 3 pts.
11	Head and neck (recurrent nasopharynx)	Mean follow-up: 23.7 mo. Twenty-four-mo actuarial overall and local-regional progression-free survival rates: 50% (with "optimal" DVH coverage vs. "suboptimal" coverage: 83% vs. 17% (P = .006)). No CNS side effects.
17	Breast (invasive nonlobular ca ≤ 3	Follow-up: 48 mo (median). Actuarial 5-yr overall survival and disease-free survival rates: 96% and 92%. No local failures. Acute toxicity: mild radiation dermatitis. Late skin toxicities: 3 grade 1 telangiectasias. No post-treatment infections, ulcerations, or other

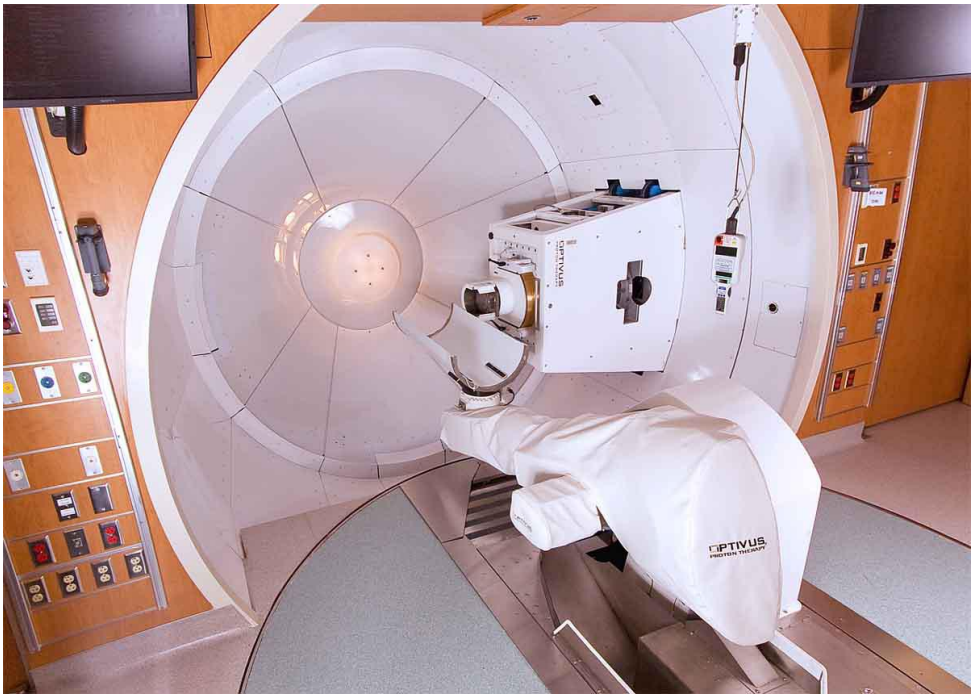
	cm.)	sequelae; virtually no dose to contralateral breast, lung, and heart.
13, 15	Lung (stage I NSCLC)	Median follow-up: 30 mo. No symptomatic radiation pneumonitis or late esophageal or cardiac toxicity. Three-year local control and disease-specific survival rates: 74%; 72%. Control in T1 vs T2 tumors: 87% vs 49%. Pts w/ higher performance status, females, and smaller tumor sizes: significantly improved survival. Analysis of 54 pts (ref 15) showed predicted mortality from concurrent disease correlating with observed comorbidity-specific mortality.
19	Liver (hepatocellular carcinoma)	Acute toxicity minimal; all pts completed full course. No RILD 6 mo post-treatment. Median progression-free survival: 36 mo; 60% 3-year progression-free survival rate for pts within Milan criteria. Of 18 pts undergoing subsequent liver transplants, 33% had pathologic complete response; 39%, only microscopic residual.
20-24	Prostate	At initial dose levels (75 Gy, ref 20), overall biochemical NED rate was 73%; 90% in pts with initial PSA </= 4.0; 87% in pts with post-treatment PSA nadirs </= 0.50. Rates were higher for early-stage tumors (ref 21) and did not vary with age (ref 22). Dose escalation trials to 79-82 Gy (refs 23, 24) yielded superior long-term control (median follow-up: 8.9 yr; overall survival: 83%) for men with localized cancer receiving high-dose versus conventional-dose radiation, achieved w/o increase in grade >/= 3 late urinary or rectal morbidity.

Figure 1



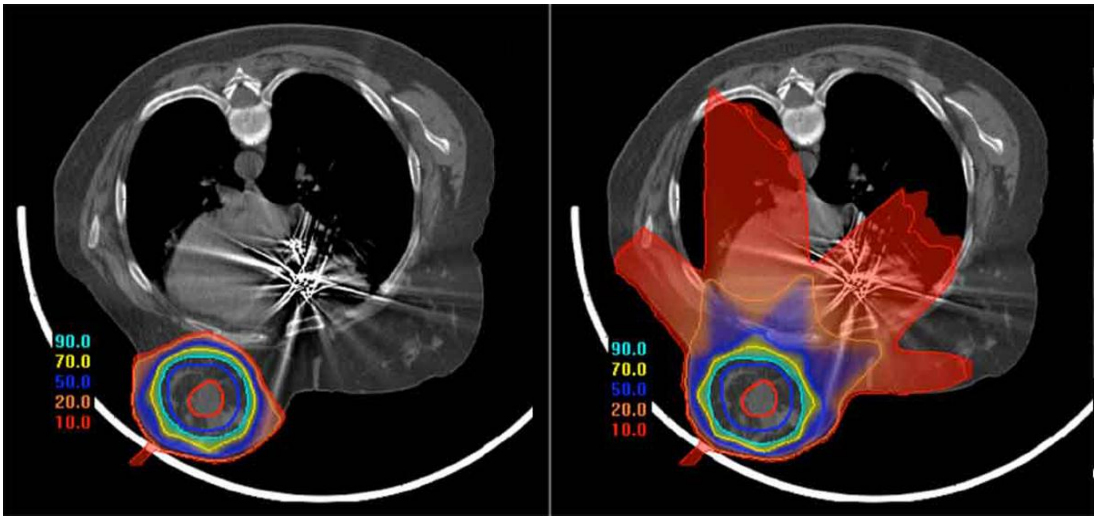
Cutaway model of the proton treatment floor at LLUMC. The fixed-beam room has two beam lines, for eye and for head-and-neck treatments. The research room has three beam lines. Unlabelled rooms at top include dressing rooms for patients, control rooms for the gantries and the fixed-beam room, and rooms for physicians and technologists to evaluate plans and consult on individual cases.

Figure 2



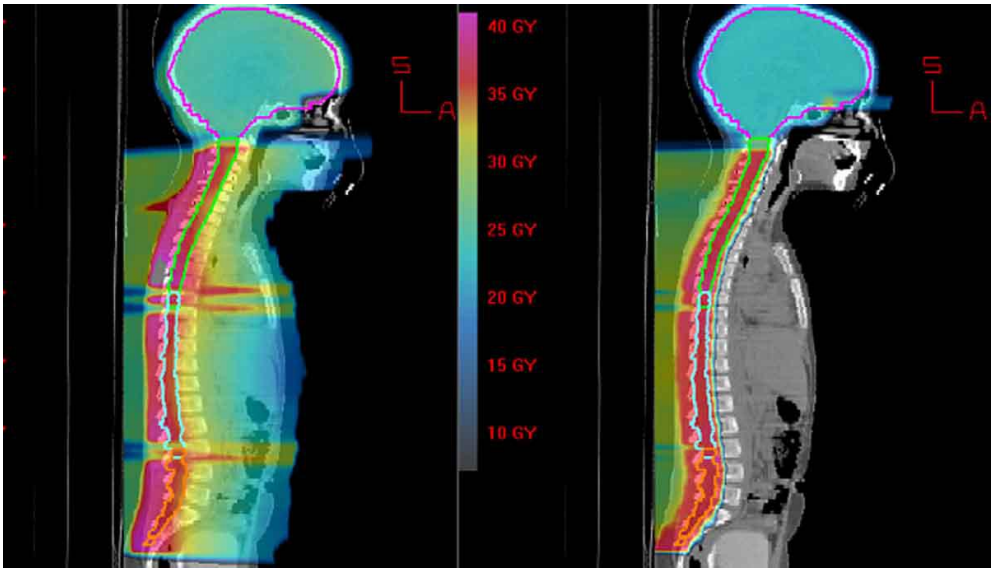
Robotic positioner in one of the gantry rooms at the James M. Slater, M.D., Proton Treatment and Research Center.

Figure 3



Plan for proton irradiation of the breast (left), compared with an intensity-modulated photon plan. The lumpectomy site is indicated by a red circle within the breast. Color washes indicate that the proton plan allows for complete sparing of both lungs, the heart, and the contralateral breast.

Figure 4



Comparison of dose distribution using X-rays (left) and protons (right) in the irradiation of the craniospinal axis and posterior fossa for treating medulloblastoma in a three-year-old child. In the proton plan there is substantial reduction of dose to the vertebral bodies, and virtual elimination of the exit dose through the chest, abdomen, and pelvis.