22 Proton Radiation Therapy of Age-Related Macular Degeneration

Les T. Yonemoto, Jerry D. Slater, Paul Blacharski, and James M. Slater

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22.1 Introduction

The rationale for radiation treatment of subfoveal choroidal neovascularization is the relative sensitivity of proliferating vascular cells to low doses of radiation, compared to the cells of the choroid and retina (DeGowin et al. 1974; Tannock and Hayashi 1972). Regression of choroidal neovascularization and stabilization of visual acuity was demonstrated with low-dose, fractionated, external beam photons (Chakravarthy et al. 1989, 1993). Other studies which followed also demonstrated promising early results with low-dose, fractionated irradiation (Bergink et al. 1994).

The goal of any therapy, including radiation therapy, is to enhance outcome by delivering the prescribed treatment while reducing the damage to normal tissue surrounding the target tissue. Proton therapy combined with three-dimensional (3D) treatment planning is used to improve precision in dose delivery to a specified target tissue while minimizing dose to normal tissue. The physical advantage of proton radiation therapy over x-ray and electron beam therapy owes to the fact that the maximum dose occurs at depth, rather than close to the surface (Fig. 22.1). This spares normal tissue to a far greater extent than is achievable with traditional radiation modalities.

![Fig. 22.1. Dose distribution of protons as a function of penetration depth in tissue compared with other forms of ionizing radiation](image-url)
22.2 Background of Proton Radiation Treatment

In the early 1930s, Ernest O. Lawrence invented the cyclotron, a circular particle accelerator that could accelerate charged particles such as protons to high energies. In the 1940s, several cyclotrons were built, including the 184-inch cyclotron at the University of California, Berkeley, and the much smaller 160-million electron volt (-MeV) Harvard cyclotron in 1948.

Robert R. Wilson (Wilson 1946) published the landmark paper that first suggested the medical application of protons. Because of the physician's inability to accurately define tumor and normal tissue boundaries using the imaging methods available at that time, however, protons were not immediately utilized for cancer treatment. However, orthogonal x-rays could localize pituitary tumors; accordingly, the first application of charged particle beams in humans occurred in 1954 at Berkeley (Tobias et al. 1956).

Clinical studies with protons were conducted at other research centers in the 1950s and 1960s. These included the Gustaf Werner Institute in Uppsala, Sweden, Harvard Cyclotron Laboratory in Cambridge, USA, the Physics Research Institute in Dubna, Russia, and the Institute for Experimental and Theoretical Physics in Moscow, Russia. Since 3D imaging was not available at that time, most of these patients had small pituitary tumors and arteriovenous malformations which could be localized with the help of orthogonal x-ray films.

In the early 1970s at Harvard, the proton beam was first used to treat uveal melanomas. A novel technique was employed to target the tumor and cause regression while preserving the eye (Gragoudas et al. 1977). By 1987, over a thousand cases of uveal melanoma had been treated.

Up to the end of the 1980s, all proton treatments had been delivered in physics laboratories using beams from accelerators that were designed for particle physics research, not for patient treatment. In 1985, an international group of physicists, physicians, and other scientists formed the Proton Therapy Cooperative Group, and plans were made to build the first medical proton facility at Loma Linda University Medical Center (LLUMC).

The proton treatment center at LLUMC was designed specifically for patient treatment and built in a hospital environment. Since treating the first patient in 1990, over 5000 persons have completed treatment: the facility currently treats more than 90 patients per day. It has four treatment rooms that operate simultaneously; this high treatment capacity has expanded the list of diseases and disease sites that can be treated with protons. One of the protocols developed was for treating the wet type of age-related macular degeneration (AMD).

22.3 Patients and Methods

The Institutional Review Board of LLUMC approved a study of the treatment of the wet type of AMD with proton therapy. This was a phase I/II dose escalation investigation designed to determine the optimum dose and technique with consideration for the toxicity and efficacy of the treatment.

Between March 1994 and August 1994, 21 patients received a dose of 8 GyE in a single fraction. Before proceeding with escalation of the dose, the toxicity of this treatment phase was assessed and subsequently reported (Yonemoto et al. 1996). No toxicity was seen; accordingly, the dose was escalated to the planned 14 GyE in a single fraction.

By January 1996, 27 patients had received doses of 14 GyE in single fractions. A statistically significant improved response was demonstrated with this dose (Yonemoto et al. 2000). Toxicity and lesion control rates were judged sufficient to continue to use the dose of 14 GyE with intent to determine the characteristics of patients that would benefit from this therapy.

22.3.1 Patient Eligibility and Pretreatment Evaluation

Enrollment into the study required a diagnosis of wet-type AMD verified by fluorescein angiography within 2 weeks of treatment. Other eligibility requirements included progressive visual loss, age more than 50 years, and that laser photocoagulation was refused or not indicated by Macular Photocoagulation Study Group guidelines. Ineligibility criteria included prior laser photocoagulation in the treatment area, diabetes, and current corticosteroid therapy.

1 GyE: Gray equivalent, the dose biologically equivalent to the same dose of cobalt-60 irradiation multiplied by a radiobiologic effectiveness (RBE) factor of 1.1.