History of radiation therapy

Becquerel in 1898 accidently left 200 mg of radium in his vest pocket for 6 hours – this unfortunate, accidental first radiobiological experiment resulted in erythema and ulceration of his skin that took weeks to heal. During the early 1900’s, several researchers expanded on the field with some ingenious experiments. Bergonie and Tribondeau demonstrated that radiosensitivity was highest in tissues with the highest mitotic index and researchers in Paris showed the beneficial effects of fractionation on normal tissues. By irradiating the testes of rams using a fractionated technique, these animals were made sterile while relatively sparing their skin. Giving them one big dose of radiation did not sterilize these animals without causing a severe skin reaction. It was thus shown early on that rapidly growing tissues appeared to react to radiation more than normal tissues. Further advances in the 1950s allowed higher energy radiation units to be built to allow further penetration of tissues with greater skin sparing properties. This was also enhanced by the advent of linear accelerators which were capable producing faster, higher energy radiation beams.

Dr Robert Wilson, a Harvard University physicist who played a central role on the development of the atomic bomb, made the first proposal for the medical use of proton in 1946 in an effort to devise a peaceful use of nuclear physics. The University of Berkeley began using proton technology after the construction of a cyclotron to treat cancer patient in 1954. As of 5/20/08, 55,000 patients have been treated with proton therapy. In the United State there are five facilities offering this treatment. Approximately 20,000 patients have been treated between these two facilities; the Harvard cyclotron laboratory at Massachusetts General Hospital and the Proton Treatment Center at Loma Linda University Medical Center (LLUMC). The other three centers currently providing this service in the US are the M.D. Anderson Proton Therapy Center in Houston, the University of Florida’s Shands Medical Center in Jacksonville and the University of Pennsylvania's proton facility in Philadelphia.

Mechanism of radiation therapy

X-rays and gamma rays produce biological damage indirectly. They release their energy by colliding with cells. This produces fast-moving electrons causing biological damage to tissues leading to cell death.
In the case of the photons and electrons, it takes some distance for the interactions to summate and reach a maximum. After this maximum is reach the energy of the beam dissipates by a constant fraction per unit depth. This fact accounts for the skin sparing properties of conventional radiation. The maximum dose occurs below the skin surface. There are several external beam radiation therapy sources. There is great overlap among several of these sources. Cobalt-60 units and lower energy linear accelerators essentially have the same energy in their radiation beams and have similar skin sparing properties. The difference between the cobalt-60 and the lower energy linear accelerators arises from the fact that the edge of the beam of the linear accelerator is much sharper than from cobalt units. This may be an important factor when irradiating close to critical structures. Lower energy beams (electron beams) reach their maximal effect upon reaching skin and subcutaneous tissue. Their energy dissipates rapidly after reaching these tissues. These beams may be more appropriate for skin and clearly visible mucosal cancers. The lowest energy electron beams do not penetrate tissues. The higher strength beams penetrate tissues to a moderate extent and then their energy drops off rapidly. This becomes important when irradiating certain neck lymphadenopathy. These electron beams are able to reach the lymph nodes fairly well but then their energy drops off quickly so that the spinal cord is spared of radiation. Radiation beams employing neutrons and protons are available but the energy required to accelerate these particles is quite high. The machines needed to this are quite expensive thus these beams are not commonly employed. Neutron beams are less affected by tumor hypoxia and repair of sublethal damage is lessened and proton beams are quite precise.

There is a significant difference between standard radiation treatment and proton therapy. If given in sufficient doses, x-ray radiation techniques will control most cancers. Even some of those are deemed radioresistant. However, the adverse effects cause by irradiation of healthy tissues prevents the delivery of tumorcidal doses. For this reason a less than desired dose is frequently used to reduce damage to healthy tissues and avoid unwanted side effects.

Protons have the advantage of conforming to the target tissue and sparing the adjacent healthy tissue and vital organs. This enables the delivery of higher therapeutic doses of radiation. The interaction probability to cause ionization increases as they lose velocity traversing through tissues, so that a peak of dose occurs at a depth proportional to the energy of each particle. This phenomenon was described by William Bragg over 100 years ago (2). When energized charged particles, such as protons pass near orbiting electrons, the positive charge of the protons attracts the negatively charged electrons. This results in ionization of the atom and the molecule within which the atom resides. The radiation damages molecules within the cells, especially the DNA or genetic material. Damaging the DNA destroys specific cell functions including the ability to divide or proliferate. If damage from the radiation is too extensive, the enzymes fail to adequately repair the injury. Since cancer cell's ability to repair molecular injury is frequently inferior, these cells are preferentially involved. As a result, cancer cells sustain more permanent damage and subsequent cell death than occurs in the normal cell population. This permits selective destruction of bad cells growing among good cells.

In the case of the proton particle their radiation energy is deposited in what is called the Bragg peak, which occurs at the point of maximum penetration. The depth at which the proton penetrates and the Bragg peak occurs, is dependent on the energy of the proton beam. This energy can be controlled very precisely. Because the protons are absorbed at this point without an exit dose, the tissue beyond the target receives very little or no radiation (7).

Intensity modulated radiation therapy (IMRT) consist of radiation portals in which the intensity of the photons varies within the field. Target structures receive photon radiation from different portals
to achieve desire dose. However, adjacent structures receive a bath effect before energy reaches the target zone and beyond as energy decreases and dissipates.

Intensity modulated proton therapy (IMPT) has the advantage of radiation portals which adds more accuracy to target zone. Also, in contrast to the two-dimensionality of IMRT, IMPT is able to modulate the Bragg peak allowing three-dimensional optimization.

**Proton therapy**

Initially, the major emphasis in clinical research for proton and light ion therapy was dose escalation for inherently radioresistant tumors, or for lesions adjacent to critical normal structures that constrained the dose that could be safely delivered with conventional x-ray therapy. Since the advent of IMRT the interest in particle therapy has gradually shifted toward protocols aimed at morbidity reduction. Lately the emphasis has mostly been placed on the potential for reduced risk of radiation-induced carcinogenesis with protons. Compared with 3D-CRT, a 2-fold increase has been theoretically estimated with the use of IMRT due to the larger integral volumes. In the pediatric setting, due to a higher inherent susceptibility of tissues, the risk could be significant, and the benefits of protons have been strongly emphasized in the literature. The dose delivered with particles is prescribed in Gray equivalents (GyE) or cobalt Gray equivalents (CGE) often used with protons. GyE and CGE are equal to the measured physical dose in Gray multiplied by the relative biological effectiveness (RBE) factor specific for the beam used. The RBE is the ratio of dose of radiation required to produce a certain biological effect with photons relative to the dose required to produce the same effect with another form of ionizing radiation such as protons and light ions. An RBE value of 1.1 is generally accepted for clinical use with proton beams. The RBE of carbon ions is difficult to calculate and for dose-reporting purposes a value of 3 is often utilized. In essence, carbon ion therapy attempts to capture the ‘best of both worlds,’ by exploiting the benefits of improved dose distributions, due to the presence of a defined Bragg peak and concomitantly taking advantage of their high RBE to increase the tumor control probability. (2)

**Uses of Proton radiation**

**Pediatric Malignancies**

In the pediatric setting, due to a higher inherent susceptibility of tissues, the risk for secondary malignancies could be significant. It is postulated that proton therapy would result in great benefit on this population. Depending on the sites of irradiation several side effects can be produce. Some of this include growth deficiency, intelligence, cosmesis, endocrine function, fertility and organ function. Radiation side effects become an even more serious concern for very young patients (age <3 years), whose tissues have been shown to be especially susceptible to radiation damage. The most devastating long-term side effect of RT remains the induction of a second malignancy.

The bath effect of IMRT configuration pose a concern for integral dose to healthy non-target tissues which may leads to higher risk of malignancies over the lifetime. Retinoblastoma is the most common primary ocular malignancy in childhood. In 20% to 30% of cases the disease is bilateral and associated with a germline mutation in the Rb tumor suppressor gene. In patients with hereditary retinoblastoma, this risk of secondary malignancy has been reported to be as high as 51% at 50 years. Retrospective research has indicated 5 Gy as a significant threshold for an increased risk of in-field sarcoma occurrence. The mean orbital bone volume exposed to 5 Gy was 10% for protons vs 25% for 3D-CRT electrons vs 41% for a single 3D lateral photon beam vs 69% for photon IMRT. Another
comparative planning study showed that with a single proton beam and to a prescribed dose of 46 CGE to the gross tumor volume (GTV), the dose to sensitive structures was negligible. Therefore, proton-beam irradiation in retinoblastoma holds the potential to significantly reduce both poor cosmetic outcomes and radiation-induced malignancies. (2)

**Sinonasal Malignancies**

The standard treatment for sinonasal malignancies involves the combination of radical surgery and postoperative radiation. Total maxillectomy is the most commonly performed surgery. Despite such aggressive therapy, the outcome is poor, with fewer than half of the patients surviving at 5 years. In advanced tumors that involve the skull base, survival is further reduced. Treatment failure at the primary site is the main pattern of failure, ranging from 30% to 100%. Higher radiation doses are associated with improved local control, but the surrounding critical normal tissues in the skull base precludes the delivery of adequate tumoricidal doses. Due to the proximity of the optic structures to the tumors in the paranasal sinuses and skull base, radiation-induced late ocular toxicity such as retinopathy or optic neuropathy is very common. At the University of Florida, 27% of pts developed unilateral blindness secondary to radiation retinopathy or optic neuropathy. 5% developed bilateral blindness due to optic neuropathy. Other common ocular toxicities with conventional radiation therapy in sinonasal malignancies: glaucoma, cataract and dry eye syndrome.

Between 1991 and 2002, 102 pts with advanced sinonasal cancers have received proton radiation therapy at the MGH. 33 SCCA, 30 carcinomas with neuroendocrine differentiation, 20 adenoid cystic carcinomas, 13 soft tissue sarcomas, and 6 adenocarcinomas. The median dose was 71.6 G, 20% of patients had undergone complete resection before proton radiation therapy. A median follow-up of 6.6 years, the 5-year local control is 86%. Distant metastasis was the predominant pattern of relapse for squamous cell, neuroendocrine, and adenoid cystic carcinomas. These results compare very favorably to that achieved by IMRT or three-dimensional conformal radiation therapy. Adenoid cystic carcinoma- worst outcome. For patients with inoperable tumors or gross residual disease, the local control rate is 0–43%. Neutron radiation therapy has a locoregional control rate of 23% for patients with base of skull involvement. Proton radiation therapy for skull base adenoid cystic carcinoma with a dose of 76 Gy, the locoregional control at 5 yrs is 93%

In multivariate analysis- decreased overall survival was seen in patients presenting with change in vision at presentation, involvement of sphenoid sinus and clivus. With a median follow-up period of 52.4 months, 5.6% of patients developed late ocular toxicity. There was no vascular glaucoma, retinal detachment, or optic neuropathy. (7)

**Nasopharyngeal Carcinoma**

Concurrent chemoradiation is the standard of care for patients with advanced nasopharyngeal carcinoma (NPC). At the MGH, proton radiation therapy has been used to treat very advanced NPC, particularly T4. Between 1990 and 2002, 17 patients with newly diagnosed T4 N0-3 tumors received combined conformal proton and photon radiation. Twelve patients (71%) had WHO type II or III histology. The median prescribed dose to the gross target volume was 73.6 Gy (range 69.0–76.8 Gy). Eleven patients had accelerated hyperfractionated radiation therapy. Ten patients received chemotherapy (induction or concurrent). Only one patient failed to complete the planned concurrent chemotherapy and radiation course. With a median follow-up time of 43 months, only one patient developed local recurrence and two patients developed distant recurrence. No neck nodal recurrences
were observed. The actuarial locoregional control and relapse-free survival rates at 3 years were 92% and 79%, respectively. The 3-year overall survival rate was 74%. (7)

**Oropharyngeal Carcinoma**

The group at Loma Linda University Medical Center (LLUMC) reported the results of re-irradiation of 16 patients with proton beam radiation with 59.4–70.2 Gy. With a median follow-up of 24 months, the overall survival and locoregional control rates at 2 years were 50%. The overall survival rates at 2 years for patients with optimal dose-volume histogram coverage versus suboptimal coverage were 83% and 17%, respectively (P=0.006). No central nervous system complications were observed. Investigators at LLUMC conducted an accelerated hyperfractionation study for stage II–IV oropharyngeal carcinoma. The LLUMC trial total dose of 75.9 Gy that was delivered in a shorter overall time of 28 treatment days. Only 25.5 Gy of the total dose was given with proton with the rest delivered with the opposed lateral photon technique. None of the patients received concurrent chemotherapy.

The intent of the study was not only to increase tumor control probability by increasing the total dose and decreasing the treatment time, but also to simultaneously decrease treatment-related morbidity by exploiting the dosimetric advantages of protons. Over a period of more than 10 years, 29 patients were accrued to the study. All patients completed the prescribed dose without any interruption. With a median follow-up of 28 months, the 2-year locoregional control and disease-free survival rates were 93% and 81%, respectively. The 2-year actuarial incidence of late RTOG Grade 3 toxicity was 16% (vs >20% in IMRT). This small study was performed over a prolonged period of time without the use of chemotherapy and employed proton radiation therapy for only 35% of the total dose. (7)

**Central nervous system tumors**

St. Clair et al. compared standard photons, IMRT, and protons for craniospinal irradiation with a posterior fossa boost. Substantial normal tissue sparing was seen with protons. The dose to 90% of the cochlea was reduced from 101% with standard photons, to 33% with IMRT, and to 2% with protons. In sarcomas of the Base of Skull a large series of chondrosarcoma and chordomas of the skull base was treated at Massachusetts General Hospital. A combination of proton and photon therapy to a median dose of 72.1 CGE was used. Local control rates for chondrosarcomas were 99% and 98% at 5 and 10 years, respectively. Patients with chordomas were found to have lower rates of local control in spite of similar doses, with 59% and 44% at 5 and 10 years, respectively. The temporal lobe damage rate was 13.2% at 5 years.(2)

Combination of radical surgery and postoperative radiation constitutes standard treatment. Total maxillectomy is the most commonly performed surgery. Despite such aggressive therapy, the outcome is poor, with fewer than half of the patients surviving at 5 years. In advanced tumors that involve the skull base, survival is further reduced. Treatment failure at the primary site is the main pattern of failure, ranging from 30% to 100%. Though it has been shown that higher radiation doses are associated with improved local control, the surrounding critical normal tissues in the skull base preclude the delivery of adequate tumoricidal doses. Due to the proximity of the optic structures to the tumors in the paranasal sinuses and skull base, radiation-induced late ocular/visual toxicity such as retinopathy or optic neuropathy is very common. At the University of Florida, 27% of patients developed unilateral blindness secondary to radiation retinopathy or optic neuropathy, and 5% developed bilateral blindness due to optic neuropathy.(2)
Other radiation-induced ocular/visual toxicities such as neovascular glaucoma, cataract, and dry eye syndrome are also common after treatment with conventional radiation therapy in sinonasal malignancies. Between 1991 and 2002, 102 patients with advanced sinonasal cancers have received proton radiation therapy at the MGH. There were 33 squamous cell carcinomas, 30 carcinomas with neuroendocrine differentiation, 20 adenoid cystic carcinomas, 13 soft tissue sarcomas, and 6 adenocarcinomas. The median dose was 71.6 Gy. Twenty percent of patients had undergone complete resection before proton radiation therapy. With a median follow-up of 6.6 years, the 5-year actuarial local control is 86%. Distant metastasis was the predominant pattern of relapse for squamous cell, neuroendocrine, and adenoid cystic carcinomas. These results compare very favorably to that achieved by IMRT or three-dimensional conformal radiation therapy. Of all histological types of sinonasal cancer, adenoid cystic carcinoma traditionally has the worst outcome. For patients with inoperable tumors or gross residual disease, the local control rate is 0–43%. Neutron radiation therapy, though an accepted treatment option for adenoid cystic carcinoma, results in a locoregional control rate of 23% for patients with base of skull involvement. Results of proton radiation therapy for patients with skull base adenoid cystic carcinoma with a median dose of 76 Gy, the locoregional control at 5 years is 93%. In multivariate analysis significant predictive factors for decreased overall survival in patients with skull base adenoid cystic carcinoma.

Change in vision at presentation and involvement of sphenoid sinus and clivus were. With a median follow-up period of 52.4 months, 5.6% of patients developed late ocular/visual toxicity. There was no vascular glaucoma, retinal detachment, or optic neuropathy. (7)

Conclusion

Proton therapy is a relatively new medical advance. It is an expensive and not widely available technology. As many revolutionary technological advances in the medical field, we can expect to become widely available in the years to come. There is promising data on both tumor control and prevention of side effects and damage to adjacent structures. As head and neck surgeons we need to familiarize with this technique as it could replace current management standards. Other applications of proton therapy include paraspinal, lung, breast and prostate.

References


