Applications of Proton Beam Radiation

Jean Paul Font, MD
Faculty Advisor: Vicente Resto, MD, PhD
The University of Texas Medical Branch
Department of Otolaryngology
Grand Rounds Presentation
June 18, 2008
History of Radiation Therapy

First accidental radiobiological experiment

– Becquerel in 1898
  Left 200 mg of radium in his vest pocket for 6 hours – resulted in erythema and ulceration of his skin that took weeks to heal

During the early 1900’s,

– Bergonie and Tribondeau
  radiosensitivity was highest in tissues with the highest mitotic index
Fractionation

- Researchers in Paris
  - 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
History of Radiation Therapy

Further advances in the 1950s

– Allowed higher energy radiation units to be built to allow further penetration of tissues with greater skin sparing

– Linear accelerators – faster & higher energy radiation beams
History of Proton Therapy

Dr Robert Wilson

- A Harvard University physicist who played a central role on the development of the atomic bomb
- Published a paper in 1946 that first proposed the medical use of protons for cancer therapy

In 1954

- The University of Berkeley began using proton technology after the construction of a cyclotron to treat cancer patient
As of 5/20/08, 55,000 patients have been treated with proton therapy World Wide

In the United State there are five facilities offering this treatment

Approximately 20,000 patients have been treated between two of this facilities
  – The Harvard cyclotron laboratory at Massachusetts General Hospital
  – The Proton Treatment Center at Loma Linda University Medical Center (LLUMC)

The other three new centers providing this service in the US are
  – M.D. Anderson Proton Therapy Center in Houston
  – University of Florida's Shands Medical Center in Jacksonville
  – University of Pennsylvania's proton facility in Philadelphia
Mechanism of radiation therapy

- Electromagnetic radiations (x-rays and gamma rays)
  - Produce biological damage indirectly
  - They release their energy by colliding with cells producing fast-moving electrons
  - Their energy is converted into heat in the form of thermal energy which breaks chemical bonds
  - These weak chemical bonds that are broken lead to cell death
Mechanism of Radiation Therapy

X-rays reach their tissues it takes some distance for the interactions to summate and reach a maximum.

This fact accounts for the skin sparing properties of conventional radiation – the maximum dose occurs below the skin surface.

After which the energy of the beam dissipates by a constant fraction per unit depth.
Mechanism of Proton therapy

- Protons pass near orbiting electrons, pulling them out of their orbits causing ionization.
- Changes the characteristics of the atom and of the molecule.
- Damaging the DNA destroys specific cell functions, particularly the ability to divide or proliferate.
- While both normal and cancerous cells go through this repair process, a cancer cell’s ability to repair molecular injury is frequently inferior.
- This permits selective destruction of bad cells growing among good cells.
Particles

Electron beams

- Lower energy beams
  - Maximal effect upon reaching skin and subcutaneous tissue
  - Energy dissipates rapidly after reaching these tissues
  - More appropriate for skin and clearly visible mucosal cancers

- 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
Neutrons and Protons

The energy required to accelerate these particles is quite high.

The machines are quite expensive thus these beams are not commonly available.

The MD Anderson Cyclotron cost approximately $150 million.
235MeV proton cyclotron used for proton cancer therapy at Boshan, China

Hydrogen plasma ion source inside of the accelerator
Neutrons

Advantages

- Neutron beams are less affected by tumor hypoxia and repair of sublethal damage is lessened

Disadvantage

- Despite encouraging local control outcomes, neutron studies have shown high rates of adverse effects and their use has been largely discontinue
Protons vs Photons

- Irradiate smaller volume of normal tissues
- Photon beam decreases exponentially with depth in the irradiated tissues
- Protons have a finite range
- Protons deposit most of their radiation energy in what is known as Braggs peak

Image courtesy of Annie Chan
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Image courtesy of Dr. Annie Chan, Dept of Radiation Oncology, MGH, Boston, MA
Bragg’s Peak

- Described by William Bragg over 100 years ago
- Depth is dependent on the energy of the proton beam
- This energy can be control very precisely

Image courtesy of Dr. Annie Chan, Dept of Radiation Oncology, MGH, Boston, MA
Photons
Protons

Tissue beyond the target receives very little or no radiation

beam entrance
beam exit
unnecessary radiation in normal tissues
rapid dose fall-off

Image courtesy of Dr. Annie Chan, Dept of Radiation Oncology, MGH, Boston, MA
Improved therapeutic index
  - Irradiate smaller volume of normal tissues

Ability to intensify dose
  - Higher doses to target zone

Improve dose conformation

Image from Greco C. Current Status of Radiotherapy With Proton and Light Ion Beams. American CANCER society April 1, 2007 / Volume 109 / Number 7
**IMRT**

- Intensity modulated radiation therapy
  - Consist of radiation portals
  - Target structures receive photon radiation from different portals to achieve desire dose
  - Adjacent structures receive a “bath effect” before and beyond the target zone

IMPT

- Intensity modulated proton therapy (IMPT)
  - 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

**Spread-out Bragg peaks (SOBP)**
- The dose peak may be ‘spread out’ to achieve a uniform dose

**Spot scanning method**
- Recently introduce
- Small pencil beams of a certain energy deposit their peaks to obtain ‘dose-sculpting’ of the target
Dose Equivalent

- Relative biological effectiveness (RBE)
  - Ratio of the photon dose to the particle dose required to produce the same biological effect
- An RBE value of 1.1 is generally accepted for clinical use with proton beams
- Gray equivalents (GyE) or cobalt Gray equivalents (CGE) often used with protons
  - Gray multiplied by the relative biological effectiveness (RBE) factor specific for the beam used
Carbon ions

- The RBE of carbon ions has an estimated value of 3
- Carbon ion therapy attempts to capture the ‘best of both worlds,’
  - Presence of the proton’s Bragg peak
  - Advantage of their high RBE to increase the tumor control probability
Uses of Proton radiation

Initially, the major emphasis in clinical research for proton and light ion therapy

- Dose escalation for radioresistant tumors
- Lesions adjacent to critical normal structures

Since the advent of IMRT

- Protocols aimed at morbidity reduction
- Emphasis for reduced risk of radiation-induced carcinogenesis with protons
- In the pediatric setting
  - Higher inherent susceptibility of tissues
  - Benefits of protons
Pediatric Malignancies

- Depending on the sites of irradiation
  - Growth, 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 (generally sarcomas)
Pediatric Malignancies

- Bath effect IMRT pose a concern
  - Integral dose to healthy nontarget tissues may lead to higher risk of malignancies over the lifetime

Image from Greco C. Current Status of Radiotherapy With Proton and Light Ion Beams. American CANCER society April 1, 2007 / Volume 109 / Number 7
Retinoblastoma

- 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
Retinoblastoma

- Lee et al., a comparative planning study
  - Proton therapy provides superior target coverage with optimal sparing of orbital bone compared with 3D-CRT and IMRT

- 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

- Proton-beam irradiation in retinoblastoma
  - Potential to reduce radiation-induced malignancies
  - Reduce cosmetic outcomes hypoplasia of the Orbit
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
Sarcomas of the Base of Skull

- A large series of chondrosarcoma and chordomas of the skull base was treated at MGH.

- 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.

- 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.
Sinonasal Malignancies

- Standard treatment- 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
Sinonasal Malignancies

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.
Sinonasal Malignancies

- 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
Sinonasal Malignancies

Other common ocular toxicities with conventional radiation therapy in sinonasal malignancies

- Glaucoma
- Cataract
- 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
Sinonasal Malignancies

- Adenoid cystic carcinoma- worst outcome

For patients with inoperable tumors or gross residual disease, the local control rate is 0–43%.

- Neutron radiation therapy
  - Locoregional control rate of 23% for patients with base of skull involvement

- Proton radiation therapy
  - Skull base adenoid cystic carcinoma
  - 76 Gy, the locoregional control at 5 yrs is 93%
Sinonasal Malignancies

- In multivariate analysis - decreased overall survival
  - 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
Nasopharyngeal Carcinoma

Standard of care - Concurrent chemoradiation in 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. 12 pts (71%) had WHO type II or III histology

The median prescribed dose to the gross target volume was 73.6 Gy
Nasopharyngeal Carcinoma

- 11 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 locoregional control and relapse-free survival rates at 3 years were 92% and 79%, respectively. The 3-year overall survival rate was 74%.
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:
- Overall survival and locoregional control rates at 2 years were 50%.
- Overall survival rates at 2 years for pts with optimal dose-volume histogram coverage versus suboptimal coverage were 83% and 17%, respectively (P= 0.006).

No central nervous system complications were observed.
Oropharyngeal Carcinoma

Investigators at LLUMC conducted an accelerated hyperfractionation study for stage II–IV oropharyngeal carcinoma

The LLUMC trial total dose of 75.9 Gy
- Delivered in a shorter overall time of 28 days

Only 25.5 Gy of the total dose was given with proton. None of the patients received concurrent chemotherapy

The intent of the study
- Increase tumor control probability by increasing the total dose
- Decrease the treatment time
- Decrease treatment-related morbidity
Oropharyngeal Carcinoma

- 29 pts accrue over a period of more than 10 years
- 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%
- The 2-year incidence of late RTOG Grade 3 toxicity was 16% (vs >20% in IMRT)
- 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
Other sites treated

- Paraspinal Tumors
- Lung Tumors
- Breast Ca
- Prostate Ca
Conclusion

- Proton therapy is a relatively new medical advance
- Expensive and not widely available
- Very promising data on both tumor control, survival and prevention of side effects
- As head and neck surgeons we need to familiarize with this technique as it could replace current management standards