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Proton therapy in clinical use

Klinik proton terapi uygulamaları

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Summary

Proton therapy (PT) has been in clinical use since 1970, and 61,122 patients have been treated as of the end of the 2008 in the world. The major advantage of PT over conventional radiatiotherapy is reduced side effects in the neighboring critical tissues, which in turn results in less treatment interruption and therefore better integration of RT with systemic chemotherapy. Indirectly, reducing late effects permits the radiation oncologist to dose escalation to a tumor which may potentially translate into higher tumor control rates. Additionally, patients experience a relatively better quality of life during and after PT. Proton therapy has been most extensively studied in the treatment of uveal melanomas and chordoma and chondrosarcoma patients. Other common tumors successfully treated with PT include central nervous system, head and neck, breast, lung, esophagus, prostate and liver tumors, and soft tissue/bone sarcomas. Proton therapy was conventinally delivered by passive scattering. Active scanning (AS) was developed at Paul Scherrer Institute. In addition to reducing scattered dose, intensity modulation and inverse planning are possible advantages offered by AS, therefore, most of the proton facilities in the world have voiced their interest in moving towards an AS system. Interest is growing in proton technology and newer PT facilities are being added to currently active ones all over the world.

Key Words: Proton therapy, efficacity, toxicity prevention.

Özet

Proton terapi (PT), 1970 yılından beri klinik kullanımda olup, Aralık 2008 tarihine kadar tüm dünyada toplam 61,122 hasta tedavi edilmiştir. PT'nin en önemli avantajlarından biri, "konvansiyonel foton" tedavisine göre normal dokuda daha az erken ve geç yan etkiye sebebiyet vermesidir. Bu avantajlar tedaviye ara verilme ihtimalinin azalmasına ve radyoterapi ile eş zamanlı kemoterapi kullanımına olanak sağlamakta dolayısıyla tedavi etkiliğinin artmasına olanak vermektedir. Ayrıca, olumsuz geç etkilerin azalması hasta hayat kalitesinde artma ile sonuçlanmaktadır. PT'nin dozimetrik avantajlarının direk olarak kliniğe en iyi yansıdığı hasta gurupları uveal melanomlar ve kafa tabanı (kordoma ve kondrosarkoma) tümörleridir. Uygulama alanı bulunan hemen tüm beyin, baş-boyun, meme, prostat, erken evre akciğer, osefagus, karaciğer tümörleri ile yumuşak doku/kemik sarkomlarında lokal kontrol ve sağ kalım oranlarının en azından fotona eşit olduğu, ancak PT ile yan etki profilinin çok daha iyi olduğu bildirilmektedir. PT kliniğinde en çok kullanılan yöntem pasif saçılmadır. Paul Scherrer Enstitüsü tarafından geliştirilen isosentrik gantry ile aktif tarama teknolojisi kullanılmaya başlanmış ve yoğunluk ayarlı PT'ye olanak vermesi, pasif saçılmaya göre daha az nötron saçılması sonucu azalan integral doz ile dünyadaki tüm merkezlerin ilgisinin bu tekniğe çevrilmesine sebep olmuştur. Dünyada PT'ye olan ilgi giderek artmakta olup varolan merkezlerin yanı sıra faaliyete geçmesi planlanan birçok merkez bulunmaktadır.

Anahtar Kelimeler: *Proton terapi, tedavi etkinliği, yan etkilerin önlenmesi.*

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Introduction

The use of protons for radiation therapy was first suggested by Robert Wilson in 1946 (1). Two years after Wilson, the 184-inch Cyclotron at the Lawrence Berkeley Laboratory became available for physics and radiobiological investigations in preparation for human use. The first therapeutical use of proton beams in humans was for pituitary hormone suppression in the treatment of patients with metastatic breast cancer in 1954. The choice of the pituitary was due to its being a well-localized gland closely surrounded by radiosensitive neural structures but also by bony landmarks which made it locatable on x-ray films.

Proton therapy (PT) has been in clinical use since 1970. It is reported that 61,122 patients were treated worldwide in more than 30 centers by December 2008 (2).

Advantages of Proton Therapy

The major advantage of proton treatment over conventional radiation is physical; the energy distribution of protons can be directed and deposited in tumoral tissue and with a reduced dose beyond the cancer site. A monoenergetic proton beam has an entrance region of a slowly increasing dose, the plateau, which is followed by an ever more rapid increase in dose leading to a sharp peak, called the Bragg peak, named after the physicist William Bragg. Beyond the Bragg peak the dose rapidly reduces to zero, with almost no additional exit dose. Multiple Bragg peaks of different energies are superimposed to create a region of relatively uniform high dose, called the Spread out of Bragg Peak (SOBP), which is suitable to cover larger treatment volumes while sparing adjacent normal structures (Figure-1).

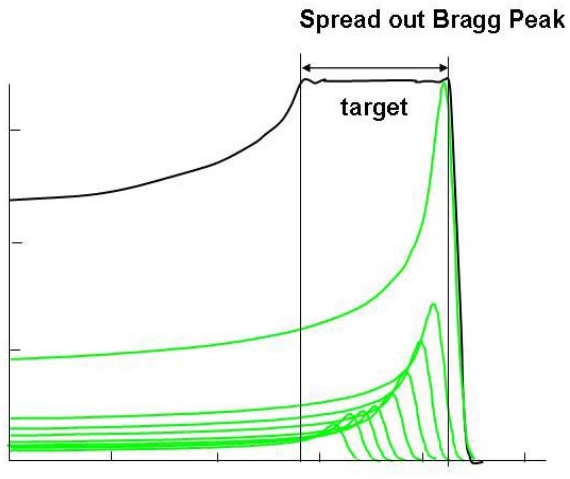

Figure-1. Depth dose curve for the proton beams. The superposition of proton beams of different energies creates a spread-out of Bragg Peak (SOBP)

Conventional photon radiation techniques control many cancers. However, because of the inability to adequately conform the irradiation pattern to the target, healthy tissues may receive a similar dose and can be damaged. In addition, less dose to normal tissue results in improving radiation therapy (RT) tolerance, uninterrupting RT and allowing integration of radiotherapy with systemic chemotherapy. Indirectly, reducing late effects permits the radiation oncologist to dose escalation to a tumor and higher tumor control.It must be emphasized that protons have biologic effects in tissue similar to those of the megavoltage photons used in conventional therapy. They are regarded as low linear energy transfer particles, unlike other non-conventional radiotherapy particles, such as neutrons or carbon ions. The Relative Biological effectiveness of protons for 70–250 MeV protons range typically form 0.9 to 1.9, with an accepted “generic” value of 1.1 in clinical proton therapy [3] and proton doses were expressed in terms of Gy(RBE) (Gy(RBE)=proton Gy×1.1) [4].

Clinical Use

Proton beam therapy has been most extensively studied in the treatment of uveal melanomas and in the skull base chordoma and chondrosarcoma patients. Other tumors successfully treated with PT are some of the central nervous system (CNS) tumors such as acoustic neuromas, ependymomas, gliomas and meningiomas, spinal tumors such as chordoma and chondrosarcoma, soft tissue and bone sarcomas, head and neck, thorax (lung and mediastinal tumor), gastrointestinal (esophagus, liver), prostate, sarcomas, breast cancer and pediatric tumors.

Ocular Tumours

Proton therapy (PT) can be an alternative to the enucleation in case of large tumors or an alternative to brachytherapy in case of small tumors, however close to macula and optic disk. The main rationale in uveal melanoma is providing adequate local control while still preserving vision. Five year local control rates in the range of %85-96 and eye retention rates between 75% and 100% were observed in the literature (5-10). Generally, a total dose of 60 Gy(RBE) was delivered in 4 fractions. Radiation induced complications resulted in secondary enucleations and were reported in approximately 6% in these series. Dose reduction from 70 Gy(RBE) to 50 Gy(RBE) has been investigated to further reduce toxicity in patients with small to medium sized choroidal melanomas (11). Although there was no difference between local control rates, less visual loss

was observed after low doses. The results from literature justify that uveal melanomas that cannot be treated satisfactorily with episcleral plaque brachytherapy but can be treated with proton.

Chordomas and chondrosarcomas

Surgery is the treatment of choice for skull base chordomas and chondrosarcomas patients. However, because of the difficulty in achieving complete removal of tumors, frequently affecting the brainstem and cranial nerves, led to the use of radiation therapy. The available evidence also suggests that particle beam radiation therapy is superior to conventional photon radiotherapy in the skull base chordoma and chondrosarcoma patients. Close proximity to organs at risk does not allow safe dose escalation with conventional 50-55 Gy photon RT that results in poor local disease control in these patients when compared to particle therapy (12-16). The reported local progression-free survival rate after conventional therapy ranges from 17% to 65% at 5 years (12-16). The principal rationale for the use of protons has been to reduce the dose to the brainstem and optic structures and allow for safe dose escalation to the primary tumor with the hope of improving tumor control and survival. A large series of patients with chondrosarcoma and chordomas of the skull base was treated at Massachusetts General Hospital (17). The patients were treated with a combination of proton and photon therapy to a median dose of 72.1 Gy(RBE). Local control rates for chondrosarcomas were 99% and 98% at 5 and 10 years, respectively, however patients with chordomas were found to have lower rates of local control with 59% and 44% at 5 and 10 years, respectively. A group at Loma Linda University Medical Center reported 59% local control rate for the chordomas and 75% for chondrosarcomas patients (18). Aduvant high dose RT is recommended and clear dose–response relationship has been demonstrated for skull base chordoma and chondrosarcomas. Altough some improvements have been achieved with PT, the long term outcome is unsatisfactory for the chordoma group and the number of local recurrens occuring after 5 years of treatment.

Pediatric tumors

Proton therapy has much more significance in the case of pediatric patients. There is no reported benefit from dose escalation studies and high dose is not generally required to treat pediatric malignancies, however, late side effects and secondary malignancy risk are of greater concern. Miralbell et al. showed improved dose distribution with proton therapy as compared to 3D conformal photon radiation and intensity-modulated photon beam radiation on the induction second malignancies (19). Treatment plans were compared for one patient with rhabdomyosarcoma of the paranasal sinus and for one patient with medulloblastoma. The expected risk of radiation-induced malignancy for intensity modulated proton therapy (IMPT) was almost 2.4 lower than the conformal photon plan and about half the risk expected for intensity modulated for photons. Because of the relatively high probability of long-term survival in pediatric cancers, the risk of second malignancy is clinically more significant than in adults. Various CNS malignancies and nasopharynx tumours can be treated with particle therapy with lower morbidity compared to photon, however when lower doses and wider fields of RT are required such as with lymphoma, Wilms tumor or neuroblastoma, proton therapy has a limited role.

Head and neck cancers

Proton therapy gains importance especially in the case of sinonasal malignancies in the head and neck region. A combination of radical surgery and postoperative radiation is the treatment of choice for most of the sinonasal malignancies, however due to the proximity of critical structures, radiation induced late toxicity is common. Conformal RT or Intensitiy Modulated Radiation Therapy (IMRT) have reduced toxicity, however, local control and overall survival were more favorable with PT (20-22). Chan et al. reported 102 patients with advanced sinonasal malignancies treated with PT at Harvard Cyclotron Laboratory Massachusetts General Hospital (HCL-MGH). The 5 year actuarial local control was 86% (23).

Lung cancer

It is expected that PT would minimize or reduce pulmonary injury, also it can reduce the dose to the osephagus spinal cord and heart compared to photon therapy. Hata et al. analyzed 21 stage I non small cell lung cancer (NSCLC) patients treated with hypofractionated high-dose PT (24). Three and 18 patients received proton beam irradiation with the total doses of 50 Gy(RBE) and 60 Gy(RBE) in 10 fractions, respectively. They reported that the 2 year overall and cause-specific survival rates were 74% and 86%, respectively. No therapy-related toxicity of Grade $\geq$ or =3 was observed. Other prospect study from the Loma Linda group reported their series with stage I NSCLC treated with 51 Gy(RBE) and 61 Gy(RBE) in 10 fractions (25). The 3 year local control rate and disease specific survival were 74% and 72%, respectively. They did not

observe symptomatic radiation pneumonitis or late esophageal or cardiac toxicity. However, comparative clinical studies with similar fractionation and total doses for PT vs stereotactic or 3D conformal X-ray RT are still unavailable, so it is difficult to draw any conclusion for the local control and overall survival.

Hepatocellular Carcinoma

Radiation therapy is one of the treatment options for hepatocellular carcinoma. We can use photon, however it is expected that proton can spare more liver compared to photon radiation treatment. Bush et al. reported one prospective study, they analysed T1-3 and selected T4 tumors treated with 63 Gy(RBE) in 15 fractions (26). Two-year actuarial local control and overall survival rates were 75% and 55%, respectively.

Prostate cancer

There have been no clinical trials showing that PT has fewer side effects or is more effective compared to IMRT treatments. The proton dose distribution is sensitive to uncertainties in the particle range in the tissue. The day to day variation in rectal and bladder filling do not allow use of oblique fields that pass through the bladder and rectum as in the 3D conformational or IMRT in the treatment of prostate cancer. Proton therapy is planned with two lateral opposed beams while IMRT spreads out the dose with several beams, results in a high dose region in the anterior rectum wall and/or bladder, and less gain than expected. Trofimov et al. from Boston reported that IMRT achieved significantly better sparing of the bladder regarding higher than 60 Gy(RBE), while rectal sparing was similar with 3D proton planning (27). A does lower than 50% of the target prescription to healthy tissues was lower with proton therapy in this study.

Beam Delivery Techniques

Until the project at Paul Scherrer Institute (PSI) in 1996, PT was delivered by passive scattering. In the passive scattering technique, the beam is spreaded laterally with double scatterer in uniform high-dose (Figure-2a).

The Bragg peak is modulated in depth by varying the energy (range) of the incident protons using a variable thickness rotating wheel. The dose is then shaped in the lateral direction using collimators. An individual compensator bolus can be added to this set-up to shift the distal edge of the dose field to conform more closely to the deepest side of the target volume. All the necessary hardware must be adapted for each single field (28).

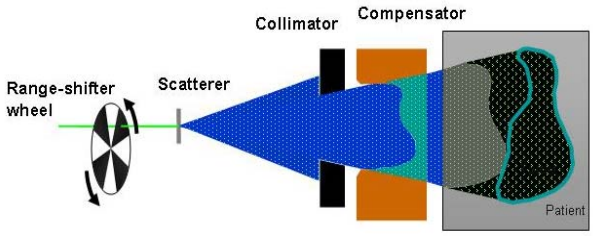

Figure-2a. Diagrammatic representation of a typical passive scattering proton beam delivery system.

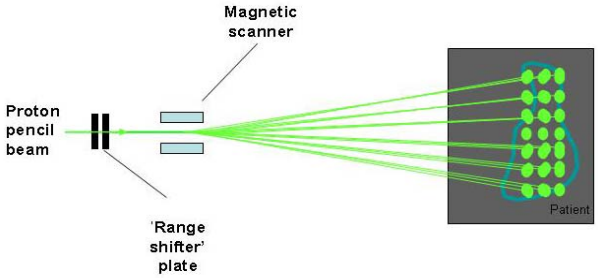

Figure-2b. Diagrammatic representation of a typical active scanning proton beam delivery system.

Active scanning technology has been developed at PSI. By using large kicker-magnets, proton-spots in 7 mm diameter are directed to gantry and to the patient using this technique. In depth, the near mono-energetic Bragg peaks are shifted through the mechanical insertion of thin polyethylene plates immediately before the patient. These movements are repeated, layer by layer, and scanning is completed by table and coach movement corresponding to the shape of the target (28). Many proton facilities in the world have voiced their interest in moving towards an active scanning system. Apart from reducing scattered dose and without need of a patient's specific hardware, intensity modulation and inverse planning are possible with active scanning. The IMPT can only be implemented with active scanning. In IMPT, dose distribution is improved even further with all simultaneous optimization of Bragg-Peaks from each field. In contrast to IMRT with photon, the dose can be modulated also in depth (29).

The dose distribution of a proton pencil beam is characterized by a shallow entrance dose, proximal dose conformation is better achieved compared to passive scattering. However, organ motion and range uncertainty are more severe for dynamic systems and lateral pneumbra is larger compared to a passive system, because of spot size and range shifter plates that exist in the current gantry of PSI.

Cost effectiveness of Proton Therapy

The high cost of particle accelerators compared with X-ray technology kept protons out of mainstream healthcare for many years. Goitein and Jermann estimated that the ratio of costs between protons and x-rays is approximately 2.4 (30). However any proven clinical benefits of PT must be taken into account in a cost-effectiveness evaluation. An analysis from Sweden showed that PT can be cost-effective and cost-saving compared with conventional RT in the treatment of children with medullablastoma if the appropriate patients are selected (31). In this study it was shown that PT provided 0.68 additional quality-adjusted life-years and €23.600 cost saving per patient, in addition, they reported that reduction in IQ loss and growth hormone deficiency contributed to the greatest part of the cost savings and were the most important parameters for cost-effectiveness.

Interest is growing in proton technology, as evidenced by the opening of dedicated clinical proton-therapy facilities in the US, Japan and Europe. Most publications were in the form of retrospective or phase I/II studies. There are no phase III (randomised controlled) trials of protons vs photons. It is hoped that with the increasing number of proton therapy facilities will allow more clinical trials.

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