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Proton therapy – Present and future☆

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ABSTRACT

In principle, proton therapy offers a substantial clinical advantage over conventional photon therapy. This is because of the unique depth-dose characteristics of protons, which can be exploited to achieve significant reductions in normal tissue doses proximal and distal to the target volume. These may, in turn, allow escalation of tumor doses and greater sparing of normal tissues, thus potentially improving local control and survival while at the same time reducing toxicity and improving quality of life.

Protons, accelerated to therapeutic energies ranging from 70 to 250 MeV, typically with a cyclotron or a synchrotron, are transported to the treatment room where they enter the treatment head mounted on a rotating gantry. The initial thin beams of protons are spread laterally and longitudinally and shaped appropriately to deliver treatments. Spreading and shaping can be achieved by electro-mechanical means to treat the patients with "passively-scattered proton therapy" (PSPT) or using magnetic scanning of thin "beamlets" of protons of a sequence of initial energies. The latter technique can be used to treat patients with optimized intensity modulated proton therapy (IMPT), the most powerful proton modality.

Despite the high potential of proton therapy, the clinical evidence supporting the broad use of protons is mixed. It is generally acknowledged that proton therapy is safe, effective and recommended for many types of pediatric cancers, ocular melanomas, chordomas and chondrosarcomas. Although promising results have been and continue to be reported for many other types of cancers, they are based on small studies. Considering the high cost of establishing and operating proton therapy centers, questions have been raised about their cost effectiveness. General consensus is that there is a need to conduct randomized trials and/or collect outcomes data in multi-institutional registries to unequivocally demonstrate the advantage of protons.

Treatment planning and plan evaluation of PSPT and IMPT require special considerations compared to the processes used for photon treatment planning. The differences in techniques arise from the unique physical properties of protons but are also necessary because of the greater vulnerability of protons to uncertainties, especially from inter- and intra-fractional variations in anatomy. These factors must be considered in designing as well as evaluating treatment plans. In addition to anatomy variations, other sources of uncertainty in dose delivered to the patient include the approximations and assumptions of models used for computing dose distributions for planning of treatments. Furthermore, the relative biological effectiveness (RBE) of protons is simplistically assumed to have a constant value of 1.1. In reality, the RBE is variable and a complex function of the energy of protons, dose per fraction, tissue and cell type, end point, etc.

These uncertainties, approximations and current technological limitations of proton therapy may limit the achievement of its true potential. Ongoing research is aimed at better understanding the consequences of the various uncertainties on proton therapy and reducing the uncertainties through image-guidance, adaptive radiotherapy, further study of biological properties of protons and the development of novel dose computation and optimization methods. However, residual uncertainties will remain in spite of the best efforts. To increase the resilience of dose distributions in the face of uncertainties and improve our confidence in dose distributions seen on treatment plans, robust optimization techniques are being developed and implemented. We assert that, with such research, proton therapy will be a commonly applied radiotherapy modality for most types of solid cancers in the near future.

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Contents

1. Introduction

1.1. Conventional radiotherapy of cancers

Most of the current practice of clinical radiotherapy utilizes photon beams of energies ranging from 4 to 18 megavolt (MV). Less than 1% of the patients world-wide are treated with protons and heavier ions, though the number is increasing as new facilities are established. As illustrated in Fig. 1, photon radiation dose as a function of depth in the patient rises initially as the electrons ejected by photons build up to a maximum and then declines exponentially as photons are absorbed. Thus, a photon beam deposits dose from the entrance all the way to where it exits from the body. A crossfire arrangement of multiple beams is used to deliver high and curative dose to the tumor target while maintaining the normal tissue doses to below tolerance limits.

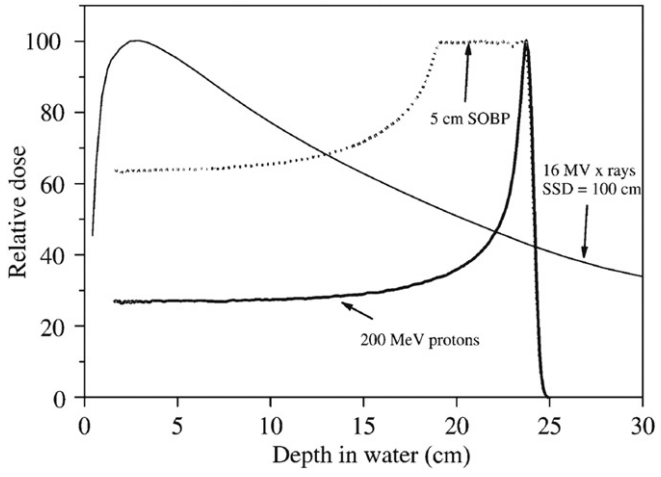

Fig. 1. Depth-dose curves for a 200 MeV proton beam: both unmodulated and with a 5 cm spread-out Bragg peak (SOBP), compared with a 16 MV X-ray beam (for 10 × 10 cm^2 fields). The curves are normalized in each case to 100 at maximum dose. (Adapted from Jones, reproduced with permission) [1].

In the mid-1990s, radiotherapy with photons took a giant leap forward when intensity modulated photon radiotherapy (IMRT) was introduced. With IMRT, each of a group of broad beams of photons is subdivided into narrow beamlets of cross-sections of the order of 1/2 cm × 1/2 cm and delivered using dynamic multi-leaf collimators. Following its introduction over 20 years ago, IMRT has continued to steadily evolve and is now considered both state-of-the-art and standard of care for many malignancies. In IMRT, intensities of the beamlets are adjusted using optimization techniques to appropriately balance the target and normal tissue dose distributions. IMRT allows considerable control to tailor dose distributions to achieve desired clinical objectives. However, given the physical properties of photons, normal tissues surrounding the target volume still receive a substantial amount of unwanted dose, which often limits our ability to deliver curative dose to the tumor without unacceptable normal tissue toxicities.

1.2. Rationale for proton therapy

In contrast to photons, when protons of a given energy (typically in the range of 70 to 250 MeV) penetrate matter, they slow down continuously as a function of depth. The rate of their energy loss (called "linear energy transfer" or LET) increases with decreasing velocity. This continues until their entire energy is depleted and then they come to an abrupt stop. This process of dose (energy deposited per unit mass) deposition produces a characteristic depth-dose curve ("Bragg curve") for a broad monoenergetic beam of protons as illustrated in Fig. 1. The point of highest dose is called the Bragg peak. The depth of the peak, i.e., the range of protons, is a function of the initial energy. Dose deposited beyond the range is negligible. As protons traverse a medium, they also scatter laterally, but the dose outside the boundary of a beam of protons falls rapidly.

Narrow, monoenergetic beams of protons for therapeutic use can be produced using cyclotrons or synchrotrons as discussed in Section 3. For clinical use, the beams are spread longitudinally (to create a "spread-out