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Proton Therapy for Head and Neck Cancers

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Because of its sharp lateral penumbra and steep distal fall-off, proton therapy offers dosimetric advantages over photon therapy. In head and neck cancer, proton therapy has been used for decades in the treatment of skull-base tumors. In recent years the use of proton therapy has been extended to numerous other disease sites, including nasopharynx, oropharynx, nasal cavity and paranasal sinuses, periorbital tumors, skin, and salivary gland, or to reirradiation. The aim of this review is to present the physical properties and dosimetric benefit of proton therapy over advanced photon therapy; to summarize the clinical benefit described for each disease site; and to discuss issues of patient selection and cost-effectiveness.
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Introduction

Radiotherapy for head and neck cancer can be delivered as a definitive treatment or as an adjuvant treatment after surgery.[1] The vast majority of treatments are currently given as external beam photon therapy. Over the past 20 years, the use of intensity-modulated photon therapy (IMRT), and more recently volumetric modulated arc therapy, has allowed considerable improvement in treatment conformality and reduction of high doses to neighboring critical structures. Consequently, this has drastically reduced the incidence of major forms of toxicity, most notably xerostomia[2,3]; however, the improvements in physical delivery of photon therapy have reached a plateau and come at the cost of alternative toxic effects such as fatigue, nausea, hair loss, and oral mucositis,[2,4] and further improvements in the therapeutic ratio require alternative methods of radiation delivery.

In this context, proton therapy has emerged as a novel means to reduce toxicity and potentially further improve tumor control. The unique physical properties of charged particles allow a steep dose gradient with a reduced integral dose delivered to the patient in a proportion that can meaningfully reduce dose-related toxicity. The aims of this review are to present the current evidence on the use of proton therapy for the treatment of head and neck cancers. After discussing the physical properties of protons and the dosimetric advantages of proton therapy over IMRT, we will review the potential clinical implications of this dosimetric benefit, the clinical experience to date in adult patients, and the best way to further collect evidence while selecting patients for the most appropriate form of radiation therapy.

References Search

Although this report is not a formal systematic review in that it does not rely on multiple databases and a broad search strategy, we conducted a Pubmed search in the process of writing this review by using the following search equation: ((“proton therapy” OR “protontherapy” OR “proton beam

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therapy" OR "particle therapy" OR "hadrontherapy" OR "hadron therapy" OR "proton radiation" OR "proton beam radiation") AND (head and neck cancer)). The final search was performed on March 22, 2017 by 1 author (P.B.) and produced 466 references.[39] Articles reporting on clinical results were included in the present review. Fourteen references evaluated cost-effectiveness and treatment selection issues. Select articles from the 373 excluded references, mostly dosimetric or physics analyses, are used for illustrative purposes. A diagram of this literature search can be found in Supplementary Appendix.

Physical Properties and Dosimetric Results

A focused beam of protons is accelerated by a particle accelerator that can be used for therapeutic purposes. The main characteristics of protons that explain their dosimetric superiority over photons are (1) the absence of exit dose beyond the target and (2) the sharper lateral dose distribution secondary to protons' heavier mass relative to photons. The Bragg peak phenomenon is the sharp increase in dose deposited at the end of the particle range, and results from the charged nature of protons (Fig. 1). Proton treatments can be delivered by using passive scattering or active scanning techniques. In the passive scattering technique, the proton beam is spread out by using scattering foils and conformed laterally by using brass apertures, similar to what would be done in 3D photon therapy. The depth modulation is done with range compensators, similar to photon therapy before the use of multileaf collimators. This technique is less flexible than active scanning, requires the production of patient-specific devices that are labor-intensive to create, generates secondary neutrons, and limits the capacity for adaptive replanning in case of tumor or anatomical changes during treatment. Active scanning, also known as intensity-modulated proton therapy (IMPT), on the other hand, relies on the magnetic properties of protons. A small proton beam is generated, the energy is varied to treat the different layers of the tumor, and magnets are used to deflect and conform the beam to the target volume. IMPT is currently the most widely used form of proton therapy and all newly constructed facilities have IMPT capabilities.

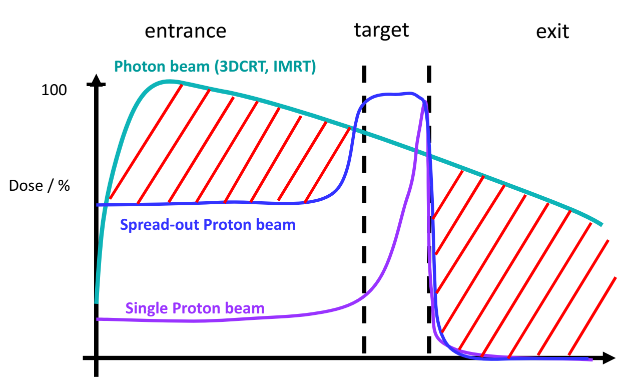

Figure 1 Dose-depth curve of photons and protons. The dashed red zone represents the unnecessary dose delivered by photons that can be "avoided" using protons. 3DCRT: 3-dimensional conformal radiation therapy; IMRT: intensity-modulated radiation therapy. (Color version of the figure available online.)

Treatment planning for head and neck cancers is done by using a multifield optimization algorithm that allows optimization of all spots from all fields simultaneously.[5] The drawback of protons' dosimetric superiority is their sensitivity to physical and geometrical uncertainties,[6,7] which needs to be accounted for before and during treatment. At the planning phase, the robustness of the optimization with regard to changes in patient setup, changes in anatomy due to tumor response or changes in weight, and changes in beam range and patient movement during treatment should be assessed before the plan is approved.[8] Quality checks at the MD Anderson Proton Therapy Center include complete quality assurance testing of each plan before delivery, verification of the accuracy of the dosimetry on a second planning computed tomography (CT) scan obtained the day before the treatment is started and on a third scan obtained during the fourth week of treatment.[9,10] For tumors at specific locations such as the paranasal sinuses, doses to organs at risk approaching the tolerance limit, or for other anatomy changes such as weight loss, additional verification CTs can be obtained. In addition, at Mayo Clinic, Monte Carlo dose calculations are performed as a second check of the treatment planning system dose calculations and for robust optimization. Verification CT scans are obtained weekly for at least the first 5 weeks. Daily CT imaging with the patient on the treatment couch in the treatment position will soon be implemented. In a prospective analysis of 50 patients with oropharyngeal cancer (OPC) treated at MD Anderson Cancer Center, adaptive replanning during IMPT because of weight loss or tumor volume changes was done for 38% of the patients, including 1 patient who required adaptive replanning twice.[11] In the first 50 patients treated at Mayo Clinic, replanning was done for 36% of cases (Dr Foote, personal communication). The final source of uncertainty is related to the relative biological effectiveness (RBE) of protons, which is the factor used to quantify the difference in the effective dose from protons compared with an equivalent biological dose of photons. The current practice is to use a uniform RBE value of 1.1, but recent reports suggest that RBE is variable,[12] and might be higher close to the Bragg peak. Although uniform consensus on the variability of the RBE has not been reached, treatment planning systems can be developed to maximize the high-RBE values within tumors, and to avoid organs at risk. At Mayo Clinic, Monte Carlo dose calculations are used to produce treatment plans based on physical dose, linear energy transfer, and variable RBE (used qualitatively, not quantitatively, and to account for the uncertainties in RBE).

The dosimetric advantage of protons over photons for the treatment of sinonasal, nasopharyngeal, or oropharyngeal cancer was suggested as early as 1989.[13-15] Scans showing comparative dosimetry for 2 patients, one with a nasopharyngeal carcinoma and the other with a maxillary adenoid cystic carcinoma, are given in Figure 2. In both cases the use of protons can spare organs from up to 25 Gy of unnecessary radiation compared with standard IMRT. Many articles have