Comparison of Efficacy of Proton Beam and ^{90}Sr/^{90}Y Beta Radiation in Treatment of Exudative Age-Related Macular Degeneration

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Abstract

Purpose - To explore the differences between proton beam and beta radiation for the treatment of choroidal neovascularization, both theoretically and in treatment outcomes.
Approach - Differences in particle mass and energy are discussed with emphasis on resulting differences in penetration depth. Concepts and terms in Radiology are reviewed, especially the terms Dose Equivalent and Cobalt Gray Equivalent used to compare radiation damage from different sources.
Results - In assessing treatment outcomes for exudative macular degeneration from proton beam and beta radiation plaque therapies, there is a discrepancy in complications if the usually-applied Dose Equivalent is applied to protons.
Conclusions - Reasons for this discrepancy are discussed and a modified Dose Equivalent is deduced. Direct comparisons from the literature are shown in an appendix.

Introduction

Radiation has been proposed for some time in the treatment of exudative age-related macular degeneration (AMD); however, some reports of radiation retinopathy using proton beam therapy have raised questions as to the safety of such treatments. These reports have not been confirmed in studies using beta emitters such as ^{90}Sr and ^{103}Pd. It is the purpose of this paper to examine the differences and similarities of these two treatments.

Protons are positively charged nuclear particles having a mass 1800 times that of a beta particle (electron). They interact primarily with target tissue electrons, but also with nuclei in complex ways, sometimes leading to neutron emission. Electrons interact only with the electrons in the shells around atoms and molecules. In both cases the primary radiation ejects electrons out of the atom, leaving behind a positively charged ion. This process happens multiple times since the particle energy is far more than required to ionize a single atom or molecule.

In addition the particle energies are different. The maximum energy in the ^{90}Sr/^{90}Y system is 2.3 million electron volts (MeV); whereas, typical energies in proton beams are 80 to 200 MeV. The particle energy is taken into account in calculating the absorbed dose, so there are many more of the lower-energy beta particles than protons in the same absorbed dose. Interaction of more energetic and more massive protons with any material, including tissue, is much different from that of beta electrons. The protons take a more direct path through tissue until they give up all their energy to surrounding atoms; whereas, the low energy and light electrons forming beta radiation take a wandering, tortuous path through target materials.

Approach

The penetration depth varies by energy in both cases, but in very different ways. Beta emission is characterized by a range of electron energies, with a tail in the distribution towards zero at the high end of the energy range. Strontium-90 is particularly complex, because it actually consists of two emissions: lower energy ^{90}Sr beta particles and higher energy beta particles from the daughter nucleus – yttrium (^{90}Y). The energy spectrum from ^{90}Y has a maximum energy of 2.3 MeV and an average energy of 0.9 MeV[1]. The maximum energy of ^{90}Sr beta particles is 0.5 MeV, and the average is 0.2 MeV[1]. The highest energy particles have the longest range (11 mm in water or soft tissue), but there are very few of them, and the lowest energy particles have such a short range that they are not therapeutically significant in most applications. A more useful range number is the average value – 1.8 mm for pure ^{90}Sr radiation and 3.6 mm for pure ^{90}Y radiation[2].

Proton penetration has a nearly opposite profile. Instead of the absorbed dose falling off exponentially with distance, it is nearly constant until the proton energy is sufficiently reduced, at which point the dose increases rapidly to a peak some 3 to 5 times the plateau value and then drops rapidly to zero[3]. The depth of that peak dose is typically 15 to 25 cm, depending on beam energy.

To take into account the different effects of various radiation types, health physicists have defined a Quality Factor or Radiation Weighting Factor to assess the degree of damage that the different radiation types will do. The weighting factor for gamma photons and beta particles is 1, for alpha particles 20, and for protons and neutrons various values between 1 and 20, depending on their energy[4].

The Dose Equivalent is measured in sieverts (Sv) and is defined as the product of the Absorbed Dose (in grays, Gy) and the Radiation Weighting Factor. The U.S. Nuclear Regulatory Commission uses the term Quality Factor instead of Radiation Weighting Factor and assigns the value 10 to high energy protons[5]. There is considerable debate regarding the proper value for such protons, and in recent years, the values have dropped much lower. The International Commission for Radiological Protection (ICRP) has recommended values of the Radiation Weighting Factor from 20 (originally) to 2 (currently) over a period of several years. Radiologists, however, usually use a value of 1.1 to calculate the 'Cobalt Gray Equivalent' (CGE), a term equivalent to Radiation Weighting Factor and Quality Factor.

Results - Treatment Differences for AMD

Radiation therapy to treat exudative AMD was first described in 1993 by Chakravarthy et al. reporting the preliminary results of a series of 19 patients treated with external beam radiation[6]. Since then there have been numerous studies evaluating the effects of radiation for the treatment of AMD.[7,8,9,11,14]

Using total doses from 2 to 24 Gy, no serious ocular or systemic complications have been reported in clinical trials with beta radiation. For example, Finger et al. recently reported the results of two long-term studies of palladium-103 plaque radiation using single doses of 12.5 -24 Gy in eyes with exudative AMD, and no radiation complications were seen in more than 50 subjects during the follow-up period of up to seven years.[10,11]

On the other hand, proton beam studies of AMD and ocular melanomas show radiation retinopathy using as little as 14 Gy.[12] The authors of that paper make an interesting comment, however: "The CGE unit of measure (cobalt gray equivalent = dose equivalent) implies equal biological effectiveness regardless of the ionising radiation source – X-rays or protons. An equal single dose X-ray and proton CGE exposure, however, may not truly have an equal biological effectiveness due to differences in duration of tissue exposure and other factors that are not fully understood."[12]

Two of these other factors are the area and volume of the retina and surrounding tissue exposed to radiation. External beams, even those delivering radiation stereotactically, have a target size of 10 mm or more, over which the beam intensity is approximately uniform; and the depth of treatment is substantial, even with mono-energetic beams. In treating AMD, the diameter of tissue to be treated is usually no more than 5 mm; thus, the required area to be exposed is less than 1/4 of the minimum area exposed to an external proton beam. Furthermore, the depth of penetration of beta particles in tissue is very small – just a few mm; therefore, the volume of tissue irradiated is very much smaller. Volume treated is significant because of the "bystander effect", which describes the death of cells neighboring those which have been damaged or killed by radiation directly. The differences in area, volume, and microscopic interactions account for some of the differences in biological effects that are reported in the literature.

In Flaxel's work[12], radiation retinopathy was seen at 3 to 30 months in 41% of the 27 subjects tested with 14 Gy protons; whereas, in Jaakkola's study[13] of 86 subjects with 12.6 and 32.4 Gy[14] ^{90}Sr plaques, only one patient was observed with "radiation retinopathy-like changes" in 36 months follow-up (that patient received the higher dose of 32.4 Gy). These results imply a weighting factor of considerably more than 2, perhaps even 4.

In a study of hundreds of subjects with plaque therapy for posterior uveal melanoma, Gündüz et al. reported an average of 44.5 Gy received at the fovea in eyes in which no radiation retinopathy was reported.[15] Compared with Flaxel, a weighting factor of more than 3 and up to 5 is implied.

Conclusion

There is a considerable degree of complication in discussion of this topic because of the variation in particle energies, penetration depth, and modes of interaction; nevertheless, at least in this application it has been shown that proton beam radiation is likely to be much more damaging to biological tissue at the same dose, by a factor of about four.

Appendix: Comparison of Exudative AMD Treatments with Radiation

$^{90}Sr/^{90}Y$	Proton Beam
Finger, *et al*, 2003[11] 12.5 to 24 Gy plaque, 1 fraction 78% of eyes had stable or improved vision at 12 months 0% of eyes had radiation complications	Yonemoto, *et al*, 1996[8] 8 Gy, 1 fraction 58% of eyes had stable or improved vision at 12 months No radiation complications
Jaakkola, *et al*, 2005[13,14] 12.6 Gy plaque, 1 fraction 39% of eyes had stable or improved vision at 12 months 0% of eyes had radiation complications	Flaxel, *et al*, 2000[12] 8 Gy, 1 fraction 44% of eyes had stable or improved vision at 12 months No radiation retinopathy
Jaakkola, *et al*, 2005[13,14] 32.4 Gy plaque, 1 fraction 78% of eyes had stable or improved vision at 12 months 6% of eyes (n=1) had radiation complications	Flaxel, *et al*, 2000[12] 14 Gy, 1 fraction 75% of eyes had stable or improved vision at 12 months 41% of eyes showed radiation retinopathy
Ávila, *et al*, 2007[16] 15 & 24 Gy epi-retinal approach (15 Gy: n=8; 24 Gy: n= 26), 1 fraction 82% of eyes had stable or improved vision at 12 months 0% of eyes had radiation complications	Zur, *et al*, 2001[17] 10 Gy, 1 fraction 80% of eyes had stable or improved vision at 12 months No radiation complications reported in abstract
	Zambarakji, *et al*, 2006[18] 16 Gy, 2 fractions 58% of eyes had stable or improved vision at 12 months 16% of eyes had radiation complications
	Zambarakji, *et al*, 2006[18] 24 Gy, 2 fractions 65% of eyes had table or improved vision at 12 months 15% had radiation complications

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