Clinical enthusiasm for proton therapy (PT) is high, with an exponential increase in the number of centers offering treatment (1). Attraction for this charged particle therapy modality stems from the favorable proton dose distribution, with low radiation dose absorption on entry and maximum radiation deposition at the Bragg peak (2). The current clinical convention is to use a fixed relative biological effectiveness (RBE) value of 1.1 in order to correct the physical dose relative to photon therapy (i.e., proton radiation is 10% more biologically effective than photon radiation). In recent years, concerns about the potential side effects of PT have emerged. Various studies and review articles have sought to better quantify the RBE of PT and shine some light on the complexity of this problem. Reduction in biologic hot spots of non-target tissue is paramount in proton radiation therapy (RT) planning as the primary benefit of proton RT is a reduction in organ at risk (OAR) irradiation. New and emerging clinical data is in support of variable proton biological effectiveness and demonstrate late toxicity, presumably associated with high biological dose, to OAR. Overall, PT has promise to treat many cancer sites with similar efficacy as conventional RT but with fewer acute and late toxicities. However, further knowledge of biologic effective dose and its impact on both cancer and adjacent OAR is paramount for effective and safe treatment of patients with PT.

**Keywords:** Proton therapy (PT); radiation biology; radiation therapy (RT)

Submitted Apr 08, 2019. Accepted for publication Jun 19, 2019.
doi: 10.21037/jgo.2019.06.08

**Abstract:** Clinical enthusiasm for proton therapy (PT) is high, with an exponential increase in the number of centers offering treatment (1). Attraction for this charged particle therapy modality stems from the favorable proton dose distribution, with low radiation dose absorption on entry and maximum radiation deposition at the Bragg peak (2). This leads to improved tumor targeting and normal tissue sparing and is particularly advantageous for the treatment of tumors positioned near crucial structures (3). The proton radiation track structure on the nanoscale and hence energy deposition differs from that of conventional photon radiation therapy (RT), leading to a different biological effect. DNA damage generated by particle tracks with high linear energy transfer (LET) are thought to be more complex and more difficult to repair (4,5).

The current clinical convention is to use a fixed relative biological effectiveness (RBE) value of 1.1 in order to correct the physical dose relative to photon therapy (i.e., proton radiation is 10% more biologically effective than photon radiation) (6). RBE is defined as the ratio of physical doses that cause the same biological effect and is calculated as \( RBE = D_{\text{control}} / D_{\text{test}} \). In this equation \( D_{\text{control}} \) is the physical dose of a reference radiation modality (X-rays) and \( D_{\text{test}} \) is the physical dose of the radiation modality being investigated (protons).

In recent years, concerns about the potential side effects...
of PT have emerged. Various studies (7-17) and review articles (18-22) have sought to better quantify the RBE of PT and shine some light on the complexity of this problem. In a 2014 review article, Paganetti showed the average proton RBE values across a spread out Bragg peak (SOBP) range from 0.9–1.7 (19). A large body of in-vitro evidence for the variation in PT RBE has been published and collected in the online, open-access Particle Irradiation Data Ensemble (PIDE) database (23).

The use of a constant RBE disregards the experimental evidence demonstrating that RBE has a complex dependency on dose per fraction, tissue type, LET, and biological endpoint (4). This translates to an uncertainty in the biological effective dose delivered to the patient, more so in the regions surrounding the Bragg peak where the RBE is hypothesized to be significantly higher, and may lead to substantial dose increases to normal tissue.

Based on the in vitro data, many RBE models that relate LET and RBE have been developed (24-30). Figure 1 represents a simple linear model between RBE and LET (26,30). Most of the models have similar features, with the major difference in the magnitude of the RBE at the distal falloff. One major item the in-vitro studies do not include is the effect of fractionation. There is evidence to suggest that with fractionation, the RBE of the high LET region may be amplified (32). Figure 2 shows that potentially high biological dose can exist in critical normal tissue and with slight modification to the overall dose distribution; these biological hot spots can be reduced.

Reduction in biologic hot spots of non-target tissue is paramount in proton RT planning as the primary benefit of proton RT is a reduction in organ at risk (OAR) irradiation. New and emerging clinical data is in support of variable proton biological effectiveness and demonstrate late toxicity, presumably associated with high biological dose, to OAR (33-39). In some situations, such as pediatric brain cancer, this has prompted expert working groups for consensus guidelines on proton planning to account for this (40-42).

With conventional RT planning, target expansions are created to account for subclinical disease, target motion, and variations in treatment set up. Often such expansions may result in target volumes extending to or within adjacent organs. The Bragg peak may in fact be within an OAR, with a higher biologic dose in OAR than tumor. This is highlighted in several examples of malignancies within the gastrointestinal (GI) tract.
For example, as illustrated in Figure 2, several cardiac structures, including the left atrium, left ventricle, and coronary arteries, may be situated just anterior to or within the radiation target volume for a distal esophageal cancer. Without considering the biologic effective dose during proton planning, proton RT may increase toxic effects to the heart (Figure 2B). Thus, despite reduction in integral heart dose, which is one of the primary considerations of PT for esophageus cancer, a proton plan not accounting for biologic effective dose may increase toxicity. Predictive modeling of biologic dose builds up and focal reduction in physical dose or reduction in the overall dose and fractionation are methods to reduce potential toxicity from biologic hotspots.

Similar to esophagus cancer, most abdominal cancers are situated in tight proximity to OAR. For cancers of the pancreas head, the duodenum, large bowel and pylorus of the stomach are adjacent OAR and may be located within the distal Bragg peak when designing a proton plan with posterior fields (Figure 3). Increase in biological effective dose in these organs may result in a higher risk of radiation enteritis, ulceration and/or hemorrhage, and possible perforation. In most cases, this can be accounted for with slight modifications to the physical dose or treating to a lower total physical dose. In some cases, it is beneficial to add an additional field, despite increasing integral body dose, to decrease the overall biological effective dose.

In the management of anal cancer, PT may reduce substantial dose to adjacent perineum, genitals, and groin thereby reducing risk such as dermatitis and long-term
sexual dysfunction. Figure 4 shows a typical proton plan with bilateral posterior oblique and anterior fields to provide dose to the pelvis and inguinal lymph nodes. The end of range biologic dose builds up in the anterior bladder, urethra and obturator tissue. Thus, while sparing perineal tissue and genitalia, the enhanced biologic dose may increase urethral or other genitourinary toxicity relative to other forms of RT.

Certain planning techniques are often useful to control OAR position or limit target motion and volume. Often these are simple, reproducible measures such as breath hold, controlled urination and bladder filling, defecation, or fasting before treatment. A patient's nutritional status may change during the course of treatment resulting in external or internal contour changes and impact on the position of the distal Bragg peak. Additional imaging and verification of proton dose is critical to ensure proper delivery of protons during the course of treatment with adaptive re-planning as needed.

Overall, PT has promise to treat many cancer sites with similar efficacy as conventional RT but with fewer acute and late toxicities. However, further knowledge of biologic effective dose and its impact on both cancer and adjacent OAR is paramount for effective and safe treatment of patients with PT. With greater understanding of the biological effect, there may be a future role for purposefully increasing this effect within the target for radiation resistant tumors.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

7. Ando K, Furuksawa Y, Suzuki M, et al. Relative biological effectiveness of the 235 MeV proton beams at the National...


