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Review Article

Relative biological effectiveness in proton beam therapy – Current knowledge and future challenges

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Introduction and outline of the review

Particle beam irradiation is increasingly popular due to its physical characteristics. It has an inverted dose profile with low dose absorption on tissue entry and the point of maximum dose deposition at the Bragg-peak. Therefore, it decreases the dose to normal tissues and is expected to also decrease treatment-related side effects. Moreover, the deposited integral dose is lower compared to modern photon-based therapies (*i.e.*, intensity modulated radiation therapy or volumetric modulated arc therapy) and thus holds the potential of reducing the risk of secondary neoplasms.

In recent years, proton beam therapy is being introduced for treatment of tumors of the central nervous system (CNS) in children and adults, *e.g.*, ependymoma, medulloblastoma, meningioma, craniopharyngioma and glioma grade II–IV [10]. For chordoma and chondrosarcoma of the skull base and sacrum as well as for adenoid-cystic carcinomas, highly conformal proton therapy is considered the gold standard since even modern photon techniques fail to deliver the required radiation doses while keeping within the dose constraints of adjacent organs at risk [44,48,56]. Besides the "standard" indications, the potential benefit of proton beam irradiation is being investigated within clinical studies for several other tumor entities, such as esophageal cancer, non-small cell lung cancer, pancreatic cancer, and squamous cell carcinomas of the head and neck.

With ever more centers offering proton beam therapy in the near future and with growing patient numbers and follow-up time, concerns about the potential side effects of protons have risen during recent years. The effectiveness of different radiation modalities, *i.e.*, photons, particles and carbon ions, regarding their potential to induce biological effects in the cells is weighted with the relative biological effectiveness (RBE). For photons, a reference RBE of 1.0 is generally used, whereas for carbon ions, most institutions use an RBE value of (approx.) 3.0. For protons, an RBE of 1.1 is used clinically, however, the uncertainty on this dose-weighting factor is thought to be one of the sources of normal tissue toxicity. The clinical evidence of RBE variations in patients is scarce since the complication rates for most treatment sites are low and follow-up times are currently too short to observe secondary malignant neoplasms in a sufficiently high number of patients as they typically arise more than 10–15 years following (radiation) treatment [15,43,51]. Thus far, (mainly pre-clinical) reports have postulated the RBE of protons compared to X-rays to be 1.1. However, it may well be that the RBE is higher than 1.1 and that it may vary depending on the position relative to the Bragg-peak, characterized by an increased linear energy transfer (LET). This uncertainty may lead to substantial dose increases to organs at risk, *e.g.*, brainstem, temporal lobe, optic chiasm, in particular if they are in vicinity of the target volume.

This review summarizes recent abstracts from international meetings and international peer-reviewed publications on the potential variation of RBE and its possible side effects, and compares these with past publications on photon beam irradiation. Moreover, recent literature on how to deal with potential RBE variations and the resulting uncertainty during treatment planning, as well as solutions to correlate dose and LET distributions to subsequent (magnetic resonance) imaging changes, are presented. Finally, the current status on RBE measured *in vitro* and *in vivo* is reviewed with further discussion on how to bridge the existing gap between the laboratory and clinic.

Clinical reports on toxicity and RBE

In present years, increasing numbers of reports on treatment outcome and toxicity of patients treated with protons have been published. These encompass (pediatric and adult) chordoma and chondrosarcoma of the skull-base and axial skeleton, and ependymoma and posterior fossa malignancies [8,18,35,44,48,56]. As the initial publications on the effect of the RBE on toxicity have focused on brain tumors, this review will also primarily focus on the toxicity reported for those tumors, and on the putative association with RBE.

The first studies discussed did not include a correlation with RBE. Murphy *et al.* [34] assessed a cohort of 236 patients with embryonal tumors who were treated with surgery, chemotherapy and proton beam therapy of the craniospinal axis and an additional boost to the primary tumor [(cumulative dose 55.8 Gy(RBE)]. In total, 8 patients developed brain necrosis (7 of the brainstem, 1 cerebellar), representing 3.7% of the entire cohort and 4.4% of those patients with an infratentorial tumor. A detailed analysis of the spectrum of brainstem injuries occurring in a cohort of 313 patients with tumors of the brain and skull base [dose > 50.4 Gy (RBE)] was published by Indelicato *et al.* [21] and reported a 2-year-incidence of brainstem toxicity ≥grade 2 of 3.8%. Risk factors for brainstem necrosis included a tumor location in the posterior fossa (actuarial rate 10.7%), age <5 years (12.5% *versus* 7.2% aged ≥5 years), ependymoma as primary tumor (crude rate 10.9%), but not chemotherapy. Notably, patients with ependymoma of the posterior fossa tend to be at higher risk since surgeons strive to achieve a (near-) complete tumor resection for better disease control. Higher risk is also due to the proximity of ependymoma to critical cranial nerves and vessels. Moreover, the authors established useful dosimetric constraints, including, (i) the maximum dose to the brainstem should not exceed 56.6 Gy(RBE) and, (ii) the mean dose to 50% of the brainstem should not be above 52.4 Gy(RBE). These parameters have since been incorporated in the Children's Oncology Group (COG) proton therapy guidelines. The same first author has recently summarized the outcome of UK children referred for proton therapy to a North American facility [20]. Of the 166 patients in total, only 1 (0.6%) patient with a posterior fossa ependymoma developed a symptomatic brainstem necrosis with a dose of 55.1 Gy(RBE). In a retrospective review of clinical and radiological data in 60 pediatric patients with primary brain tumors treated with proton therapy [to the tumor (bed), in 21 patients combined with proton-based craniospinal irradiation to a mean total dose of 54 Gy(RBE); range 21 Gy-59.4 Gy(RBE)], Kralik *et al.* [24] reported an imaging-based radiation necrosis rate of 31% with a median onset time of 5.0 months (range, 3–11 months). They identified multiple (>3) chemotherapeutic agents and atypical teratoid rhabdoid tumor pathology as risk factors for developing radiation necrosis ($p = 0.03$, respectively). The median time to complete resolution was 5.3 months (range, 3–12 months), with complete resolution of enhancement seen in 50% of patients at 3 months, in 75% of patients at 6 months, and in 100% of patients at 12 months. Twenty-five percent of the patients with imaging changes (*i.e.*, 8% of the whole patient group) of radiation necrosis required medical intervention for severe symptoms. The small locations of necrosis (largest focus of contrast enhancement measured 0.9 cm) did typically not occur immediately adjacent to the resection cavity, but instead in the periventricular white matter and corpus callosum as well as the pons and cerebellum.

The recent reports on toxicities following proton therapy may suggest that these unwanted side effects, even though still few in number, only occur when having applied proton beam therapy. In past series on 3D-conformal photon therapy, however, the rate of brainstem toxicity was also reported to be in the range of 2.5–18%, even though the definitions of the endpoint were heterogeneous [28,45]. Contrary to the argument that increased precision using intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) may overcome this issue of toxicity, Nanda *et al.* [35] recently reviewed 60 pediatric patients with

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