Application of Hadrons in Radiation Oncology and consequences of Relative Biological Effectiveness (RBE) and dose escalations

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Introduction

Radiotherapy has evolved empirically, with progressive understanding of radiobiology, dosimetry and synergy of technological innovations there has been a paradigm change in better clinical outcomes either as a better cure rate, or reduced complication rate, or both. More than two-thirds of cancer patients receive radiation therapy alone or in combination with most cases utilizing photon beams. However, recent advances have led to the development of highly sophisticated photon-based external beam radiation techniques including intensity-modulated radiation therapy, image guided radiation therapy, and stereotactic body radiation therapy which have resulted in a significant widening of indications and improvement of outcomes. There are still many tumor sites and histology that remain challenging to cure using these modalities as there is substantial spillage of radiation to healthy tissues. It has long been recognized that proton or heavier ion therapy (also collectively termed hadron therapy), which uses accelerated charged particles, provide signicant physical, biological, and potential clinical benets over photon-based external beam radiation techniques [1].

Mechanisms of Relative Superiority of Hadrons

Introduction of hadrons into radiation therapy aims at improving the physical selectivity of the irradiation (e.g. proton beams), or the radiobiological differential effect (e.g. fast neutrons), or both (e.g. heavy-ion beams). Each of these new therapy modalities requires several types of information before prescribing safely the doses to patients, as well as for recording and reporting the treatments. Proton therapy delivers higher doses of radiation to the targeted area, spares healthy tissue and avoids critical structures. Minimizing the entrance dose of radiation before it reaches the tumor;

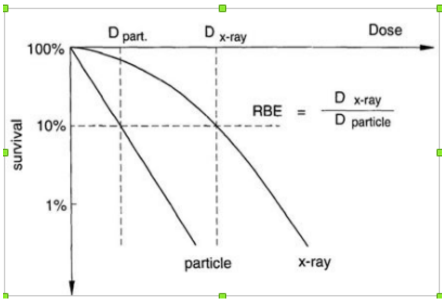

FIG. 1: Hadrons more biologically effective than photons: lower dose required to cause same biological effect.

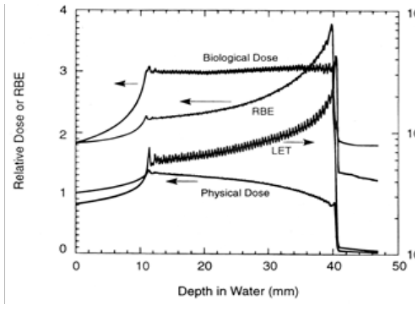

FIG. 2: Radiobiological Complexities of Ion SOBP (T. Kani et al, Rad Res, 147: 78-85, 1997 HIMAC, NIRS, Chiba, Japan).

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eliminate the exit dose of radiation past the tumor; and Sparing normal tissue, organs and previously irradiated tissue. Thus, theoretically protons offer new vista in radiation oncology and seems to be a futuristic modality to replace x-ray photon-based treatment in many sites. For the same dose to the target volume, protons deliver a lower physical dose to the uninvolved normal tissues than do high-energy X-rays.

RBE-Linear Energy Transfer (LET) Relationship

LET may be expressed as linear intensity of energy released on a microscopic scale in the medium which is independent of volumetric dose. Increasing LET, is experienced in proton therapy which occurs mostly within Bragg Peak (BP) regions. The spread-out Bragg Peak (SOBP) is attained by various means by differentially attenuating the proton beam to cover a defined clinical target volume. RBE is of paramount importance since it determines the dose given to the patient in Equivalent-Gy as shown in, Fig-1. RBE depends on multiple factors LET, beam energy, particle nuclear charge (z), target volume and depth, as well as multiple biological factors that influence DNA repair capacity and radiosensitivity in different cellular types and tissues. For protons, the RBE values range between smaller limits (about 1.0 to 1.2). A clinical benefit can thus not be expected from RBE differences. However, the proton RBE problem cannot be ignored since dose differences of about 5% can be detected clinically in some cases. The accepted RBE for Carbon-ions used in clinical RT is generally estimated to be 2.5 to 3, however, values as high as 5 have been reported [2]. For fast neutrons, the RBE varies within wide limits (about 2 to 5) depending on the neutron energy spectrum, dose, and biological system. The determination of RBE is most complex with heavy ions of SOBP for clinical situations, Fig-2. The RBE of a given type of radiation will vary with particle type and energy, dose, dose per fraction, degree of oxygenation, cell or tissue type, biological end point, etc. [3].

Results and Discussions

It is important to investigate the LET-RBE relationships greater precision, to determine accurate coefficients that control radiosensitivity changes with LET. The RBE may be varying in the ascendance and descending portion of the BP curve as the energy depositions rapidly alters, it is imperative to study the initial slopes and turnover point positions in a sensibly chosen panel of human cell lines and tissue systems capable of providing clinically applicable information. The available predictive models could then be compared. Compared with standard radiation treatment, Hadron therapy has several benefits. It reduces the risk of radiation damage to healthy tissues in the path may allow radiation dose escalations to be directed at some types of tumors and may result in fewer and less severe side effects (such as low blood counts, fatigue, and nausea) during and after treatment.

Conclusions

Multidisciplinary approach with robust data (statistically significant) is necessary to obtain optimally analyze treatment outcomes with hadrons in Radiotherapy. The concept of RBE is one of the important issue to determine dose on the target. Dose, LET and RBE needs to be computed and assigned to tissues, organs and tumors. Much more experimental work is required to determine RBE and its changes with LET and dose for protons and heavier ions so that they can be modelled to be clinically applied into treatment planning systems. Hadrons have indicated their advantage in the treatment of certain types of tumour and this information may be of use in the selection of patients for ion irradiation. Intensity modulated proton therapy has made significant progress in precision radiotherapy specially brain tumours, paediatric tumours and some other tumours located at on critical sites. This is a modality which may be poised to be the future of modern radiotherapy.

References

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