RESEARCH ARTICLE OPEN ACCESS

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

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ABSTRACT

Hadrons have unique relative biological effectiveness, oxygen enhancement ratio and depth dose profile compared to photons beam. For these biological and physical properties are more favourable than those of photons and may be used to treat tumor systematized. Hadron therapy show many superiority over photons like, delivers higher doses of radiation to the targeted area, spare normal tissue and critical organs. Relative Biological Effectiveness for hadrons 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. Hadrons offer new vista in radiation oncology and seems to be a futuristic modality to replace x-ray photon-based treatment in many sites.

Keywords: Hadrons in Radiation Oncology, Relative Biological Effectiveness of Hadrons, Dose Escalations

Date Of Submission: 26-05-2019 Date Of Acceptance: 09-06-2019

I. 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. Early and late tissue tolerances exhibited by the tumor and healthy tissue are important in delivering a course of radiotherapy. These impediments frequently limit the delivery of prescribed doses to the target volume. It is also observed that tissue radiation tolerances also effected by surgery, concomitant medical conditions, and various forms of chemotherapy.

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 (IMRT), image guided radiation therapy (IGRT), and stereotactic body radiation therapy (SBRT) 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, which uses accelerated charged particles, provide significant physical, biological, and potential clinical benefits over photon-based external beam radiation techniques [1,2].

The use of heavy charged particles and fast protons for cancer therapy (**also collectively termed hadron therapy**) was first proposed by Robert Wilsonin1946 [3], and the first treatments using protons. and helium ions began in 1954 and 1957 at Lawrence Berkley National Laboratory, respectively [4,5]. The potential of protons to lose energy at a given depth with little spillage elsewhere inspired many researchers to explore its application in cancer treatment. As the use of heavy charged particle therapy becomes more widespread, the need for a greater understanding of the biological mechanisms and factors that may affect treatment outcomes becomes more apparent.

The energy required by protons for attaining the similar penetration as 10-15 MV X-rays would be around 150-200 MeV. Thus, acceleration of protons to such high energy posed a challenge and using ultra heavy cyclotron were economically not a viable option beyond research centers. The future face of ever evolving modern-day anti-cancer therapy based on charged particles like protons could potentially involve using laser accelerators. The laser-based acceleration is thus explored vigorously for use in medical centers. A new study by radiation oncologists at Mayo Clinic comparing the world's literature on outcomes of proton beam therapy in the treatment of a variety of advanced head and neck cancers of the skull base compared to IMRT has found that proton beam therapy significantly improved disease-free survival and tumor control when compared to IMRT.

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; 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. Hence, a concept of cobalt equivalent dose is being prescribed for understanding the dosimetric and RBE aspect of the planning.

There is very little difference in tissue response per unit dose between protons of therapeutic energies as compared with high-energy X-rays, so that the only relevant differences are physical.

RBE-LinearEnergyTransfer (LET) Relationship

Linear energy transfer (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. Thus, mixing BP and non-BP regions the target volume is precisely matched for clinical applications. Although LET increases may be relatively modest yet it may always cause increased cellular radiosensitivities. In higher LET regions there is increased clustering of DNA damage, which is less amenable to repair by cellular enzyme systems, resulting in greater—effectiveness of lethal chromosomal aberrations. Increased radiosensitivities lead to a modification of dose required to achieve the same biological effect, hence improved RBE may be obtained. RBE is of paramount importance since it determines the dose given to the patient in Equivalent-Gy as shown in **Fig-1** [6].

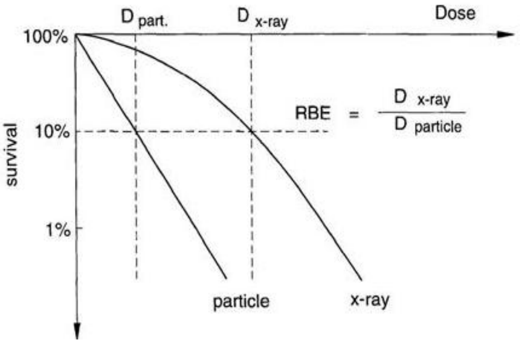

Fig: 1- Hadrons more biologically effective than photons: lower dose required to cause same biological effect.

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 [7]. For fast neutrons, the RBE varies within wide limits (about 2 to 5) depending on the neutron energy spectrum, dose, and biological system. The situation is most complex with heavy ions since RBE variations are at least as large as for fast neutrons, as a function of particle type and energy, dose and biological system. 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. [8]. The determination of RBE is most complex with heavy ions of SOBP for clinical situations, **Fig-2** [9].

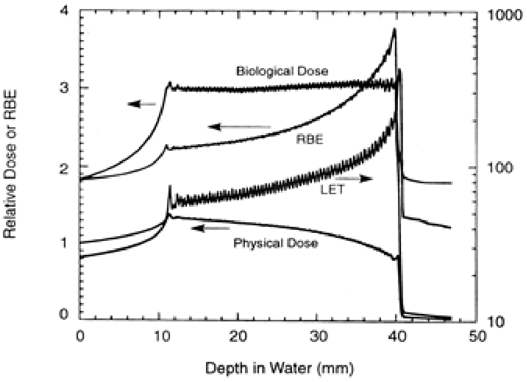

Fig-2 Radiobiological Complexities of Ion

In addition, RBE varies with depth. Radiation quality thus has to be taken into account when prescribing and reporting a treatment.

II. RESULT AND DISCUSSIONS

Since the data base available for all models that attempt to estimate RBE with increasing proton LET is far from comprehensive hence basic research is necessary to provide more precise parameters for predictive modelling. The most reliable radiobiological model would provide important information for clinical applications. It is thus 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. ICRU reports 83 and 91 such a centre could also become a world data collection system, with high quality analysis using the ICRU framework to provide radiation tolerance parameters in high LET treatments where unexpected adverse effects have occurred. More clinical research is necessary on RBE of protons and molecular targeted approaches which might capitalize on the apparent reduction of RBE due to reduced repair capacity in some tumor types. Identification of RBE values in late reacting tissues, all of which might further improve hadron therapy results offer opportunities for research and clinical evaluations. 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.

III. 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 (IMPT) 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.

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R. J. Pathak" Application of Hadrons in Radiation Oncology and consequences of Relative Biological Effectiveness (RBE) and dose escalations." International Journal of Engineering Research and Applications (IJERA), Vol. 09, No.06, 2019, pp. 68-70