Proton, Helium and Carbon Radiation Beam Targeting Reactive Oxygen, Nitrogen and Halogenated Species in TRIM-SRIM Model

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Abstract

Nowadays proton beam radiation therapy is considered in few centers for management of malignancies. This study is aimed to explore the effect of proton, helium or carbon irradiation on free radicals. This study was conducted in Department of Physiology/Medical Physics, College of Medicine, Al-Mustansiriya University in Baghdad, Iraq during October 2009. TRIM-SRIM software version 1998 and 2003 were used for computed Bragg peak and for calculated the effect of proton, helium and carbon ions against free radicals related to oxygen, nitrogen and halogen species.The lowest stopping power near Bragg's peak of proton targeting free radicals was against superoxide anion and its curve (the stopping power against energy) was shifted down while that of peroxynitrite ($ONOO^-$) was shifted up. The stopping powers of helium targeting all studied free radicals were lower than corresponding proton irradiation but it required higher energy. Lower stopping power of carbon irradiation targeted hydroxyl (OH^-) and halogenated radicals than the other reactive species were observed. It concludes that such form of external beam irradiation is associated with direct scavenging effect on free radicals of whatever sources.

Keywords: Free radicals, Proton, Helium, Carbon, Irradiation

Introduction

There is no doubt that ionizing radiation of whatever source is associated with production of free radicals in vitro and in vivo [1,2]. These free radicals, whether they are related to oxygen or nitrogen species, exert a potential harmful effect on living tissue [3-5]. Reactive oxygen species or nitrogen species can cause cell death by both nonphysiological (cell necrosis) or regulated pathways (apoptosis)[6]. Recent advances in oncology is the application of proton beam therapy in management of malignancies[7]. In the past several particles like pions, oxygen, neon and helium ions have been investigated but more recently only protons and carbon ions are used in clinical practice. There is an evidence that proton beam therapy is associated with the production of reactive oxygen species that caused cell death [8]. Cell lines (PC3, Ca301D, MCF7) Irradiation with a dose of 10 Gy and energy of a 26,7 Mev proton beam altered cell structures such as membranes, caused DNA double strand breaks, and significantly increased intracellular levels of hydroxyl ions [9]. Furthermore, Jang et al reported that proton irradiation significantly inhibit in vivo vascular development possibly due to increased vascular cell death via reactive oxygen species formation [10]. In one study using single crystals of anhydrous thymine an increased production of hydrogen addition or abstraction radicals was found after exposure to alpha particles (35 MeV) in comparison with exposure to protons (20 MeV) [11]. From the logic point of view, the principle of proton beam therapy is straggling the atoms of living tissue like nitrogen, oxygen carbon…etc, therefore, protons can also straggle these atoms in free radicals and thereby scavenged them. This study is aimed to clarify the extent of straggling effect of proton, helium ion and carbon ion on the atoms of free radicals in a simulated model, using "The Stopping and Range of Ions in Matter (SRIM)" softetware, impinging onto free radicals in living tissue that are commonly reported in patients with malignancies.

Materials and Methods

This study was conducted in the Department of Physiology / Medical Physics, College of Medicine, Al-Mustansiriya University in Baghdad, Iraq during the 1st of October to the 1st of December 2009. The software "The Stopping and Range of Ions in

Matter (SRIM)" version 1998, and 2003 was used. A model of targeting certain free radicals related to reactive oxygen, nitrogen and halogen species was created. These are superoxide anion (O^-), hydroxyl (OH^-), nitric oxide (NO^-) nitroxyl ($NO2^-$), peroxynitrite ($ONOO^-$), nitrous acid (HNO_2^-) , hypochlorous acid ($HOCl^-$), hypobromus acid ($HOBr^-$). Each target was subjected to ion beam radiation of proton (H), helium (He) and carbon (C) at different range of energy seeking for the Bragg peak. The specification of the target (in living tissue) of each free radical sources were listed in Table (1).

The stopping power (S) is given by:

S= - dE/dx

The quantity S is in (KeV/μ) is referred to specific energy loss

E: charged particle kinetic energy

-dE: the energy increment lost in infinitesimal material thickness (dx)

The specific energy loss is expressed by Bethe-Bloch formula [12,13].

For heavy charged particle:

$$-\frac{dE}{dx} = \frac{4\pi e^4 z^2}{m_o v^2} NB$$

Where

B = Z

$$\left[\ln \frac{2m_o v^2}{I} - \ln\left(1 - \frac{v^2}{c^2}\right) - \frac{v^2}{c^2} \right]$$

With the following definitions:

v	velocity of the charged particle
ze	charge of the charged particle
N	number density of absorber atoms
Z	atomic number of absorber atoms
m	electron rest mass
e	electron charge
I	A parameter, treated as experimentally determined, representing average excitation and ionization potential

B is known as the stopping number (atomic number scaled for stopping).

Bethe-Bloch formula for electrons :

$-dE/dx = (2\pi e^4 / m_\circ v^2) NB$

$$B=Z\left[\ln \frac{m_o v^2 T}{2I^2(1-\beta^2)} - (ln2)\left(2\sqrt{1-\beta^2} - 1 + \beta^2\right) + 1 - \beta^2 + \frac{1}{8}\left(1 - \sqrt{1-\beta^2}\right)^2\right]$$

Where $\beta = \frac{v}{c}$

T: kinetic energy

The total stopping power for electron can be given as a combination of collisional (inelastic collision with atomic electrons) and radiative (inelastic collision with nucleous) types of interaction; (Bremsstrahlung)

[dE/dx] total = [dE/dx]collision + [dE/dx] radiative

For heavy particles, orbital electron interactions are only considered since the probability of nuclear interaction resulting in energy loss is much smaller.

$$-\left(\frac{dE}{dx}\right)_r = \frac{NTZ(Z+1)e^4}{137 m_0^2 c^4}\left(4\,ln\frac{2T}{m_0 c^2} - \frac{4}{3}\right)$$

The percent of the energy loss goes to emitted rays is expressed by:

$$(\frac{dE}{dx})_r / (\frac{dE}{dx})total = EZ/1000$$

where E is in MeV, where Z is the atomic number of the absorber.

The range of a charged particle can be derived from stopping power formula:

$$R = \int_E^0 dx(cm) = \int_E^0 \frac{dE}{dE} dx = -\int_0^E \frac{1}{dE/dx} dE = \int_0^E \frac{dE}{S}$$

The summal distance elements as kinetic energy goes from *E* down to 0 is the total distance along the incident direction, or the range.

The scavenging activity of each ion against each target (free radicals) was calculated by:

$$\text{The molar concentration} = \frac{\text{The volume of target } (cm^3) \times \text{density } (g/cm^3)}{\text{Molecular weight of target}}$$

The volume of target = projected range x longitudinal straggling x lateral straggling

The concentration of scavenging activity of each ion was calculated at the Bragg's peak (pico Mol). Microsoft Excel 2003 was used for calculations and figures plotting.

Results

The straggling effect of proton against the atoms of reactive nitrogen species is differed from that of reactive oxygen species. The stopping power near Bragg's peak of proton targeting superoxide anion ($O^{\bullet\bullet}$) was 29.95 KeV/µ which was less than that of hydroxyl radical ($OH^{\bullet}$) which amounted 50.16 KeV/µ (Table (2), Fig. (1)). The stopping power of proton targeting nitric oxide radical ($NO^{\bullet}$) was 34.3 KeV/µ which was less than the corresponding values of other nitrogen species (Table (2), Fig.(1)). The stopping power of halogenated free radicals (65.5 and 52.39 KeV/µ for $HOCl^{-}$ and $HOBr^{-}$ respectively) were higher than superoxide anion ($O^{\cdot\cdot}$), hydroxyl radical (OH^{-}) and nitric oxide ($NO^{\bullet}$) (Table (2), Fig.(1)). The curve of energy loss (-dE/dx) for proton targeting superoxide anion ($O^{\bullet\bullet}$) was shifted down while that of peroxynitrite ($ONOO^{\bullet}$) was shifted up (Fig.(1)). The stopping powers of helium (He) targeting the reactive species were lower than corresponding powers of species targeted by protons despite of using higher irradiated energy (Table (2), Fig.(2)). Lower stopping power of carbon ion targeted hydroxyl free radical ($OH^{\bullet}$) and halogenated radicals than the other reactive species were observed (Table (2), Fig.(3)). The irradiated energy of carbon was amounted more than five and forty time of helium and proton respectively.

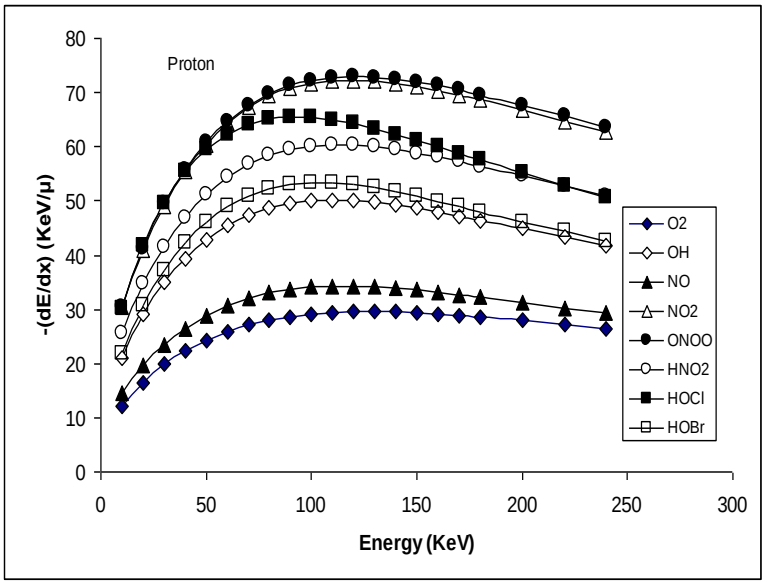

Fig. (1) Stopping power of proton targeting free radicals.

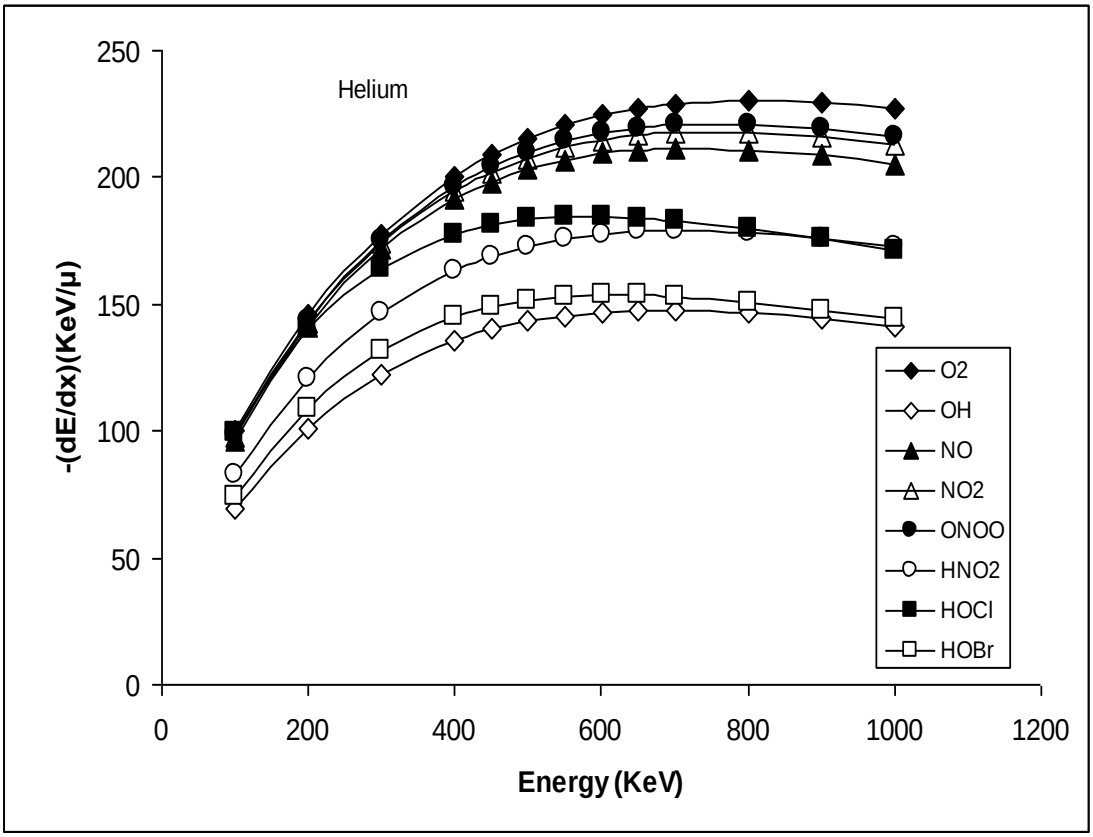

Fig. (2) Stopping power of helium targeting free radicals.

Table (1)
Specifications of the free radicals (quoted from The Stopping and Range of Ions in Matter (SRIM)" version 1998, and 2003).

Radicals	***Density***		***Mass (%)***
	gram / cm^3	***atoms/cm^3***	
Superoxide anion (O^-)	1.426	2.1203×10^{22}	O (100)
Hydroxyl (OH^-)	0.74875	5.3025×10^{22}	O (94.7), H (5.93)
Nitric oxide ($NO^·$)	1.2226	2.3185×10^{22}	N (53.32), O (46.68)
Nitroxyl ($NO2^-$)	1.2928	5.0766×10^{22}	N (30.41), O (69.59)
Peroxynitrite ($ONOO^-$)	1.3260	5.1514×10^{22}	N (22.59), O (77.41)
Nitrous acid (HNO_2^-)	0.98738	5.0590×10^{22}	H (2.14), N (29.79), O (68.06)
Hypochlorous acid ($HOCl^-$)	1.1316	3.9841×10^{22}	H (1.92), O (30.45), Cl (67.63)
Hypobromus acid ($HOBr^-$)	1.5657	2.9183×10^{22}	H (1.04), O (16.50), Br (82.46)

Table (2)
Effect of ion beam (proton, carbon, helium) on scavenging the free radicals at stopping power (Bragg's peak).

Ion beam	*Proton*				*Helium*				*Carbon*			
Free radicals	*Energy (MeV)*	*Stopping Power -(dE/dx) (KeV/μ)*	*Projected Range (μm)*	*Concentration Pico Mol*	*Energy (MeV)*	*Stopping Power -(dE/dx) (KeV/μ)*	*Projected Range (μm)*	*Concentration Pico Mol*	*Energy (MeV)*	*Stopping Power -(dE/dx) (MeV/mm)*	*Projected Range (μm)*	*Concentration Pico Mol*
$O^{\bullet}$	0.13	29.95	5.48	0.1885	0.8	23.04	5.10	0.0779	4.5	92.71	6.98	0.0842
$OH^{\bullet}$	0.11	50.16	2.82	0.0115	0.7	14.75	6.96	0.0858	5.5	55.64	12.49	0.1509
$NO^{\bullet}$	0.11	34.3	4.12	0.0381	0.7	21.14	4.92	0.0323	4.5	82.92	7.52	0.0426
NO2	0.12	72.32	2.09	0.0038	0.8	21.77	5.28	0.0250	4.5	86.25	7.32	0.0282
$ONOO^{-}$	0.12	73.10	2.08	0.0025	0.9	21.93	5.68	0.0213	4.5	87.89	7.23	0.0211
HNO2	0.11	60.36	2.34	0.0034	0.7	17.90	5.78	0.0255	4.5	69.55	8.86	0.0338
HOCl	0.09	65.50	1.69	0.0221	0.6	18.46	4.52	0.0236	4.5	66.81	8.17	0.0349
HOBr	0.11	53.39	2.13	0.0071	0.6	15.35	5.31	0.0571	5.0	57.83	10.44	0.1163

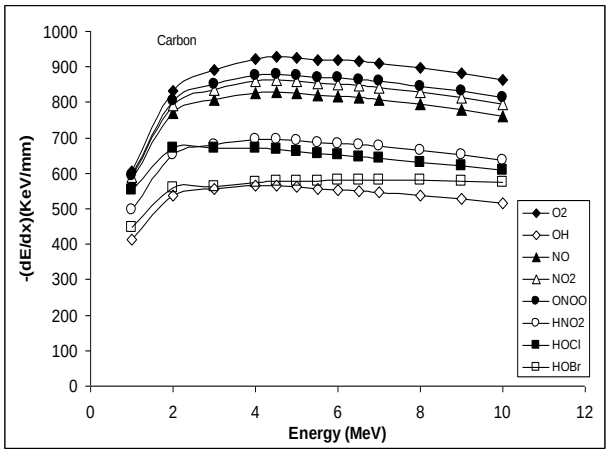

Fig. (3) Stopping power of carbon targeting free radicals.

Discussion

There is no doubt that proton, helium or carbon radiation has an effect on the free radicals of whatever source. The magnitude and the extent of this effect is related to the source of radiation. The highest effect is observed with proton radiation of energy 0.13 MeV against superoxide anion at stopping power 29.95 followed by carbon radiation of 5 MeV against hydroxyl radical at stopping power of 55.64. It is well known that radiation causes cell death either directly through induces a change in the bioactive molecule like DNA or indirectly through reactive oxygen species that resulted from interaction of radiation ions with water molecule in the cell [14]. Therefore, the scavenging effect of proton, helium and carbon against free radical is direct and specific i.e. proton against superoxide anion and carbon against hydroxyl radical. This finding is of great importance because it addressed the following points: firstly, the efficacy of proton beam radiation has been clinically proven in prostate, lung, hepatocellular, uveal melanoma, sarcomas of the skull base and cervical spines, astroctyomas, thyroid and esophagus cancer [15-18]. And there is no doubt that tumors are associated with significant high level of reactive oxygen and/or nitrogen species [19,20] . Therefore, irradiation of such tumors not only resulted in tumor cell death but it contributed in scavenging the free radicals. Secondly, as a result of scavenging the free radical that play a role in vasodilation of blood vessels like nitric oxide, the tumor oxygen level become low i.e. hypoxia. There is an evidence that hypoxia is associated with metastasis and recurrences [21] and the radiation's ability to kill cancer cell i.e. radiosensitivity is rapidly decreases in areas of oxygen depletion because the new free radicals can not produce due to limited oxygen supply i.e. indirect effect of radiation [22]. It is recommended to use radiosensitizers e.g. misonidazole [23], carbogen and nicotinamide [24]. Thirdly, on the other hand, cellular hypoxia is implicated in the activation of angiogenic cytokines especially vascular endothelial growth factor [VEGFs] that are necessary for the growth of new tumor blood vessels [25] and thus tumor growth. Irradiation with proton, helium or carbon, scavenged to the same extent the free radical nitric oxide, may be a promising tool in prevention new tumor blood supply and it can substitute the use of lead agents e.g. combretastan A-4 which have now advanced into clinical trials [26]. This study adds a further advantage of proton, helium or carbon radiation [27] superior to the other external beam radiation by straggling the free radicals of whatever sources and its consequent events on biological tissues. Estimation of free radicals and the scavenging activity in human is one of the study limitations.

Conclusion

It concludes that such form of external beam irradiation is associated with direct scavenging effect on free radicals of whatever sources.

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