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**MINI-REVIEW ARTICLE**

# Brain Tumor Causes, Symptoms, Diagnosis and Radiotherapy Treatment

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The strategy used for the treatment of given brain cancer is critical in determining the post effects and survival. An oncological diagnosis of tumor evaluates a range of parameters such as shape, size, volume, location and neurological complexity that define the symptomatic severity. The evaluation determines a suitable treatment approach chosen from a range of options such as surgery, chemotherapy, hormone therapy, radiation therapy and other targeted therapies. Often, a combination of such therapies is applied to achieve superior results. Radiotherapy serves as a better treatment strategy because of a higher survival rate. It offers the flexibility of synergy with other treatment strategies and fewer side effects on organs at risk. This Review presents a radiobiological perspective in the treatment of brain tumor. The cause, symptoms, diagnosis, treatment, post-treatment effects and the framework involved in its elimination are summarized.

**Keywords:** Radiation therapy, brain cancer, treatment options, ionizing radiation therapy, post-radiation effects, carbon-ion therapy.

## 1. INTRODUCTION

The use of science for the treatment of diseases has been an idea of interest for scientists like Newton and Galileo since the 16th century [1]. In the 18$^{th}$ century, the famous Scottish surgeon, John Hunter suggested for a surgical remedy for treating cancers, which led to the birth of the modern pathological study of a tumor in the 19$^{th}$ century [2]. There were multiple theories proposed to explain the cause of cancer, which included popular ones such as the humoral theory, the lymph theory, the trauma theory and the infectious disease theory. It was after much research and technological advancements that the idea of viral and chemical carcinogens occurred to the scientist of the 20th century [3]. Soon, research on oncogenes and tumor suppressor genes was done to develop targeted therapies [3]. After much further development, humans have reached a stage wherein multiple options are available for the treatment of cancer.

Cancer accounts for a large section of grief and fatality in the world. With an increase in cases of cancer-related to the central nervous system (CNS), the need for a biologically advanced treatment has become more than ever. The World Health Organization has catalogued around 150 different types of CNS tumors to date [4]. Amongst the cancers affecting CNS, brain tumors are the most aggressive type with higher mortality rate and over decades of study, medication for them has become more proficient since the onset of radiotherapy/radiation therapy [5].

Radiotherapy uses photons (x-rays) and charged particles (protons and heavy ions) to treat a tumor; and has two major branches, external and internal (brachytherapy) [6]. Brachytherapy is a highly conformal therapy involving the use of a radiation source inserted into the patient's body and is majorly used to treat prostate, breast and gynaecological cancers, whereas, in external radiation therapy, the patient gets irradiated from outside the body [7, 8].

Approximately 67% of the cancer patients are treated with radiotherapy and among them, the proportion of people receiving charged particle therapy is very less, which is increasing gradually over the years [9]. 1952 marks the beginning of the application of charged [helium and deuteron] beams for treatment purposes in humans [10]. Emerging proton facilities and their higher biological impact over X-rays have appealed the experts' attention towards heavy ions [11]. Among the many favourable physical properties of charged particles, the Bragg peak strengthens the concept of charged particles application X-rays [12]. A single beam of charged particle radiation can reduce the effect on neighbouring healthy tissues when compared with X rays [13]. This results in higher relative biological effectiveness (RBE) of charged particles over photons [14]. The radiobiological difference produced by particles with high linear energy transfer reduces the impact of the cell cycle phase and oxygenation in tumor radiotherapy [15].

Technological developments in radiation oncology to enhance tumor dose and normal tissue radiation have led to a higher therapeutic ratio [16]. Further advancements have led to the use of high-energy charged particles for the treatment of a tumors in sensitive organs and children [14]. The primary purpose of particle therapy co-operative group (PTCOG) was to develop hospital-based particle facilities for the treatment of tumors anywhere in the body, comparable to standard clinical photon linear accelerators [17]. However, due to the high cost of initial investment (US$200 million) and large equipment, charged particle therapy is not accessible to the masses [18, 19]. This review article summa-

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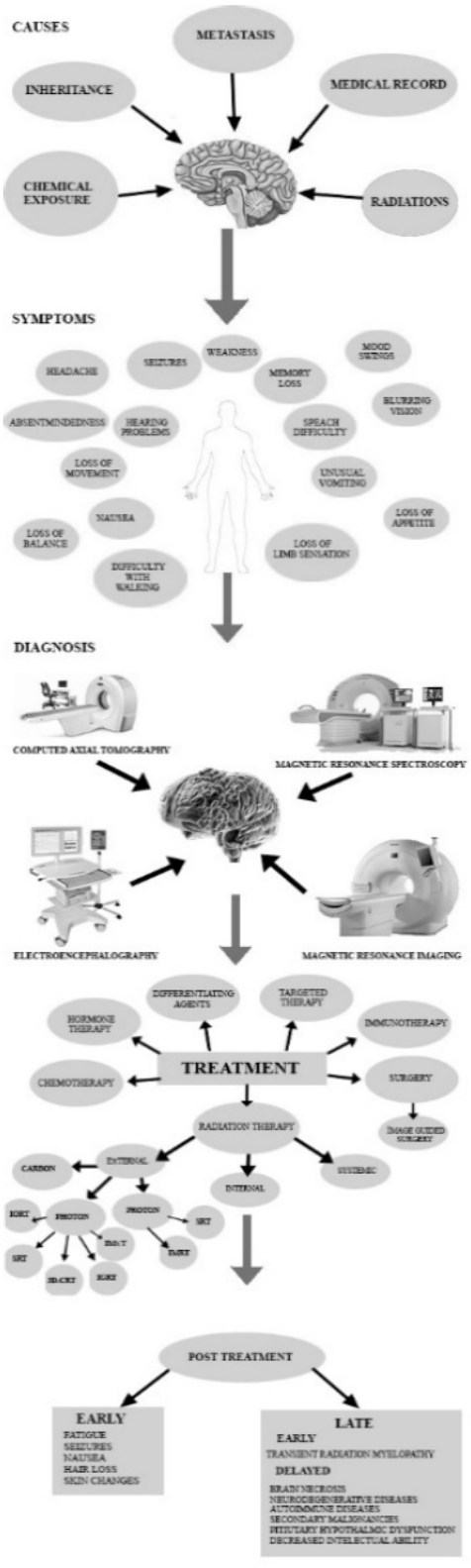


**Fig. (1).** Schematic diagram involving an overview of the radiobiologist's view of brain cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

rises the various factors involved in the treatment of brain cancer, beginning with its causes till the post-treatment effects due to poor prognosis and involvement of radiation during the therapy (Fig. **1**).

## 2. CAUSES

At the molecular level, damage in the genes inside cells is the principal cause of cancer [20]. The reasons for most brain cancers are undiscovered but scientific research has led to the identification of some risk factors that might lead to the development of a brain tumor [21]. Mutation/ damage leading to turning on and off oncogene or tumor suppressor gene respectively causes cancer [22]. Chances of these gene damages are high during a patient's lifetime than inheriting the mutated gene from parents, which originated the studies on external risk factors [21].

### 2.1. Inheritance

Family history with a few types of brain tumors increases the chances of being affected by a brain tumor [23]. Syndromes responsible for this are tuberous sclerosis, turcot syndrome, neurofibromatosis (type 1 and 2), li- fraumeni syndrome, turner syndrome, gorlin syndrome and von hippel-lindau, might be associated with hereditary genetic agents [24].

Statistically, it has been observed that the Caucasians are more likely to be diagnosed with brain cancer than other ethnicities. Hence, the race/ethnicity is also one of the factors to be considered [25].

### 2.2. Chemical Exposure

Certain chemicals used at workplaces may lead to an increased risk of brain cancer, for example, chloroform and ethylene dibromide, which are used at laboratories to conduct experiments [26, 27]. Studies have proven that nitrates and nitrites found in cured meats, cigarette smoke and cosmetics can lead to brain cancer [28-31]. However, these carcinogens do not play a significant role in causing brain cancer because the brain is comparatively more guarded [21]. Nevertheless, further research is being done to make a conclusive statement.

### 2.3. Medical Record

Examination of viral infection and their association with brain cancer revealed that mononucleosis increases the risk of developing CNS lymphoma whereas, chickenpox is observed to decrease the chances of brain cancer [32-35]. Hence, the effect on the development of brain cancer by viral agents varies from case to case.

### 2.4. Exposure to Radiations

Radiations are the only definite factor for brain cancer, even if it is responsible for a small percentage of the cases [36-38]. The World Health Organisation (WHO) has recognized ionizing radiation to be a carcinogenic agent and is presently assessing the role of electromagnetic radiations from mobile phones in causing a brain tumor in adults and children [39, 40]. UV rays used at industries and laboratories contribute to the high risk of cancer [41]. Patients who have previously undergone radiotherapy for the brain are more prone to developing a brain tumor [42, 43]. Likewise, inhabitants of areas near nuclear plants with previous leaks are likely to be diagnosed with a brain tumor [44-46].

### 2.5. Metastasis

It is the worst part of a systemic tumor and spread to the brain leads to undesirable effects on many critical functions controlled by this organ [47-49]. Poor prognosis in patients with solid cancers always determines fatal outcomes and brain metastasis [49, 50]. Due to underdevelopment technologies, no reliable measures are available to avoid this event. Treatment of metastatic brain lesions by selective use of radiotherapy in combination with chemotherapy and surgery has proved to be efficacious [51, 52]. Primary cancer in lungs contributes to 40-50% of the brain metastasis, followed by breast cancer and melanoma with about 20% each [53, 54].

## 3. SYMPTOMS

Determination of a tumor at an early stage is difficult, as some brain tumors develop without any symptom while some develop symptoms gradually [55]. Location and size of a tumor decide the characteristic symptoms and their impact [56]. These symptoms could be misunderstood as not to be diagnostic signs hence the patient does not seek medical attention, for example, headaches and nausea are standard symptoms of brain cancer although not witnessed till advanced stages [57-59]. People experiencing a constant feeling of nausea, headache, loss of appetite and unusual vomiting should immediately check for the presence of a brain tumor [59]. Brain cancer affects the motor skills of the patient thus causing seizures like convulsions [motor seizures], loss of limb sensation, movement, weakness, difficulty with balance and walking [60]. A tumor affects the thinking and feeling capabilities of the patient, which result in speech difficulty, mood swings, change in concentration levels, memory loss and absent-mindedness, blurring vision and hearing problems [61-64].

## 4. TREATMENT

Patients reported to suffer from the above symptoms of a brain tumor are recommended for the assessment of the following parameters: tumor type, grade, size, location, its complexity with the nervous system and their medical history (Table **1**). These assessments are conducted using various diagnosis techniques like computed axial tomography (CT), magnetic resonance imaging (MRI), electroencephalography (EEG), perfusion MRI, functional MRI (fMRI), and magnetic resonance spectroscopy (MRS) [65-68]. The results of these scans are compiled by various medical specialists to form an optimized treatment strategy for the tumor. Molecular profiling of the patient also plays a crucial role in understanding the genetic makeup of the tumor, which helps in designing the best treatment strategy. Among the current

**Table 1. Types of brain tumor with their respective treatment options available.**

| Type of Brain tumor | Treatment Options Available | Reference |
|---|---|---|
| Acoustic Neuroma | Microsurgery, Traditional radiotherapy | [123] |
| Chordoma | Surgery, Chemotherapy, Adjuvant high-dose radiotherapy, Preoperative radiotherapy, Hypo fractionated radiotherapy [image-guided and stereotactic intensity modulated radiotherapy] | [124] |
| Pilocytic Astrocytomas | Complete surgical resection, Adjuvant therapy [chemotherapy and traditional radiotherapy] | [125] |
| Low-grade Astrocytoma | Radical tumor resection, Chemotherapy, Adjuvant therapy, Postoperative radiotherapy | [126] |
| Anaplastic Astrocytoma | Surgical resection, Radiotherapy, Postoperative chemotherapy | [127] |
| Glioblastoma | Surgical resection followed by radiotherapy and postoperative chemotherapy, Adjuvant therapy | [128] |
| CNS Lymphoma | Chemotherapy, Whole brain radiation therapy, Chemoradiotherapy | [129] |
| Schwannoma | Surgical removal, Gamma-knife radiosurgery | [130] |
| Craniopharyngiomas | Surgery, Radiation therapy, Adjuvant radiotherapy and chemotherapy | [131] |
| Primitive Neuroectodermal [PNET] | Surgical resection, Radiotherapy, Adjuvant chemotherapy | [132] |
| Pituitary tumor | Surgery, Stereotactic radiotherapy, Radiosurgery, Chemotherapy | [133] |
| Oligodendrogliomas | Fluorescence-guided surgery, Chemotherapy, Radiation therapy | [134] |
| Brain stem Glioma | Surgical resection, 3-D conformal radiation therapy, fractionated radiation therapy, Chemotherapy | [135] |
| Metastatic Brain tumors | Surgical resection followed by postoperative radiotherapy, Whole brain radiotherapy | [136] |
| Ependymoma | Surgical treatment, Whole brain radiation therapy | [137] |
| Sub ependymoma | Surgical resection | [138] |
| Optic nerve glioma | Fractionated stereotactic radiation therapy, Image-guided radiation therapy | [139] |
| Medulloblastoma | Surgical resection | [140] |
| Meningioma | Surgical, Adjuvant radiation therapy | [141] |

treatment alternatives available, surgery is preferred to be the preliminary step for the removal of a tumor and is often curative [69, 70]. However, if the tumor still spreads, then it is followed by a range of treatment techniques such as radiotherapy, chemotherapy, image-guided surgery or biologically targeted therapy [71].

Neuronal complexity will define the partial or complete removal of a tumor. Sophisticated image-guided surgery involves the development of virtual human anatomy guiding the surgeon at different steps throughout the procedure of tumor removal [72, 73]. However, due to excessive neuronal complexity, surgical removal of a tumor exposes the patient to a higher risk of neurodegenerative diseases and secondary malignancies. Along with the neuronal complexity of the tumor, the presence of blood-brain barrier is also a crucial factor to be considered as it physically and functionally isolates the brain from the immune system of the body, such that they do not have a memory of the brain cells as endogenous cells. Any damage to this barrier, due to the poor prognosis of the brain and nearby tissues, results in the exposure of the brain cells to blood, which acts as a carrier for all humoral and cell-mediated immune responses. These immune cells attack the brain cells, treating them as antigens, leading to autoimmune disorders. In such conditions, chemotherapy and radiation therapy are a reliable treatment.

Chemotherapy involves the intake of anti-cancer drugs and chemicals directed to kill the cancer cells [74]. The rapid proliferating nature of cancer cells makes them a better target for chemotherapeutic agents. Chemotherapy seeks to find equilibrium between eliminating the cancer cells and sparing the healthy ones, as the traditional practice usually targets a phase of the cell cycle, which is responsible for the attack on both cancerous as well as healthy cells [75-77]. Targeted therapies, differentiating agents, Hormone therapy, and Immunotherapy are some of the alternatives offered along with chemotherapy to reduce its effects on healthy tissues [78]. While Targeted therapy explicitly kills cancer cells, differentiating agents tend to evolve cancer cells into normal cells. Hormone therapy influences the availability of certain growth hormones to the tumor cells whereas, Immunotherapy approaches *via* enhancing immune responses towards the tumor cells [79, 80]. The major challenge faced during the application of chemotherapy and its combinations for cases with brain cancer is the difficulty in permeating the blood-brain barrier by the drug [81].

With a high success rate, radiation therapy is more explicit than surgery for the treatment of cancer. Radiation therapy works on the principle of DNA damage by causing small breaks in the genetic sequence, thus killing the cells and inhibiting their proliferation [82]. Fundamentally, radiation therapy has three major categories: external, internal and systemic. While in systemic radiation therapy, radioactive substances reach the site of a tumor through the patient's veins, in internal radiation therapy [brachytherapy], a radioactive source is injected at/near the tumor site [83, 84]. External radiation therapy involves irradiation of a tumor using high energy beams of photons or charged particles [84]. These therapies are used preoperatively [neoadjuvant therapy] to shrink a tumor and postoperatively [adjuvant therapy] to avoid the recurrence of a tumor [85]. Prevalent applica-

tions of radiation therapy include photodynamic therapy, which involves the use of radiosensitizers, thus working as a combination of chemotherapy and radiotherapy [86, 87]. Palliative therapy is used to counter and mitigate pain, bowel blockages and other similar complications caused by advanced cancer [88].

Radiation therapy comprises the use of ionising radiations, which involve electromagnetic waves and particle radiation for treatment. Electromagnetic waves consist of x rays, microwaves, radio waves and gamma rays, while particle radiation includes the use of subatomic particles and heavy ions. Conventional radiation therapy extensively uses low LET (linear energy transfer) x-rays and gamma rays generated by a linear accelerator and radioactive decays, respectively. A range of external radiation therapies like Photon-beam radiation therapy, Three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), helical-tomotherapy, image-guided radiation therapy (IGRT), stereotactic radiation therapy (SRT) and intraoperative radiation therapy (IORT) involve the use of x-rays and gamma rays to irradiate a tumor. 3D CRT is more precise at treating tumors when compared to external beam radiation therapy with an average survival rate of 47.2% as it models a virtual 3-dimensional image of the area to be irradiated which helps in designing of radiation dosage [89]. IGRT is a mode of 3D CRT where a CT scan is used to refocus the beams on the tumor. IMRT uses automated linear accelerators, which design a series of intensity-modulated radiation dosages for small volumes of the cancer cells, thus reducing the damage of healthy tissues [90]. A more refined version of IMRT is the helical radiotherapy wherein small amounts of external beams irradiate the body from different angles [91]. SRT is comparatively more accurate than other treatments since it involves focused irradiation of a tumor with high doses of pencil-thin beams, hence it does not cause much harm to the healthier cells. IORT is like photon-beam radiation therapy and utilises radiation shielding walls to reduce the effect on neighbouring cells [92]. It is chiefly involved in the treatment of tumors with a high risk of malignancy. The efficacy of the mentioned therapies has been significant for the treatment of prostate, lung, and breast cancers but their application on brain cancer is under progress due to the complex and fragile nature of the brain. However, prophylactic (preventive) therapy is in use to inhibit metastasis of cancer from the lungs to the brain, which is observed to be quite common [93].

Photons lead to a higher risk of damage to surrounding non-malignant tissues due to their sharp bragg peak, which is required to be wider for more precise treatment. Bragg peak defines the depth of energy deposition varying with dosage, which is determined by initial energy and the intensity of the beam [94]. The lethal results for exposure of healthy cells to radiation have urged the need for optimisation of the therapeutic ratio *via* maximising the dosage and minimising irradiation of normal tissues. Charged particle therapy addresses this issue with subatomic particles such as protons, neutrons and deuterons, and heavy ions such as helium, neon and carbon, which are known to have a broader bragg peak. The physical property of dose diminution beyond the Bragg peak makes charged particles a better choice for application in case of brain tumors (Fig. **2**).

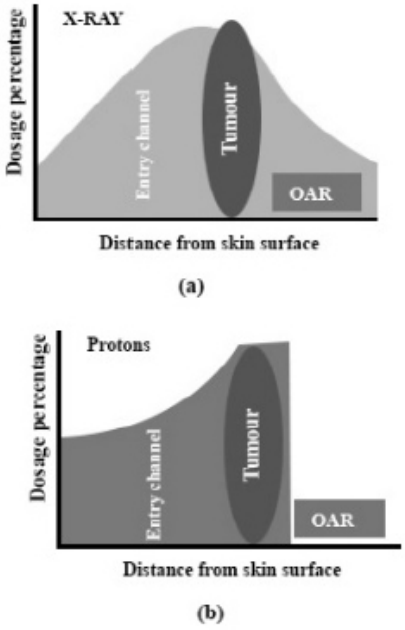


**Fig. (2).** Energy channel distribution of **[a]** X-rays and **[b]** proton beam. OAR: Organs at risk. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

### 4.1. Proton Therapy

The use of protons in a charged particle therapy has proven to be better than photons with an observed decrease in the risk of second malignancies [95]. These resulted in the replacement of photons with protons in commonly used radiation therapies such as IMRT and SRT. Passive scattering of protons due to collisions with solid brass leads to the generation of an unacceptable fraction of neutrons (neutron toxicity) when compared to pencil beam scanning, which has more than 50% lower possibilities of neutron toxicity [96, 97]. Even a low dose of neutrons induces a significant effect on cells due to their high biological effectiveness, which often leads to secondary malignancies. The use of superconductors in the gantry for the dose delivery has increased the precision of pencil beam scanning and reduced the risk of dose delivery to neighbouring organs [98]. Recent studies *via*Raman spectroscopy have also reported the highly sensitive nature of the phosphate group stretching in DNA, encouraging the involvement of Raman spectroscopy for the improvement of risk assessment during radiobiology research [99].

Research on the normal tissue complication probability (NTCP) of proton therapy was found to be lower than that of IMRT when tested on oropharyngeal cancer [100].

Results from NTCP calculation have further proven the efficiency of proton therapy in the treatment of brain tumors. RBE compares the efficacy of any particle beam on a

tumor to that of a photon beam of the same intensity. The treatment for brain cancer by intensity-modulated proton therapy (IMPT) confronts the common practice of using proton radiations (RBE 1.1) by varying the LET of the dosage and producing a maximum RBE of 1.4. Proton beam therapy is a common practice in the treatment of paediatric cancers, brain tumors, CNS related cancers, Hodgkin disease, sarcomas and neuroblastoma. Nevertheless, due to its high efficacy, radiation oncologists using proton therapy need to be highly experienced and precise with tumor localisation and treatment pattern (Fig. **3**)

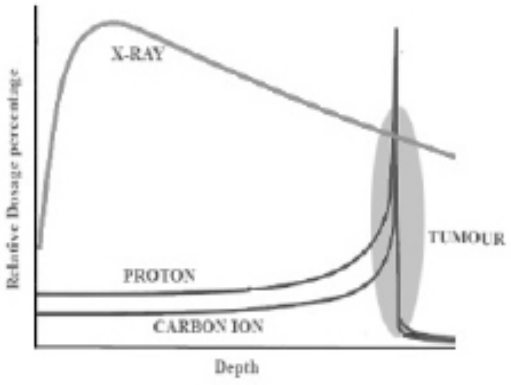


**Fig. (3).** Characteristic bragg peak or energy distribution of x-ray, proton and carbon-ion with an approximation of their effectiveness on a tumor.

### 4.2. CIRT

1957 marks the establishment of the first heavy-ion accelerator at the National Institute of Radiological Sciences (NIRS) Japan for clinical research on its therapeutic usage. Trials conducted by Eleanor Blakely at Lawrence Berkeley National Laboratory on carbon, neon and argon for their effectiveness on the treatment of cancer led to the origin of carbon radiotherapy in the year 1979. The conclusions from these trials introduced the use of heavy ions for the treatment of a tumor. With the construction of heavy ion medical accelerator in 1984 at NIRS, followed by their first heavy ion radiotherapy in 1994, led to the availability of charged particle therapy on the public from 1996. Japanese Government Ministry of Health, Welfare and Labour approved the primary carbon-ion radiotherapy (CIRT) to be constructed by NIRS in 2003, which developed and started active scanning treatment in May 2011 [10]. The use of carbon in radiotherapy emerged with its high effectiveness and efficacy for photon and proton resistant tumors. Broader Bragg peak of carbon-ion is a prime property of interest for its application, used as a criterion for the determination of precise dosage. With the oxygen enhancement ratio (OER) defining the radiological sensitivity of cells in the presence of oxygen, carbon ion was found to have an optimum balance between OER and RBE (Fig. **4**).

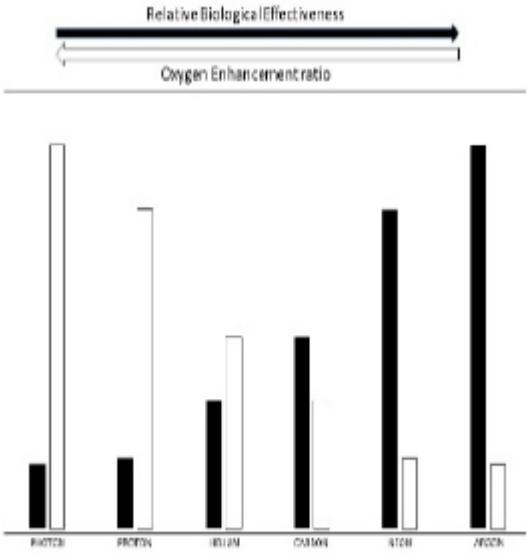


**Fig. (4).** Relative representation of relative biological effectiveness and oxygen enhancement ratio of a photon beam, proton beam, helium-ion beam, carbon-ion beam, neon beam and argon beam.

Carbon ion also has 36 times higher LET and nuclear fragmentation beyond the bragg peak when compared to other alternatives for the same beam speed [101]. It ensures the breakage of double-strand DNA by one hit, which is not feasible in the case of protons or photons (Fig. **5**). Even so, due to the underdeveloped strategies in the field of CIRT, customised treatment is the suggested approach for the treatment of brain tumors.

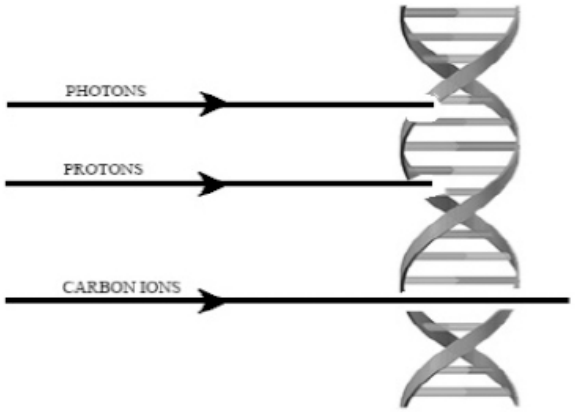


**Fig. (5).** Double strand breaking potential of carbon-ions compared to single-strand breaking potential of proton and photon.

Availability of a wide range of treatment options ensures the patient to receive a customised treatment specific to his/her tumor. Radiotherapy assisted by chemotherapy such as photodynamic therapy is observed to be efficacious in

case of small cell lung cancer, which increases its chances of the positive effects on brain cancer [102]. It presents a promising aspect of radiotherapy and its combination with other therapies for improvement in the precision and success ratio.

## 5. POST-TREATMENT EFFECTS

Regardless of its efficacy, radiation therapy of the brain leads to after-effects ranging from mild cognitive impairment to overt brain necrosis. These affect the essence of life and duration of post-treatment survival, depending upon various factors such as the size and location of a tumor, and the age of the patient. These factors define the nature of side effects experienced by patients depending on the time of their development; early or late side effects [103].

Early side effects emerge at neighbouring organs of the domain exposed to radiations and are observed to develop during the treatment or a few days later. In the case of brain tumors, it may result in swelling, leading to moderate short--term side effects such as fatigue, seizures, nausea, hair loss, and skin changes, which can be treated by medication [104].

Higher radiation doses affect both malignant and healthy tissues and cause late radiation injury. Patients operated with radiation therapy to the head and neck region were observed to experience transient radiation myelopathy (electric shock--like sensations below the neck) due to temporary demyelination of the sensory neurons [105]. These sensations were neither recognised immediately to be an early effect nor too late to be a delayed effect. It led to further division of delayed radiation effect as early (1-3 months) and late (3 months - 1 year). While transient radiation myelopathy is categorised as an early delayed post-treatment effect, late post-treatment effects usually involve pituitary-hypothalamic dysfunction and abate intellectual ability. The symptoms under late-delayed post-treatment effects emerge after several months to years following radiotherapy and are the most hazardous concerns associated with radiation exposure to the brain, usually resulting in necrosis. The expression of these effects depends on the frequency, dose and volume of brain irradiated and is prevalent in the white matter, especially in the glial cells [106]. Apoptosis of brain cells takes place due to oxidative stress, mitochondrial dysfunction, and protein degradation, often causing neurodegenerative diseases [107]. The possibility of developing secondary malignancies is higher in the case of radiation therapy, due to genetic makeup, style of living and linear dose responses for 0.2 Sv to 2 Sv. Metastasis following brain tumor is observed because of the isolated location of the brain. Chronic low doses of ionising radiation are known to cause leukaemia, breast cancer, eye diseases, cardiovascular and cerebrovascular diseases, and various mental health and psychological effects [108]. These effects reduce the quality of life by a significant measure, thus being one of the principal limitations of radiation therapy.

A range of radioprotective agents and drugs are available for reducing the adverse post-treatment effects due to radiation therapy without any compensation in doses. These radioprotective agents involve thiols and pharmacological agents such as alcohols, morphine, heroin, dopamine, serotonin and hormones [109]. The formation of sulphides and the free radical scavenger are few of the many radioprotective mechanisms proposed to explain the working of these drugs [110].

## CONCLUSION

Since the discovery of x-rays in 1896, followed by its use in the diagnosis of tumors, radiations have become a better alternative for the treatment of brain tumors. The flexible nature of x-rays has led to its use in IGRT, SRT and IMRT [111, 84]. The concept of broader Bragg peak and optimal RBE has led to experimentation on heavy-ions and subatomic particles thus introducing proton and carbon-ion as much precise and effective alternatives for x-rays. While carbon-ion has proven to have an RBE of 3.0, and reduced lateral scattering, oncologists cannot ignore the higher risk on the organs at risk (OAR), owing to the existing facilities and financial feasibility of most cancer treatment centres [112]. Treatment strategies planned to encounter brain tumor involve surgical removal in combination with chemotherapy or radiation therapy. When compared to chemotherapy, radiation therapy has proven to be more efficient with higher cancer survivorship [84]. The optimal value of RBE and OER for carbon-ion has proven its therapeutic use in the treatment of cancer. When analysed on a mouse model, the RBE of the carbon-ion is observed to vary from 3.2 to 1.5 due to its sensitive nature towards the peripheral nervous system, which is further suggestive of the test in case of a human model [113].

Research also led to the understanding of radiation as a significant cause of brain cancer along with inheritance, exposure to carcinogens and secondary malignancies. Observations have led to the interpretation of neural disorders caused due to the use of low (< 2Gy) and high (> 45Gy) ionising doses [114]. The lack of high-skilled professionals is a necessary objective to be tackled along with the idea of preparing a compact, accessible, feasible and more precise dose-delivering model for CIRT. With advancements in technology and skilled professionals, the excellent efficacy proven by carbon-ions in the therapeutic range (2 - 45 Gy) makes them a perfect replacement for the current use of photons and protons in radiation therapy [114].

Recent advancements in the field of superconductor and its application in gantry improve dose delivery efficiency in the treatment procedure [115]. Cisplatin (chemotherapeutic drug) - assisted carbon-ion radiotherapy has shown good results on moderate-sized advanced uterine cervical squamous cell carcinoma while research on external carbon-ion radiotherapy combined with brachytherapy can help in the reduction of severe post-radiation effects [116]. Volumetric image-guided carbon-ion radiotherapy can be a methodical way to avoid irregular dose distribution and improve the accuracy of the treatment as it is sensitive to small anatomical changes in the tumor, which lead to minimal error [117]. Exploring the prospects for the use of carbon-ion in traditional

radiation therapy can replace photons thus increasing the accuracy and survival-ratio [118]. The promising nature of carbon-ion has motivated scientists to experiment on other heavy ions with excellent therapeutic properties. Trials conducted on less complex organs of the volunteers presented convincing results, which suggest the scope for further enhancement for effective treatment of brain cancer. Lack of technology and cases act as hurdles for the complete understanding of the mode of action of radiation therapy on a brain tumor. Nevertheless, progress in research and technology can ensure that radiation therapy has the potential to become a conventional treatment option in the future [119-122].

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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