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Head and Neck Cancer Treatment with Particle Beam Therapy

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Abstract

In this century, cancer incidence has become one of the most significant problems concerning human. Conventional radiotherapy damage healthy tissue and in some cases may cause new primary cancers. This problem can be partially solved by hadron therapy which would be more effective and less harmful compared to other forms of radiotherapies used to treat some cancers. Although carbon ion and proton therapy both are effective treatments, they have serious differences which are mentioned in this paper and compared between the two methods. Furthermore, various treatments have been performed on head and neck cancer with hadrons so far will be discussed.
Keywords: *cancer; proton therapy; carbon ion therapy; Boron neutron capture therapy (BNCT); head; neck*

1. Introduction

Cancer is the major cause of mortality in economically developed countries claiming about 350,000 lives annually, and is a leading factor of death in developing countries. Head and neck cancer is ranked sixth and considered as the most prevalent cancers throughout the world. Global statistics show the fact that there are about 640,000 cases of head and neck cancer per year, resulting in nearly 350,000 deaths per year [1]. Treating with conventional radiation therapy often harms healthy tissue and organs near the tumor site. Proton therapy uses a highly precise beam in order to target radiation directly at the tumor site, minimizing damage to nearby healthy tissue and organs and greatly reducing the risk of both acute and long-term side effects. Cancers of the oral cavity and pharynx are the most prevalent type of head and neck cancer with approximately 480,000 cases per year [1]. Therapy by radiation, with surgery or chemotherapy can produce lasting locoregional disease control in a high percentage of patients with head and neck cancer. Radiotherapy is usually delivered using high-energy X-rays produced by linear accelerators. Theoretically, it would be possible to treat and cure most patients suffering head and neck cancer by using a high dose of radiation. However, in many treatment situations, the dose is limited and by the presence of adjacent radiosensitive normal tissues. The limitations of X-ray radiotherapy can be substantially overcome by using hadrons (i.e., protons and light ions such as helium, carbon, oxygen and neon, in particular carbon ions). Proton and ion therapy both started in 1954 with patient treatments at the 184-inch cyclotron at LBL Berkeley, first with protons and in later stages with helium beams. Until the closing of the accelerators in the year of 1992 more than 2000 patients went through the treatment and therapy process at Berkeley center. Proton therapy started at Uppsala/Sweden in 1957 while the same treatments activities started at Harvard cyclotron in the year of 1961 (more or less 9000 patients were treated and mostly cured until the year of 2002). Studies indicate that hadrons therapy can be replaced with conventional photon therapy specifically for tumors with low radio sensitivity and critical location. In this research proton, carbon ion therapy and BNCT will be described. In addition the number of treatments and clinical experiments conducted in head and neck cancer will be discussed and compared.

2. STATUS OF PROTON THERAPY

In Proton therapy a highly precise beam is used to target radiation directly at the tumor locating point, this act minimizes the possible damages to close healthy tissues and the rest organs and substantially reduces the risk of both severe and long-term side and subsequent effects. Therapy with traditional radiation treatment method often damages the healthy tissues and organs near the tumor site. Proton and ion therapy started in 1954 with patient treatments at the 184-inch cyclotron at LBL Berkeley, first with protons and in later stages with helium beams. Until the closing of the accelerators in 1992 more than 2000 patients were treated at Berkeley. This precision makes proton therapy useful specially for treating brain tumors, head and neck cancers, and tumors located near the spinal cord, heart or lungs. Since the energy emission of the proton beam is confined to the narrow Bragg peak, collateral damage to the surrounding tissues should be reduced, while an increased dose of radiation can be delivered to the tumor. Currently, there exist 10 hospital-based proton therapy centers working around the world and 15 others are being constructed or are in final completion phases. The PSI or Paul Scherer Institute is the only center in the world has the experience of treatment with intensity modulated proton therapy. Paul Scherer Institute, is the first proton therapy center, has the world's only gantry so far using so-called spot-scanning-technology. For most disease therapy sites and treatment centers, proton therapy treatments typically take about quarter to half an hour each day and are delivered five days a week for nearly four to seven weeks. The course of treatment and time duration per treatment each day differs based on each patient's individual case.

3. Carbon Ion Therapy

Since 1990s, the researchers have treated about 5,000 patients using carbon ions in Japan and about 440 patients in Germany. Heavy Ion Medical Accelerator in Chiba (HIMAC) was the central therapy site of the world's first carbon-ion treatment in 1994 and the facility has now treated approximately 3795 patients [2]. In the body, the 12C carbon isotope is able to exchange a nucleon in an interaction to convert it to 11C, after that the 11C decay starts via ß decay, giving off a positron which annihilates, emitting a pair of photons. Carbon ions can also be employed before surgery to shrink a tumor or immediately after surgery because, unlike x-rays or protons, they don't damage the skin. Furthermore, this method might offer a useful tool for assessing unpredictable deviations between planned and actual treatment. They can produce extreme damage to tumor cells by depositing their maximum energy in the Bragg peak. Another advantage in the use of carbon ions is that they can be formed as narrow focused and scanning pencil beams. Therefore, any parts of the tumor will be irradiated. Targeting critical areas such as back bone or spinal cord or optical nerves can be monitored with on-line positron emission tomography (PET) [3-5].

4. Biological Factors Related To Radiation

Linear Energy Transfer (LET) is a method used to express and describe beam quality. It is the rate of energy deposited or lost per distance travelled. Hadrons may have the property of low or high Linear Energy transfer. High LET radiation creates various and multi-dimensional damages and harms in DNA and other cellular structures, yielding tumor killing with fewer side effects on normal tissue [4,6]. Since the biological effect is not predicted by absorbed dose, a coefficient of relative biological effectiveness (RBE) is introduced to take in to account the dissimilarity in the effect of radiations of various types for the same physical dose. The effectiveness is defined as the ratio between the absorbed dose of a reference radiation and that of the test radiation required to produce the same biological effect. RBE depends on radiation quality of linear energy transfer, radiation dose, number of fractions, dose rate and the like [5]. Many chemicals can change the response of cells to radiation. The one chemical which has a very big effect and has possible importance in Radiation Therapy is Oxygen. It acts at the level of free radicals which are formed when radiation interacts with water molecules in the cell. Repairing the damage caused by the radiation can take place in the absence of Oxygen. The oxygen enhancement ratio or 'OER' is the ratio of the doses of radiation necessary to present or yield similar and identical biological impacts and effects in the nonexistence of oxygen and in its presence. The oxygen effect is vast and important for LOW LET radiation (x and gamma) [7].

5. Proton and Photon in Contrast With Carbon

Although Protons and carbon ions deeply penetrate tissues and emit most of their energy near the end of their range where the tumor is existed, they have some differences given as follows:

- Carbon ions disperse or scatter much less than protons and concentrate their radiation in a smaller area [8], [9].
- However protons and carbon ions both have sharp Bragg peaks as shown in fig.1, protons are characterized by low LET whereas carbon ions are characterized by high LET [6].
- A significant benefit of carbon ions is that, unlike x-rays and protons, they do not need oxygen to work and can, therefore, reach and kill or terminate hypoxic areas of tumors, which are notoriously hard to treat [9].
- Bone and soft tissues tumors can be treated and cured by carbon, but not even by protons and certainly not with x-rays [10].
- The OER is more than 3/2 times better than that of protons. Another distinction is that carbon ions bring about more irreparable harms and damages to the cancer cells. Protons and x-rays have about the same relative biological impact, which is an assessment of the damage from ionizing radiation while the RBE of carbon ions is three times higher; this means that they damage DNA in a way that is double-stranded and irreparable.
- Today, 24 proton facilities are working worldwide, and almost 20 more such sites are planned to be constructed, while there are only 3 carbon facilities currently treating patients of mentioned disease. One is situated in Germany and two others are working in Japan [11]

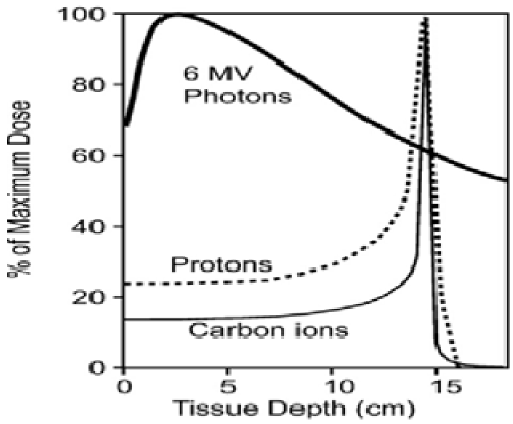


Figure.1. Comparison between Carbon and Proton Bragg peak

6. Boron Neutron Capture Therapy (BNCT)

BNCT is a combined treatment method including thermal and epithermal neutron beams. BNCT derived from ^{10}B nucleus tendency to capture thermal neutrons. As a result unstable 11B nucleus generates a lithium ion and an α particle. The yields of this reaction have high LET characteristics. Thus, it is able to selectively irradiate tumor cells which have received appropriate amount of ^{10}B. The initial idea to use neutron capture reactions in cancer treatment was broadcasted by Locher in 1936. In May 1999 the first patient was treated with BNCT at the Finnish Research Reactor. By this way cancer cells will be killed selectively as well as treating tumors by a cell-by-cell basis. BNCT would be effective in treating malignant melanoma (skin cancer), malignant brain tumor, head and neck cancer, lung cancer, liver cancer. In order to estimate the number of monitor MU which should be delivered to the patient in BNCT treatment, the on-line beam monitor system requires to be calibrated. Each patient was planned to receive two BNCT treatments in 3-5 weeks apart. Furthermore, CT (for constructing 3-dimensional model), MRI and PET (for specifying target volume) images can be assumed with each other.

7. Intensity-Modulated Radiation Therapy (IMRT)

IMRT is a high accuracy radiotherapy technique with the ability of releasing precise doses to virulent tumor or characteristic areas within the tumor. IMRT can be assumed for cancers in the nasopharynx, sinonasal region, parotid gland, tonsil, buckle mucosa, gingiva, and thyroid [12]. Due to its potency to spare healthy tissues, this method may be beneficial for re-treatment of formerly irradiated with head and neck cancers. In traditional radiotherapy, the doses given to the healthy tissues are the real limiting and restricting factor. IMRT increases the doses delivered to the healthy tissues and then dispenses it over a large mass in order to provide an enhanced dose for the tumor cells. Owing to some reasons IMRT would be appropriate for children. Child's body is highly sensitive to radiation. Moreover, scattered radiation created by radiotherapy is very serious in children [13]. In CT scanning and IMRT both rotating beam is used. Though, in IMRT beams delivers radiation. Conventional three dimensional conformal radiotherapy, modificated three-dimensional conformal radiotherapy and IMRT are compared in figure.2 [14]. Furthermore, side effects of conventional radiation therapy and IMRT are approximately the same. However, the proton therapy would cost about 2.4 times more than IMRT [15].

8. Clinical Experience in Head and Neck Cancer

Chondrosarcomas and Chordomas are uncommon tumors which respectively arise from notochordal remnants and primitive mesenchymal cells. Skull base Chordomas and chondrosarcomas are close to dose-limiting structures such as optic pathways, brainstem, and spinal cord. .A series of 621 cases of chordoma and chondrosarcoma of the base of skull treated at the Massachusetts General Hospital in Boston to a total dose ranging from 66 to 83 GyE indicated local control at 10 years of 54% and 94%, respectively [16]. In all cases, surgery was performed before radiotherapy to eliminate the tumor. Salivary gland tumors can also treated by particle beam. Because of the low radiosensitivity of these tumors, conventional radiotherapy is not effective for them. Three- dimensional conformal radiation therapy (3D-CRT) and IMRT can be used for these cancers [17]. Another approach is to use neutron beam radiation. In this way, high-energy neutrons assumed in place of using x-ray beam. Furthermore, in 18 patients with salivary gland carcinoma, survival rate of 59% were observed. Although therapies with carbon ions and neutrons may give the same results, treating with carbon ion has lower toxicity. Treating skin carcinomas with conventional radiotherapy is limited. 45 patients suffered from skin carcinomas were treated and cured with carbon ions RT from 2006 to 2009 which caused 1- and 3-year overall survival rates for 45 patients between 88.9% and 86%, respectively [18]. Five randomized studies of particle beam therapy in malignant glioma were compared. None of these trials detected a significant survival benefit for particle therapy. This study is divided into two types of therapies as the table.I represent, with neutrons (first four studies) and with photons or Pions (fifth study) [19]. Since 2001, 26 patients with salivary gland carcinomas, sarcomas, squamous cell carcinomas were treated with BNCT. All patients survived 1 up to 72 months after the treatments. The mean survival times were 13.6 months. Entirely, BNCT has the potential to be used for the reappeared

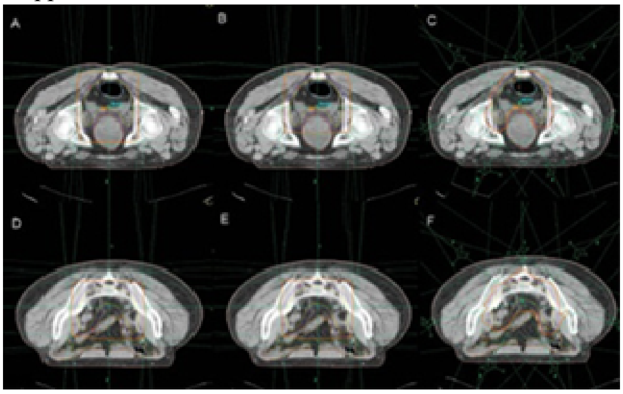


Figure 2. Three method planning in patient with a uT3N+ medial rectal cancer, conventional tridimensional conformal radiotherapy (A and D), modificated tridimensional conformal radiotherapy (B and E) and IMRT (C and F).

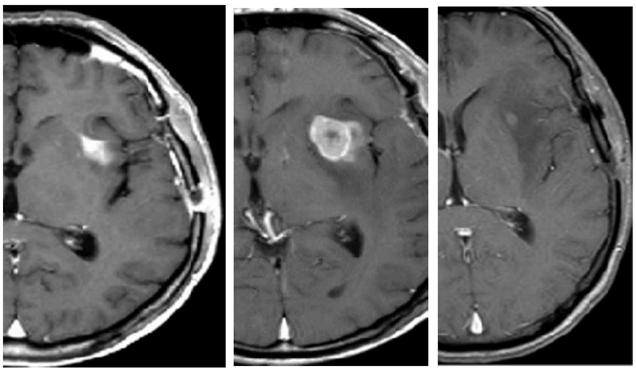
tumors [20]. Another example of BNCT treatment effect is an old man (36 year old) with glioblastoma multeforme (GBM) which is shown in Figure 3[21]. Several paranormal head and neck cancers, such as laryngeal sarcomas, bone and soft tissue sarcomas and glomus tumors were treated with combined proton and photon radiotherapy. Moreover, hadron therapy has been applied for the treatment of numerable cases of carcinoma of pituitary, thyroid gland and ear.

9. Facilities

Every year, several thousand cancer patients with both early and advanced tumors are treated in the proton therapy centers as Loma Linda Institute and PSI with encouraging results. Although in both centers many successful treatments carried out for meningiomas, chordomas, chondrosarcomas, sarcomas, eye tumors ,children cancers and etc. , ORL tumors (nose and throat region tumors) were only treated at PSI. Moreover, in 98% of aforementioned cancer types complete cessation of tumor growth has been reported. Loma Linda has the smallest variable-energy proton synchrotron which delivers adequate energy to the deep-seated tumors. Furthermore, it includes four treatment rooms with approximately 90 tones gantries. In contrast PSI applies the Spot-Scanning technique in order to uniformly spread out radiation dose overall tumor region. In addition, a new gantry called gantry2 is setting up at PSI and will be provided at the end of 2012 for patient treatment [22]. On the other hand, HIT (Heidelberg Ion Centre) has the capability of treating patients with protons as well as various heavy ions such as carbon, oxygen, and helium ions. Another considerable facility of this center is intensity-controlled rasterscan method leading to maximum accuracy in the three-dimensional radiation of tumors. Two treatment rooms of HIT devoted to fixed horizontal beamline and one other room hosts heavy ion gantry which would be able to rotate 360° around the patient. MIT BNCT includes fission converter epithermal neutron beam (FCB), thermal neutron beam and Prompt gamma neutron activation analysis (PGNAA) facilities .In order to treat a patient in less than one hour with BNCT, the proton-Lithium reaction will require a proton beam current between 10 and 100 mA at 2.5 MeV as well as proton-Beryllium reaction needs 5-10 mA at 20 MeV [23]. Moreover Carborane (composed of boron and carbon atoms nucleotides) can be beneficial to be a boron-10 delivery agent for BNCT.

10. Conclusion

This paper deals with hadron therapy as an operative treatment for critical organs. In particular, carbon ion and proton therapy are described and compared in terms of their features and preferences .Although hadron therapy can be effective method for decreasing damage to adjacent healthy tissues and treating with fewer fraction , due to high cost of equipment that requires such as magnet, huge gantry and synchrotron ring it has almost slow development. Accordingly, major investigation is required to reduce costs by finding alternative methods for gantry rotation. On the other hand, because of the extremely complex nature of cancer, extensive calculation must be performed to estimate absorbed dose rate of various organs. Also calculating the probability of new primary cancers and other side effects should not be ignored.



Before BNCT 1 month after BNCT 3months after BNCT

Figure 3. MRI image of patient with glioblastoma multeforme treated following BNCT

FIFTH STUDIES OF PATICLE THERAPY IN MALIGNANT

Study	Treatment	No. of patients randomized (analyzed)	Median survival (months)
Griiffin et al., 1983	50 Gy photon WBRT + 15Gy photon boost	83 (78)	8.6
	50 Gy photon WBRT + 15Gy photon boost	83 (80)	9.8
Duncan et al., 1986	47.5 Gy photon	30 (Not reported)	8
	5.1 Gy neutron + 28.5 Gy photon	31(Not reported)	4
Laramore et al., 1988	45 Gy photon WBRT + 3.6 Gy neutron boost	17 (17)	13.9
	45 Gy photon WBRT + 4.2 Gy neutron boost	13 (12)	Not reported
	45 Gy photon WBRT + 4.8 Gy neutron boost	29 (28)	Not reported
	45 Gy photon WBRT + 5.2 Gy neutron boost	53 (44)	8.6
	45 Gy photon WBRT + 5.6 Gy neutron boost	61(59)	Not reported
	45 Gy photon WBRT + 6.0 Gy neutron boost	30 (30)	Not reported
Duncan et al., 1986	47.5 Gy photon	16 (16)	11
	13.8 Gy neutron	18 (17)	7
Pickles et al., 1997	60 Gy photon	Not reported (41)	10
	33–34.5 Gy pion	Not reported (40)	10

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