Evolving to Heavy Ion Species: Carbon Ion Therapy for Radiation Therapy Treatment

**Abstract**

**Background:** Radiation therapy for cancer treatment has been evolving for several years; shifting from conventional photon therapy, to proton therapy, and now to heavier carbon ion therapy. Carbon ion therapy utilizes heavier particles to treat cancer in a similar way as proton therapy. Therapy with carbon ions allows the radiation beam to be directed closer to organs at risk and maintain exceptional tissue sparing.

**Purpose/Objective:** To educate the cancer community on the use of carbon ion therapy or heavy ion therapy in the treatment of cancer; by explaining how it was developed, how it works, what types of cancer it treats, advantages and disadvantages compared to conventional treatments, and its future role in radiation therapy.

**Methods:** A literature review was completed using several scholarly articles to gain a knowledge and understanding on how carbon ions can be used for treating cancer. Various search engines, scholarly articles, and limited search parameters provided accurate and trustworthy information.

**Results:** Previous research and studies have been completed to provide evidence of the benefits of using carbon ion therapy, over conventional photon therapy, to treat several different types of cancer. Research shows advantages and limitations of using carbon ions; to better understand these advantages it is important to acknowledge how carbon ion therapy works and why it might be the next standard of care for cancer patients.

**Conclusion:** Carbon ion therapy is a rapidly developing radiotherapy that limited members of the cancer community are aware of or understand. As cancer continues to be one of the leading causes of death in the United States, it is critical to find more effective and safer ways of treating it. With more research and funding, the United States may potentially introduce the use of carbon ion therapy.

**Introduction**

Cancer is currently the second leading cause of death in the United States, which could potentially become number one with the increased aging population.1 Nearly half the patients diagnosed with cancer complete radiation therapy (RT) and most patients receive external-beam RT using photons.2 With the increasing mortality rate and use of radiation therapy for cancer treatments, it is critical to implement new and effective treatment options. Patient safety is the most important part of cancer treatment, so maintaining or decreasing toxicities is especially valuable. A solution to these problems may be the evolution and development of a new way to treat cancer utilizing carbon ions, which have unique physical characteristics.

Carbon ions are charged particles, like protons, but have a much heavier mass; the heavier mass can improve aspects of treatment.1,3,4 Unlike conventional photon radiation therapy, particle therapy provides a distinctly different biological and physical properties.1,4 Photon beams deliver doses that travel continuously in and through the patient, while particle beams release energy and deposit a majority of the doses to a corresponding site.3,4 This results in a decrease in the entry dose and elimination of the exit dose, which increases healthy tissue sparing.4 Carbon ions work by immediately transferring their kinetic energy to the tissue when entering a patient.3 The energy is released inversely to the velocity, and dose will be deposited to a specific site.1,4 The depth of this dose can vary depending on the strength of energy applied to the carbon ions, similar to photons. Even though carbon ions function like photons, they are not yet used for cancer treatment in the United States.

Carbon ions are not currently being used in the United States to treat cancer, but with increased funding and research there has been an elevated interest in its role in cancer treatment.1 The purpose of this literature review is to educate the cancer community on the use of carbon ions for treating various types of cancer. Carbon ion therapy is a modern, but rare form of a radiotherapy that offers superior dose conformity, higher relative biological effectiveness, and better overall outcomes for various deep malignant tumors compared to conventional radiation therapy (see Figure 1).3 The recent development of a complex physical mechanism of how carbon ions are used in therapy has led to advantages and disadvantages over other types of therapies. This may continue to evolve with advancements in technology and research, potentially playing a role across the United States.

**Methods**

A literature review was conducted and completed on the use of carbon ions for radiation therapy. This literature review can be used to educate the cancer community on the use of carbon ion therapy; by explaining how it was developed, how it works, what types of cancer it treats, advantages and disadvantages compared to conventional treatment, and its role in future radiotherapy. Several databases, including CINAHL Plus with Full Text (EBSCOhost), MEDLINE with Full Text (EBSCOhost), and other EBSCOhost Health Professions Databases, were analyzed using many key terms and search limitations to discover pertinent information.

Key terms searched were “carbon ions,” “carbon ion therapy,” “carbon ion therapy and history,” “carbon ion therapy and cancer treatment,” and “carbon ions and beam delivery.” These searches all provided adequate amounts of information for this research. In addition to databases, online publications were used to help define and understand several other carbon ion related terms. The results were limited to full text publications that were published within the past five years. The variety of source types and authors provided reliable and scholarly information. Several sources reinforced information from other sources, preventing any author biases. Research from these articles will be used throughout separate headings below to encapsulate information analyzed about carbon ion therapy, beginning with the history of carbon ion therapy.

**Literature Review**

**History**

The history of all radiotherapy began with the discovery of x-rays in 1895 by Wilhelm Roentgen, leading to a rapid increase in radioactive research.In 1897, JJ Thomson had research that lead to the discovery of electrons and other important atomic characteristics. Following the discovery of electrons, the nucleus was founded. A gold foil experiment completed by Ernest Rutherford in 1909, provided evidence of the nucleus. Rutherford continued to research emitted particles that formed during radioactive interactions with nuclei.1,3 Now that all the major atomic structures were uncovered, it led to interest in ways particles could be used in medicine.

The first particle accelerator was created by John Cockcroft and ETS Watson at the Cavendish Laboratory in Cambridge, England, in 1932.1,3 This particle accelerator was not capable of delivering high enough energies to penetrate skin or treat cancer.1,3 The first accelerator used to treat cancer was created by Robert Van de Graaff in 1937; this accelerator created x-rays, not particles for radiation therapy.1,3 Ernest Lawrence later created a particle accelerator with a higher energy than Cockcroft, but it was only strong enough to be utilized in atom and subatomic particle research.4 Ernest Lawrence continued researching at the Berkeley University Laboratory, later renamed Lawrence Berkeley National Laboratory (LBNL).1 He finished researching and developing accelerators that produced higher energy beams, which provided evidence to support the theory of nuclear fission.1 This led to the creation of nuclear weapons and produced the theory of using particles in disease treatment.

It was not until 1946 when Robert Wilson proposed the idea of using particles, accelerated protons, and heavy ions to treat cancer.1,3,5 The first to experimentally treat cancer using carbon ions was at LBNL in 1977.1 Research on carbon ion therapy may have begun in the United States, but it has been carried out more across the globe. In 1984, Japan created the first heavy ion medical facility in Chiba, Japan (see Figure 2).1,3-7 It was first operational in 1993 with clinical trials and research.1,3 Research on carbon ions in the United States began to diminish, however it began to excel in China, Japan, and Germany.3 Data collected from research on clinical trials in Germany and Japan has ignited a renewed interest within the United States. For reintroduction into the United States to happen, it is important for radiation researchers and members of the cancer care team to understand how it works.

**How it works**

Heavy carbon ions interact with tissues differently than photons. A photon therapy beam continuously travels through tissues, while releasing a constant amount of dose along the beams path.1,3,8 There is a constant decline of dose as it travels in and completely through tissue. A higher entrance dose is required to accommodate deeper seeded tumors.1,3,8 A common characteristic of a photon beam is the maximum depth dose (Dmax) for different energies; the higher the energy used, the deeper the Dmax.8 If the tumor exceeds the maximum depth dose, while using photons, the entrance and exit doses must be higher leading to more detrimental effects on healthy tissue.8 Particle beams, on the contrary, can travel deeper into tissues and release less dose upon entering and exiting the tissue.1,3 This is not the only characteristic of photons that differ from particles.

Photons also carry another characteristic that is difficult to control, which is scatter. Scatter typically occurs between the collimator on the gantry head and the treatment site.1,8 Scatter occurs due to the lack of photon charge because without charge they can’t be controlled magnetically or electrically.1 A physical collimator is required to manage this scatter.8 The scatter of photons can also increase the dose to healthy tissues and have a more toxic effect. Carbon ions lack scatter and can be controlled magnetically or electrically, but their heavy mass can make them interact with tissue differently.

Carbon ions interact much differently than photons because they are heavy and have a charge. Upon entering the skin, the kinetic energy created from carbon ion sources force dose to be released inversely to the velocity.1,3,8 This inverse relationship creates a low entrance dose and an increased dose delivered to the treatment site.1,3,8 It also reduces, almost eliminating, dose beyond the treatment site. Increasing the energy of ions will result in a deeper penetration and complete dose delivery to the treatment site.1 The charge of particles, or carbon ions, allows the treatment machine to magnetically control the shape and direction of the beam.1 Dose distribution and tumor control from carbon ions allow therapy to be more safely executed in the treatment of cancer.

**Uses**

In the United States, there has not been any carbon ion therapy facilities created for the use of cancer treatment. Initially, the United States used particle (no carbon ion) accelerators to research atoms and subatomic particles.1,3 Early particle accelerators provided evidence of nuclear fission, which could be used to produce new elements.3 Results from fission were also used to develop atomic bombs and other nuclear weapons.3 There continues to be large amounts of research around the globe that supports the use of carbon ions for therapy. It has become the standard of care over other types of radiotherapies for treating cancer in other places around the world.3 Phase one and phase two clinical trials are being conducted in Germany, Japan, China, and Italy.1,3 The most common cancer sites treated with carbon ion therapy are prostate, bone/soft tissue, head/neck, and lung cancers; these treatment sites are currently being enrolled in clinical trials.4

Most of the phase one and phase two clinical trials for prostate cancer are related to the standard dose fractionation for carbon ion therapy.1 Phase one and phase two trials are typically completed to determine the best overall outcome, using the more superior dose. One study1,3 conducted by the Nuclear Information and Resource Service (NIRS) organization used different carbon ion beam doses delivered at 54 Gy and 72 Gy over five weeks, to determine which dose was more superior. The higher dose caused extra toxicity but had a better local control.1,3 Researchers then tested 57.6 Gy, which is still being tested.1,3 Results from this test will be used to set the new standard dose for treating prostate cancer with carbon ions.1 Following this research, other studies will be completed to compare conventional photon therapy to carbon ion therapy to determine which is the best treatment option for prostate cancer. There have also been similar studies completed on osteosarcomas and soft tissue sarcomas.

Several studies have been completed to provide evidence that using carbon ions are safer and more successful for treating osteosarcomas and soft tissue sarcomas. In a study1 completed at the Heavy Ion Medical Accelerator (HIMA) in China, 47 patients were enrolled in a clinical trial that studied spinal sarcomas. Patients received dose from 52.8 Gy to 70.4 Gy in 16 treatments over four weeks.1 Five years following treatment, results suggested a progression free survival rate of 48 percent, an overall survival rate of 52 percent, and tumor control rate of 79 percent.1 There was only toxicity issues limited to one patient, but no fatality occurred.1 From this study, authors suggested that carbon ion therapy can be effective and safe for treating bone cancers.1 Another study1 conducted at HIMA was for soft tissue sarcomas. With a similar dose given for osteosarcomas, the soft tissue sarcomas resulted in a five-year tumor control rate of 62 percent and an overall survival rate of 33 percent.1 These results have higher percentages compared to conventional photon radiotherapy.1 Conclusions can be drawn from this data that support more successful treatment outcomes for soft tissue sarcomas and osteosarcomas when treating with carbon ions. Successful tumor control while using carbon ions is not limited to only soft tissue sarcomas and osteosarcomas, but also improve in specific head and neck cancers.

Head and neck cancers are currently treated well with conventional photon therapy, except for recurrent squamous cell carcinomas (RSCC). Along with RSCC, adenoid cystic carcinomas, mucosal malignant melanomas, and other head/neck sarcomas are typically difficult to treat with conventional photon therapy, which is where carbon ion therapy can play a role.1,3,5 A study3 completed at the University of Heidelberg, provided evidence that carbon ion therapy can increase local control rate by 53 percent for patients with unresectable head/neck cancers. This study suggests carbon ions can be used to treat radioresistant unrespectable head and neck cancers.3 It supports the theory of using carbon ions as the next standard of care for these types of malignancies. Successful results in head/neck cancers, were not observed in clinical trials for lung cancer patients.

Lung cancer is the deadliest type of cancer, resulting in 155,000 deaths per year.9 Several studies10,11 completed by the NIRS have been completed to compare conventional photon therapy, stereotactic body radiation therapy (SBRT), and carbon ion therapy treatment for lung cancer patients. Results from a study10 completed by the NIRS on small cell lung cancer and non-small cell lung cancer provided unique trends. The results for carbon ion therapy is similar to SBRT treatments, but both are superior to conventional photon therapy.10 Overall survival for SBRT and carbon ion therapy where 70 percent and 74 percent respectively, much higher than conventional photon therapy.10 Few toxicities were reported during this study for all modalities.10 Another study11 conducted at NIRS was completed for unresectable early stage non-small cell lung cancer; results from carbon ions suggest they may act like a total resection for this type of disease, providing evidence that surgery is as beneficial. More research must be completed to determine that carbon ions are a better treatment option than SBRT treatments. Research on other types of cancer can introduce a new standard of care for diagnosed patients.

Like other types of radiotherapies, carbon ion therapy can treat a variety of other types of cancer. It can potentially be used to treat childhood cancers, recurrent tumors, osteosarcomas, soft tissues sarcomas, and tumors located in the lung, head/neck, prostate, cervix, liver, pancreas, and brain.1,3,6 As carbon ion therapy continues to be studied and data is shared in literature, several other types of cancer may have a better treatment option. The advantages seen in several cancer clinical trials is due to the physical and biological effects of particles on tissue.

**Advantages**

Carbon ion therapy has several advantages over other particle therapies, along with superiority over photon therapy. Particles can be used to spread out the Bragg peak, unlike photon therapy. The Bragg peak is a term that refers to the energy released near the end of its energy range within tissue. The range a particle can travel in tissue can be adjusted according to the energy, so the Bragg peak can shift to the location of the treatment site.1,3,5 It results in better dose distribution and target control (see Figure 1).1,3,5 Treatment plans can be made closer to the target and further from organs at risk, this decreases the possibility for toxicity.1

There is a higher dose delivered to the tumor and less to the healthy surrounding tissue when using particles, rather than photons.1 The different characteristics between photons and particles allows for decreased entrance dose and increased dose delivered to the tumor site.1,3 With particles, since there is a larger Bragg peak, there is little dose delivered beyond the target.3 This decreases the toxicity to normal tissues. Particles also decrease the amount of scatter that occur between the collimator and the treatment site.1 Photons typically have increased amounts of scatter, which can only be controlled by the collimator.1 Particles benefit by having the ability to prevent scatter and maneuver it magnetically to the treatment site.1 Carbon ions are also known for having a higher linear energy transfer (LET).

Particle therapy has a high LET, compared to photon therapy.5 The LET is the rate of energy deposited in different tissue ranges. Higher LET results in more damage to the cells.This results in an increased complexity of damage to deoxyribonucleic acid (DNA); the DNA damage is typically irreversible.1,3,5 Particles also have the advantage of delivering low LET initially and higher LET at the targeted site.1,3,5 This is possible because of the ability to release energy inversely to the velocity.1,3,5 As energy slows down in the tissue, LET increases releasing more dose to the targeted volume and increasing the biological effectiveness.

Higher LET also results in an increase in the relative biological effectiveness (RBE).1,8 The RBE is the ratio of biological effectiveness on tissue of one type of radiation over another type. Radiation with higher RBE results in a higher percent of cells being destroyed. An RBE can be determined by the intensity of LET, type of particle, dose fractionation, tissue/cell type, oxygen levels in tissue, and stage of the cell cycle.1,3-5,8 A higher RBE results in more complex tumor damage, typically double-strand breaks.8 Double-strand breaks are difficult, almost impossible, to repair.If the double-strand break is repaired, it typically leads to other disfunctions in the DNA.8 A higher RBE is seen in protons and carbon ions, but carbon ions have another characteristic that make it more beneficial than protons.

Carbon ions also have an advantage over other particle therapies, including protons. Carbon ions have a smaller penumbra from scatter, allowing more healthy tissue sparing compared to protons.1,3,5 The decreased penumbra is due to the heavier mass of carbon ions.5 The mass also plays a role in LET, which is considered higher in carbon ions than protons.1 The RBE of carbon ions is three times higher than protons, so it has a greater impact on cancerous tissues.1 These advantageous suggest carbon ion therapy may be more beneficial than conventional photon or modern proton therapy. All the advantages from carbon ions appear to make it the next standard of care, but with the advantages comes several disadvantages that prevent it from being used around the world.

**Disadvantages**

Even though there are benefits of carbon ion therapy, that does not discount its disadvantages. Although particle therapy is known for its Bragg peak, carbon ions have a fragmentation tail.1,3 It results in a slight amount of dose delivered beyond the target site. This dose must be taken into consideration during treatment planning to prevent overdosing organs at risk or underdosing targeted volumes.1 The fragmentation tail of carbon ions is difficult to account for, but it is not the major preventative factor for implementing it in the United States.

Disadvantages that currently limit the use of carbon ion therapy in the United States, are its costs and physical features. To complete a carbon ion therapy treatment, it is estimated to be three to four times more expensive than proton therapy.1,3 Proton therapy is already extremely expensive compared to conventional photon therapy. Insurance companies around the world are not insuring carbon ion therapy due to the lack of literature and research, which can’t be conducted without funding or patients.1 Typically, a carbon ion therapy treatment machine does not use a 360-degree rotating gantry, limiting what can and cannot be treated.3 There are only two current machines in the world that have 360-degree rotating capabilities; one is in Germany, which weighs 670 tons.1 Most of the gantry weight comes from the bending magnet. It is three times more difficult to bend carbon ions than protons, because of the weight of the particle.1 It has not been implemented within the United States because of the lack of funding and research literature. If funding was not an issue, the lack in number of treatments per day can prevent its use.

Another disadvantage is the inability to treat patients on different machines at the same time, within the same facility.3 There is only enough energy created in a facility to treat patients on one machine at a time. Within the treatment room there is also a possibility of gas exposure, since most carbon ion sources are created by using carbon dioxide and methane gas.3 If patients and employees are exposed to these gases it can lead to additional illnesses. Typical treatments are conducted in rooms other than the carbon ion source (see Figure 2).1 Lack of research and data has limited the use of carbon ions to countries outside of the United States.

Although there are several carbon ion therapy facilities across the globe, there is still not enough research to prove the risk vs. reward of using carbon ions over other radiotherapies. Most of the current trials on carbon ion therapy are phase one or phase two trials, which are looking at the dose schemes and toxicities. Currently there is not enough research and clinical trials to assure that the advantages of carbon ion therapy outweigh the disadvantages. As research continues to grow, the advantages of carbon ion therapy need to outweigh photon and proton therapy, before it can be the new standard of care. There’s been few treatments completed around the world, therefore it can’t be the new standard of care.

**Future and current research**

Currently there have been 15,000-20,000 cancer patients treated with carbon ions around the world and about 150,000 patients with protons.1,4,12 As of 2017, there are 11 carbon ion therapy facilities functional around the world, none of which are in the United States.1,4These facilities are located within five countries, Austria, China, Germany, Italy, and Japan; Germany and Japan being at the forefront of carbon ion use.1 Although the United States does not currently have an operational carbon ion therapy facility, it is home to 27 proton therapy facilities.1 As research results continue to show improvement of tumor control and dose distribution using particle therapy, the introduction of carbon ion therapy will more than likely be developed in the United States.

For carbon ions to be implemented in the United States, the development of an established funding and research program must be in place. In recent years the National Cancer Institute (NCI) organization started searching for grants specific for carbon ion facilities.1 The NCI have currently accepted two grants that support creating a carbon ion radiotherapy treatment facility for research and cancer treatment.1 It is essential to continuously fund research for carbon ions because they have several advantages over other radiotherapies. With more funding, comes more research, and improved ways to successfully treat cancer. The most promising location for creating a carbon ion facility is on the campus of the University of Texas Southwestern because they have been working with the North American Particle Therapy Alliance and other organizations to accept grants.1 Currently, there are plans for a carbon ion radiotherapy facility to be constructed in the United States and potentially be a new standard of care for treating cancer.

**Conclusion**

Cancer is one of the deadliest and most common diseases around the world. With the increasing amounts of cancer cases around the globe, it is more important to discover better treatment options to improve the overall survival rates for cancer patients. Carbon ion therapy research has demonstrated superior dose conformity, higher relative biological effectiveness, and a better overall outcome compared to conventional radiation therapy for treating cancer. With recent funding and research, the development of a carbon ion therapy facility might be possible in the United States within the next ten years.

Figure 1. Representation of Dose Distribution for Photon Radiotherapy and Carbon Ion Radiotherapy

A dose distribution representation provides evidence for the advantage of using carbon ions for therapy over conventional photon therapy. There is a smaller entrance dose and no exit dose for the carbon ion dose distribution (on left), as there is for photon therapy (on right).13

Figure 2. Visual Representation of Carbon Ion Facility and Treatment Room in Chiba, Japan

A carbon ion facility is very complex, made up of separate rooms for the ion source, treatment room, linear accelerator, control room, and dual rings. A typical treatment room is made up of a couch, gantry, image system, laser system, and a power supply.14

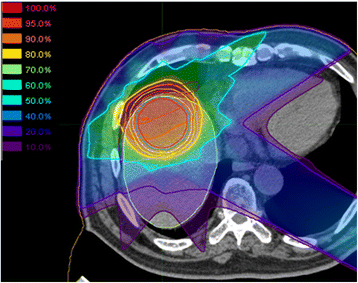
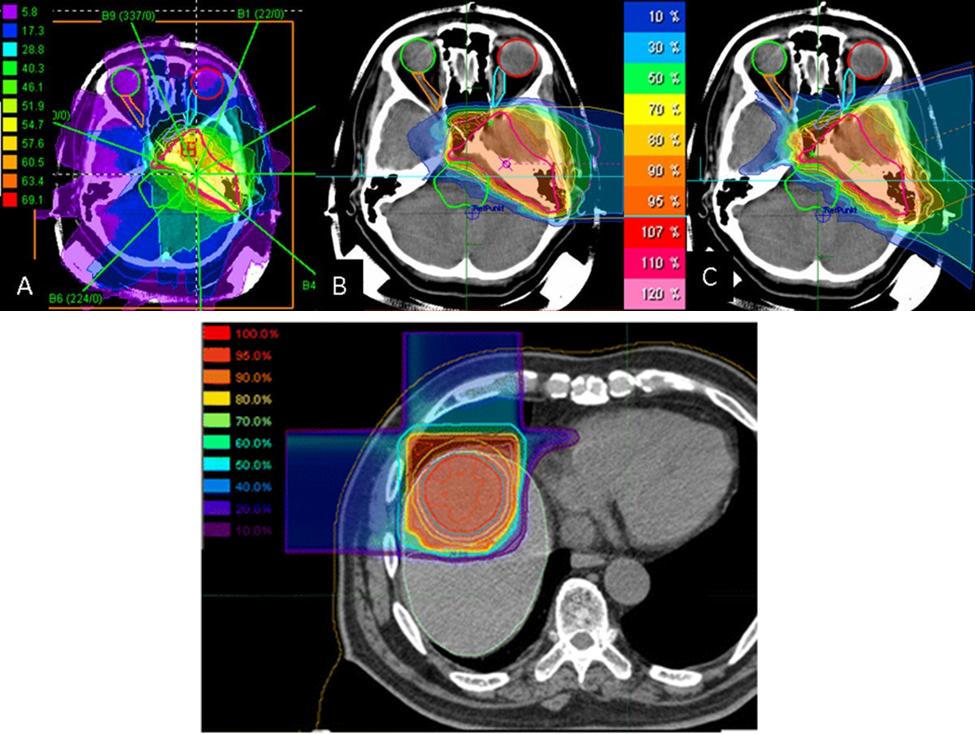
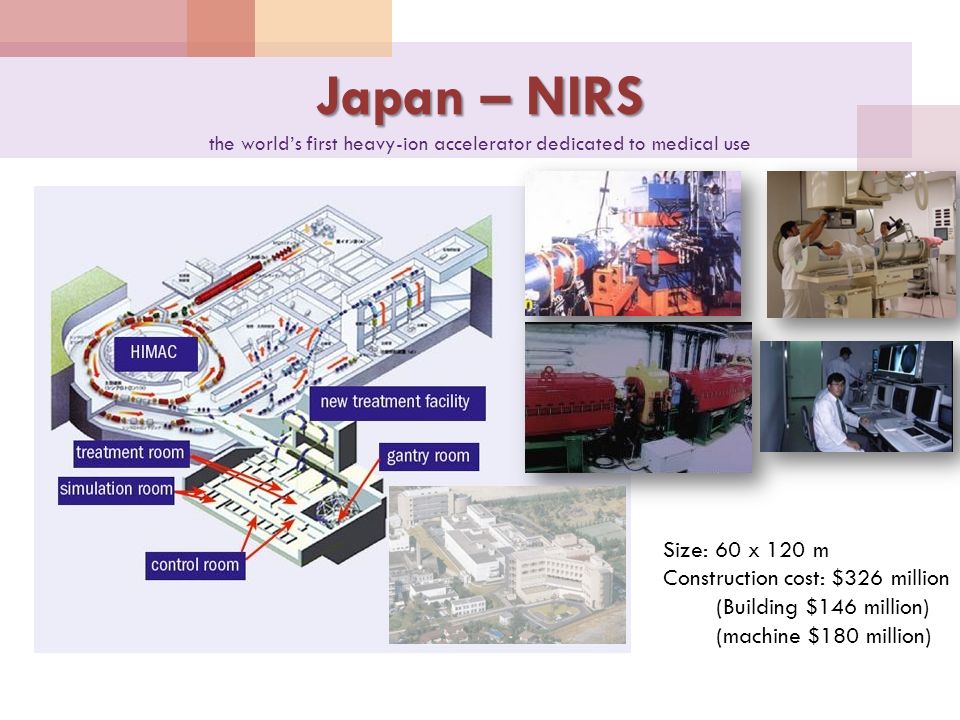
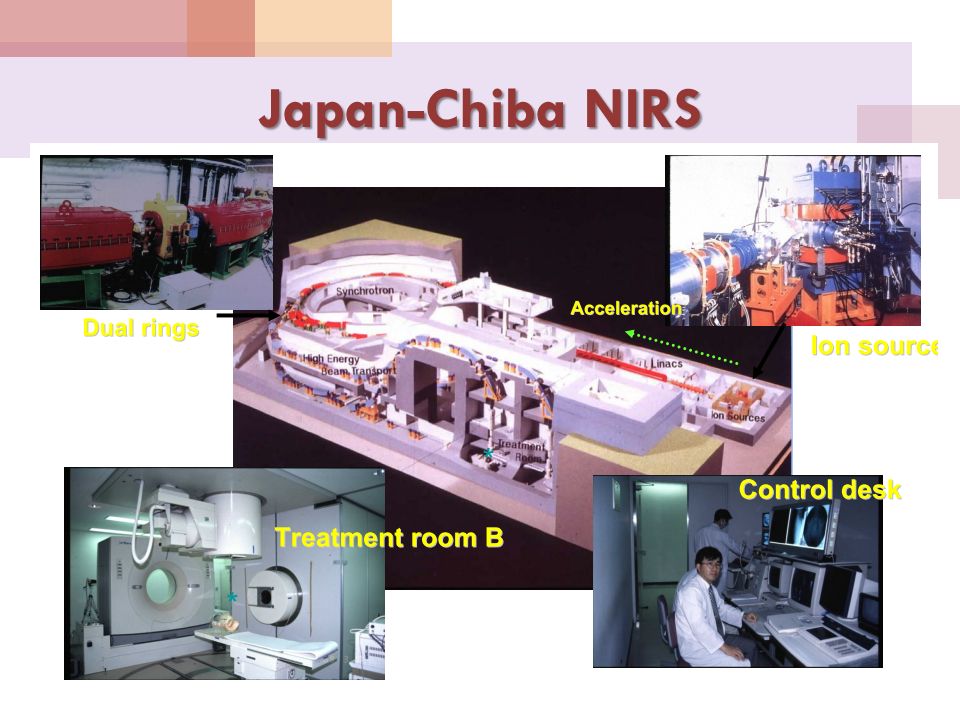


Figure 1.

Figure 2.



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