СЕКЦИЯ 5
МЕТОДЫ, ОБОРУДОВАНИЕ, ПЛАЗМЕННЫЕ И РАДИАЦИОННЫЕ ТЕХНОЛОГИИ

SECTION 5
METHODS, EQUIPMENT, PLASMA AND RADIATION TECHNOLOGIES

ADVANCE PARTICLE RADIOTHERAPY TECHNOLOGY – BNCT & PT FROM RAY SYSTEM CORPORATION

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Advanced particle radiotherapy represented by Proton Therapy and Boron Neutron Capture Therapy (BNCT) can achieve more accurate dose delivery, thereby killing tumor cells while protecting normal tissues to the maximum extent. They have broad prospects in modern tumor treatment technology. Continuous development and optimization of equipment at the technical level are the basic guarantee for improving clinical effects. This article briefly describes Boron Neutron Capture Therapy and Proton Therapy, some discussions are given on the challenges of these two type devices development. Combining future development needs, this article presented an overview of the boron neutron capture therapy device and the high-frequency linear proton therapy device developed by Ray System Corporation, which are expected to be used as effective tools for further development and improvement of advanced treatment technologies.

Keywords: Proton Therapy; Boron Neutron Capture Therapy; Advanced Particle Radiotherapy Technology.

Introduction

With the rapid development of modern medical technology, particle therapy has received increasing attention as a high-precision and efficient tumor treatment method. Traditional radiotherapy methods have played an important role in treatment, but their common problems such as uneven dose distribution, radiation damage to normal tissues, and recurrence after treatment have limited their clinical efficacy. Proton therapy and boron neutron capture therapy are advanced particle therapy techniques that extend the possibilities of tumor treatment by precisely controlling the energy and intensity of particles,as well as accurately pinpointing the tumor abnormalities.

Proton therapy uses proton beams to precisely control the release of therapy doses within tumor tissues and avoid or reduce the damage to surrounding normal tissues. Owing to the specific physical properties of protons, proton beams can effective release the maximum dose inside the tumor, and enhancing the treatment effect. Proton therapy has been widely used in various types of tumors such as head and neck, brain tumors, pediatric tumors, and tumors located in sensitive organs. Its efficacy has been confirmed in many clinical studies.

Boron Neutron Capture Therapy (BNCT) uses the interaction between neutrons and boron-10 to induce neutron capture reactions, releasing high linear energy transfer (LET) alpha particles and Li-7 ions for tumor destruction at the cellular scale. When there is a significant disparity in the concentration of boron-10 between normal tissue and tumor tissue, effective tumor cell destruction can be achieved under the tolerance capacity of normal tissue, thereby inhibiting tumor growth. BNCT holds unique advantages for infiltrative, diffuse, and inoperable tumors. Currently, boron neutron capture therapy is still under development, but early studies have shown its effectiveness in melanoma, glioblastoma, and head and neck cancer.

This article will focus on two advanced particle therapy techniques: proton therapy and boron neutron capture therapy. We will introduce their basic principles, advantages, and indications, and explore their clinical applications in depth. In addition, we will also discuss the development trends and prospects of advanced particle therapy techniques, including technological improvements, research progress, and challenges. By gaining a deep understanding of the characteristics and advantages of proton therapy and boron neutron capture therapy, we can better understand the significance of these advanced particle therapy techniques for tumor treatment. Committed to advanced cancer treatment technology, Ray System Corporation has developed China's first AB-BNCT device with fully independent intellectual property rights and is conducting research and development on advanced proton therapy devices. This article will report some of our work.

Proton Therapy Technology

Proton therapy, as an advanced particle therapy technology, uses high-energy proton beams to precisely treat tumor lesions. Compared to traditional X-ray radiation therapy, proton therapy boasts many advantages, such as superior dose distribution and less radiation damage. At present, the advantages of proton therapy have been increasingly recognized within the industry, but in order to improve clinical outcomes, further work still needs to be conducted.

Basic principles of proton radiotherapy

Protons are positively charged particles, and their characteristics allow for controllable penetration depth within human tissues. Unlike X-rays, protons exhibit the Bragg peak effect, where the dose is lower at the leading edge of the proton beam and gradually increases upon penetration into the human tissue until it reaches a peak. Figure 1 illustrates the dose deposition behavior of protons and photons during their incidence on human tissues. This enables protons to release the maximum dose within tumor tissue, while causing minimal damage to surrounding normal tissue.

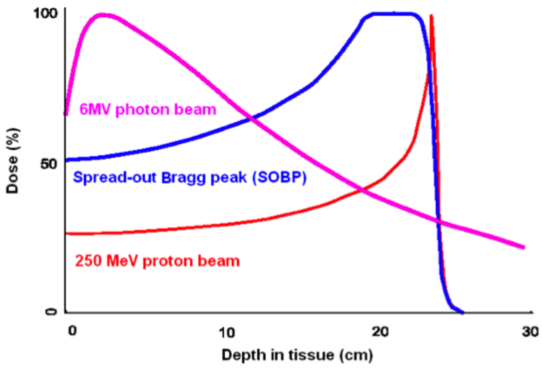

Fig. 1. Dose deposition behavior of protons and photons in tissue

Generally speaking, the proton beam produced by the accelerator is monoenergetic and needs to be broadened in the depth direction by means such as active energy adjustment, range modulation, ridge filter, etc., in order to construct a broadened Bragg peak (SOBP) that can cover the depth range of the tumor. The size of the beam produced by the accelerator is 3mm-5mm and needs to be broadened by means such as scattering or scanning. Then, through collimator or scanning path planning, the proton irradiation area is limited to the target treatment area.

Advantages of Proton Therapy in Cancer Treatment

Dose precision: The penetration depth and Bragg peak effect of proton beam allow proton therapy to deliver radiation dose more precisely to the tumor lesion, minimizing damage to surrounding normal tissues.

Reduced radiation damage: The proton beam has virtually no radiation damage when entering and leaving human tissue, reducing the risk of long-term side effects caused by treatment.

Broad indications: Proton therapy can be used for a variety of types of tumors, including head and neck, brain, bone marrow, lung, breast, and prostate.

Suitable for pediatric patients: As children's tissues are more sensitive to radiation, proton therapy is particularly important for the treatment of pediatric tumors.

Clinical Application and Efficacy Evaluation of Proton Therapy

Head and neck tumors: Proton therapy is widely used in head and neck tumors, such as nasopharyngeal carcinoma, laryngeal cancer, etc., can provide a higher local control rate and survival rate.

Pediatric tumors: Pediatric patients have a lower tolerance for radiation, so proton therapy is of great significance in pediatric tumors. For example, tumors like pediatric neuroblastoma and osteosarcoma, proton therapy has shown good treatment effects and side effect control.

Prostate cancer: Proton beam can better adjust the dose, reduce radiation damage to the normal tissues and organs around the prostate, thus showing significant advantages in the treatment of prostate cancer.

Treatment of distant metastases: Proton therapy can be used for the treatment of metastatic tumors, accurately targeting metastatic lesions, minimizing radiation damage to surrounding tissues. For those patients who cannot undergo surgery or traditional radiation therapy, proton therapy offers an effective choice.

Although proton therapy has advantages in reducing treatment-related side effects, it can still cause some side effects, such as fatigue, nausea, vomiting, skin reactions, etc. For different side effects, doctors will develop corresponding management strategies to minimize adverse reactions.

Current Challenges and Development Directions for Proton Therapy

Cost and accessibility of proton therapy facilities: The construction and operation costs of proton therapy equipment are high, limiting its promotion and popularization worldwide. Future developments include improving equipment technology and reducing costs to increase the accessibility of equipment.

Further clinical studies: Although many clinical studies have proven the advantages of proton therapy, more research is needed to clarify its best application in different tumor types and clinical situations. In addition, more research data is needed to support long-term follow-up and treatment effect evaluation.

Technical improvement: The continuous improvement and innovation of proton therapy equipment and technology is the key to the development of proton therapy. For example, the new generation of proton therapy equipment can more accurately control the energy and intensity of the proton beam, achieving a more accurate dose distribution.

In summary, as an advanced particle radiation therapy technology, proton therapy has obvious advantages and a wide range of clinical applications. With the continuous progress of technology and in-depth research, proton therapy is expected to play a more important role in cancer treatment, bringing better treatment effects and quality of life for patients. However, it is still necessary to solve the challenges of cost, accessibility, and technical improvement to ensure the continuous development and widespread application of proton therapy.

Boron Neutron Capture Therapy

BNCT is a radiotherapy technique predicated on the principle of neutron capture, which employs the nuclear reactions resulting from the excitation of the boron-10 isotope by neutrons to produce high-energy ionizing radiation to eliminate cancer cells. The succeeding discourse will delve into the fundamental principles, technical facilities, clinical applications, and efficacy evaluation related to Boron Neutron Capture Therapy.

Principles of Boron Neutron Capture Therapy

BNCT is relaying on the selective enrichment of the boron-10 isotope within tumorous tissues and the profound penetrative depth of neutron beams. During treatment, the boron-10 isotope is introduced into cancer cells and then irradiated via an external apparatus that utilizes a neutron beam source. Neutron beams react with the boron-10 isotope through neutron capture, yielding alpha particles and boron-11 isotopes. These particles have a path length of merely 5-9 μm within the human body, enabling the eradication of cancer cells on a cellular scale.

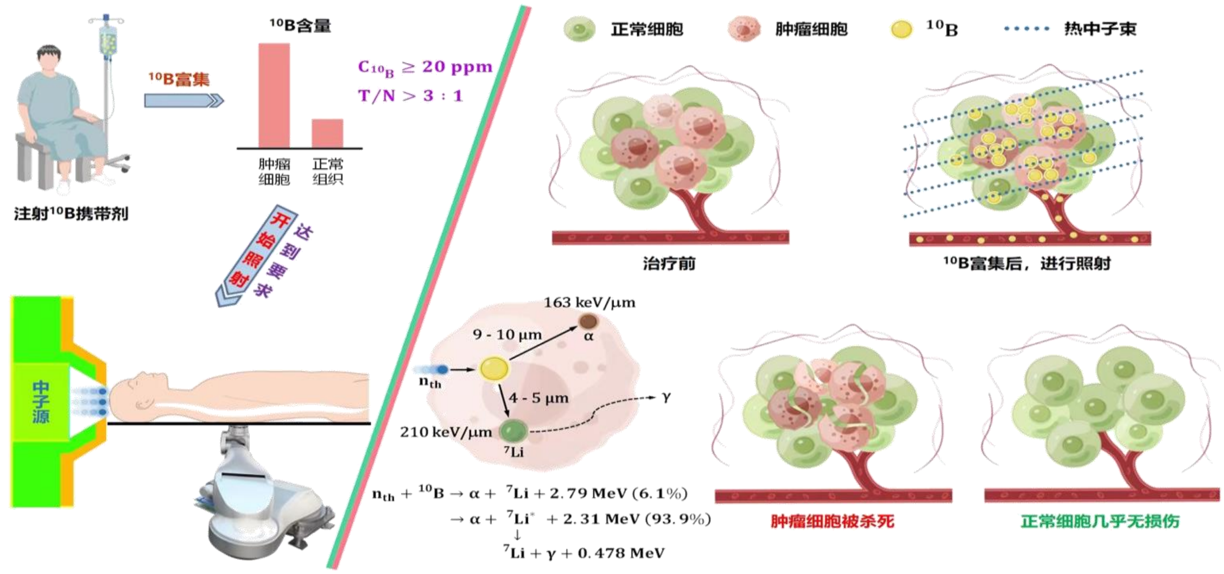

Fig. 2. Principles of BNCT

Facilities and Techniques for BNCT

Neutron Source: BNCT requires high-intensity neutron beams. For the treatment of surface conditions such as melanoma, thermal neutrons are needed, while for deeper tumors like head and neck cancer or gliomas, epithermal neutrons are necessary. Common sources of neutron beams include accelerators and nuclear reactors. However, due to the regulatory requirements for nuclear fuel, safety requirements for nuclear facilities, and public acceptance, reactor-based neutron sources are not feasible for widespread implementation in hospitals. In recent years, with the development of accelerator technology, neutron sources driven by medium and low energy high-current proton accelerators have become the preferred option for BNCT and have been quickly implemented in hospitals. Regarding the neutron generation method, two major reactions are primarily used: 1) one involves low-energy protons interacting with metallic lithium to generate neutrons, which requires high proton current. The low melting point of lithium is also a key issue in the production and use of target materials; 2) the other method involves mid-energy proton bombardment of Beryllium. The required proton energy for this reaction is 8-30 MeV, with relatively low current, but the induced neutron energy is higher, posing a potential threat from fast neutrons during treatment. Additionally, induced radioactivity produced during the transportation of high-energy protons is a key issue to consider during device operation and maintenance.

Boron isotope delivery: BNCT requires a specific boron targeting drug, the drug should accumulate in tumor cells at a level at least 3 times higher than in normal tissue, and the atomic concentration of B-10 in cancer cells needs to be above 20ug/g. For a long time, boron drugs have been a critical factor limiting the clinical efficacy of boron neutron technology. Currently, BSH and BPA have shown promising clinical results in BNCT. Their accumulation characteristics, pharmacokinetic behavior, and biocompatibility have been proven and are applied in current clinical treatment devices.

Clinical Application of Boron Neutron Capture Therapy

BNCT, considered the "fifth therapy" after surgery, traditional radiation therapy, chemotherapy, and immunotherapy, has significant clinical advantages for recurrent, infiltrative, and locally metastatic tumors. It has been clinically proven in thousands of cases worldwide that BNCT has notable and reliable therapeutic effects on various solid tumors such as recurrent head and neck cancer, malignant brain tumors, and melanoma. Although BNCT has demonstrated reliable therapeutic effects in some types of tumors, further clinical research and promotion are needed to validate its applications in a broader range of tumor treatments. Additionally, the appropriate selection of cases and formulation of treatment plans are key to ensuring the effectiveness of BNCT.

Head and neck cancer: A clinical trial targeting recurrent head and neck cancer demonstrated higher survival and control rates in patients treated with BNCT. In one study, 80% of patients survived within a year, and tumors in 50% of patients were controlled. Another study treated 51 patients with recurrent or inoperable head and neck cancer with BNCT, finding a disease control rate of 75%.

Malignant brain tumors: A clinical trial on malignant brain tumors found a significant improvement in survival rates among patients who underwent BNCT. Research results showed that the one-year survival rate for malignant brain tumor patients was 74%, and the three-year survival rate was 48%.

Melanoma: A clinical trial on melanoma observed the treatment results of 31 patients, finding that BNCT could effectively control the recurrence and progression of melanoma. In a 42-month follow-up, the conditions of the majority of patients were controlled.

Challenges and prospect for BNCT

As a radiotherapy technology based on the principle of neutron capture, BNCT has potential advantages and broad prospects for clinical application. With the further development of technical facilities and in-depth clinical research, BNCT is expected to play a more important role in tumor treatment and provide patients with better treatment options and outcomes. However, further researches are still needed to address issues related to technical facilities and costs, Boron-10 drugs and delivery methods, in-depth research on physics and biology models, clinical research, and standardization of treatments.

Advanced and reliable neutron production devices: The BNCT technology needs to use epithermal neutrons, and its flux level needs to reach above 10^9 n/cm^{2}s. Currently, accelerator-driven neutron sources are the preferred option. It is necessary to develop more advanced and stable neutron beam devices and equipment with the development of accelerator technology to ensure accurate neutron beam transmission and dose control, thereby achieving more precise treatment effects. Additionally, with technological progress and cost reduction, BNCT facilities will be easier to construct and operate, thereby achieving wider application in clinical practice.

Advanced boron drug development and drug delivery technology: As a binary targeting treatment method, the boron drugs and their delivery methods in BNCT are key to expanding the application of BNCT technology and improving treatment effects. It is necessary to develop targeted drugs corresponding to specific diseases to extend indications, ensure their pharmacological and toxicological satisfaction, improve the concentration of B-10 in tumor cells, increase the concentration ratio in normal and healthy tissues, and have good pharmacokinetic behavior combined with the human metabolic process.

In-depth research on physical and biological models: Unlike traditional photon radiotherapy and proton therapy, the physical and biological effects of BNCT still need to be continuously optimized. Physical research needs to solve problems like accurately monitoring boron concentration and boron dose, reliable monitoring technology for neutron photon doses, and high-precision dosimetry measurement technology, as well as optimize treatment planning and dosimetric evaluation methods. Biological effects need to combine the specific distribution of boron drugs, and the characteristics of the treatment beam to obtain more accurate relative biological effectiveness (RBE) factors and combined biological effectiveness (CBE) factors. This will deepen the understanding of the mechanism of boron neutron capture in killing tumor cells, thereby guiding the choice and optimization of treatment methods.

Clinical studies and treatment optimization: Although some clinical studies have demonstrated the potential advantages of boron neutron capture therapy, more research is still needed in conjunction with the development of new boron drugs to further assess its effectiveness and safety in different types of tumors and clinical situations. At the same time, it is necessary to establish uniform treatment standards and guidelines to ensure the quality and safety of the treatment, and improve the reproducibility and comparability of the treatment effects.

Multidisciplinary cooperation and technical innovation: Boron Neutron Capture Therapy requires multidisciplinary cooperation, including collaboration among physicists, chemists, pharmacologists, radiation technicians, and doctors. Technical innovation and continuous improvement of equipment are also key to promoting the development of boron neutron capture therapy.

Advanced particle therapy equipment of Ray System Corporation

BNCT and Proton Therapy are internationally recognized high-end particle radiotherapy technologies, which have shown good clinical effects in the treatment of complex and difficult-to-cure cancers. A stable and reliable particle beam supply is the premise for BNCT and Proton Therapy to treat patients more efficiently and accurately. Ruisi, based on the technical accumulation of Lanzhou University and several units in China, has developed an accelerator-based boron neutron capture treatment device and proposed and is developing a proton therapy device based on a high-frequency linear accelerator. This section will provide a simple introduction to these two advanced particle therapy devices.

Boron Neutron Capture Therapy Device Based on RFQ

The boron neutron capture therapy device developed by Ray System Corporation uses a radio frequency quadrupole (RFQ)accelerator to provide a continuous wave proton with an energy of 2.6 MeV. The maximum proton output current can reach 30mA. The proton beam bombards lithium material to produce neutrons. The primary neutrons produced have energies in the range of tens of keV to 1 MeV. For final treatment use, further shaping and moderation are performed, and the main neutron beam energy is reduced to 0.5 eV-40 keV, which is guided out after further collimation. Design work and preliminary neutron experiments show that a proton current of 12mA can output a super-thermal neutron beam of 1×10^9n/cm^{2}s.

Figure 3 provides an overall layout of the device with two treatment terminals. The device can be divided into two parts: the neutron system and the treatment system.

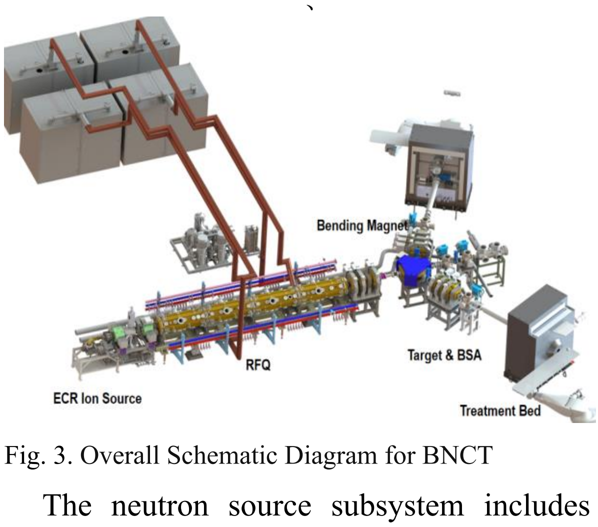

Fig. 3. Overall Schematic Diagram for BNCT

The neutron source subsystem includes ECR ion source, radio frequency quadrupole accelerator, beam transport line, magnets and vacuum system, efficient target chamber system, beam shaping assemblies, neutron beam monitoring system, and their corresponding control systems. The treatment system includes the treatment planning system, treatment room monitoring equipment, and their corresponding control systems, etc. The neutron source system adopts the "high-current proton source +RFQ" structure, which consists of an electron cyclotron resonance type (ECR) ion source, low energy transmission line (LEBT), linear accelerator, medium energy transmission line (MEBT), and target station system. To realize the effective power output during the proton bombardment process, a rotating target structure is used. Calculations show that when the proton beam intensity is 15mA, the highest temperature of the lithium target can be controlled below 100℃, far below the melting point of lithium. At the same time, several special techniques were adopted in the target processing process to achieve long-term operation of the target, with a designed lifespan of 15.000 mAh.

The therapeutic subsystem uses a scheme coupled with the treatment planning system, image guidance system, and patient support system, composed of the treatment planning system, treatment control system, patient positioning and verification system, image guidance system, and beam blocker. This scheme can be used by the treatment planning system to calculate the distribution and concentration of drugs in the target area at different times based on measurement data, optimize the contributions of different parts under different boron drug concentrations within the same target area range, and give the dose isodistribution map and dose volume equivalent map under the specified boron concentration in the target area to optimize the irradiation scheme. The treatment control system further controls the patient positioning system and image guidance system to ensure the accuracy of the patient's position in the treatment room and the target area's position. The beam blocking system realizes two-way interlock through quick blocking of the proton beam and the addition of a neutron shutter at the end of the target chamber system. After the treatment is completed, the outlet will be closed to ensure that medical staff are free from mis-exposure and reduce the induced radioactive dose that the patient bears during transfer.

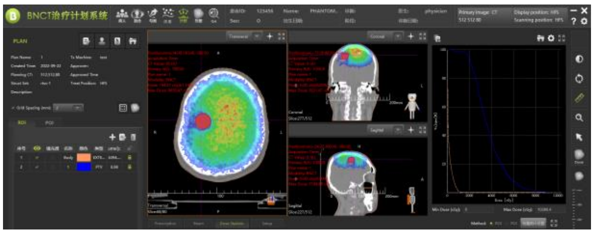

Fig. 4. Dose distribution and DVH calculated by the treatment planning system dose engine

The treatment planning system is the core part of BNCT treatment, and the success of the treatment is closely related to the accuracy of the dose algorithm in the treatment plan, the precision of the patient's target area delineation, and the accuracy of the target area dose calculation. Using a high-fidelity Monte Carlo computational engine, it can accurately describe the interaction process between photons and materials, and perform boron neutron-related dose calculations. The system can realize automatic delineation of the target area and manual delineation based on standard shapes, accurate conversion of plan position and dose delivery position. The external dose calculation engine supports specified model grid and grid merging, accurate output of dose cloud image and histogram, and treatment goal output based on the critical normal tissue tolerance dose. The treatment planning system is also equipped with a dose verification module to meet the experimental needs of verifying the planning system before clinical application.

The first equipment has been installed at Fujian Union Hospital, as shown in the layout of the device on site in Figure 5. Currently, it is in the commissioning phase. Preliminary experiments show that the super-thermal neutron flux per unit proton beam strength is 8.72×10^{9} $n\cdot cm^{-2}\cdot s^{-1}/mA$ (Figure 6), i.e., under the condition of 12mA proton beam strength, the super-thermal neutron flux can output a

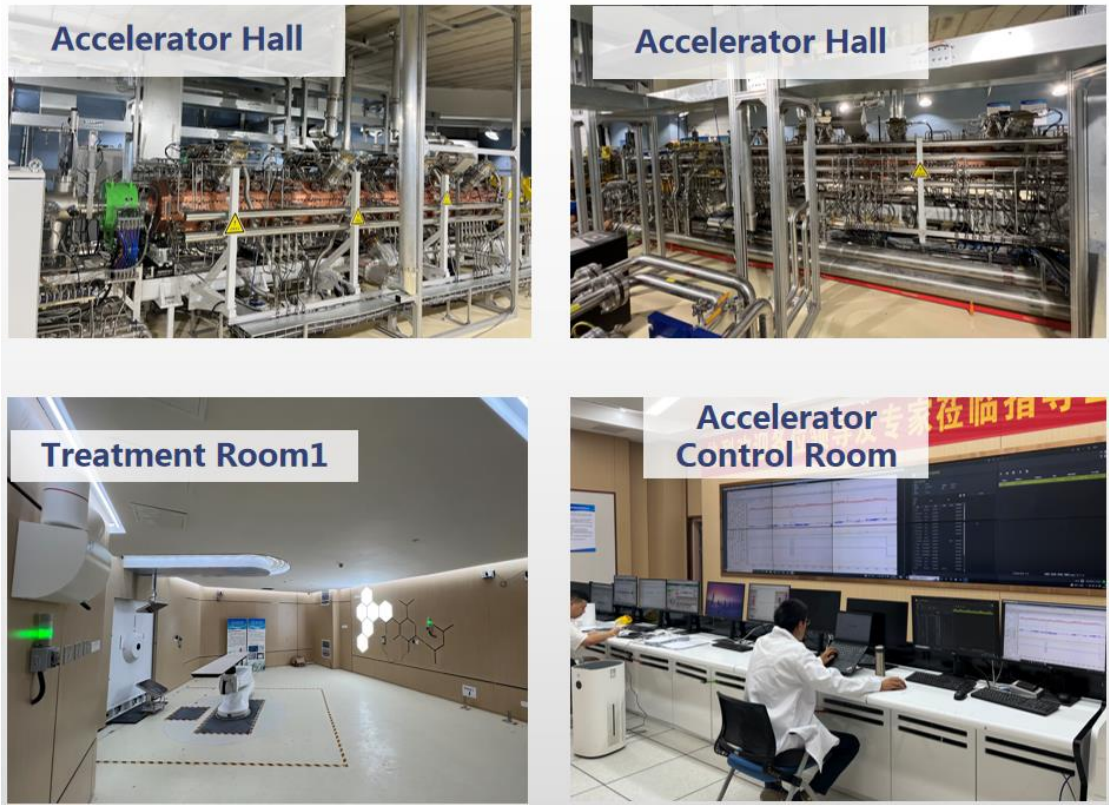

Fig. 5. BNCT device at Fujian Union Medical College Hospital

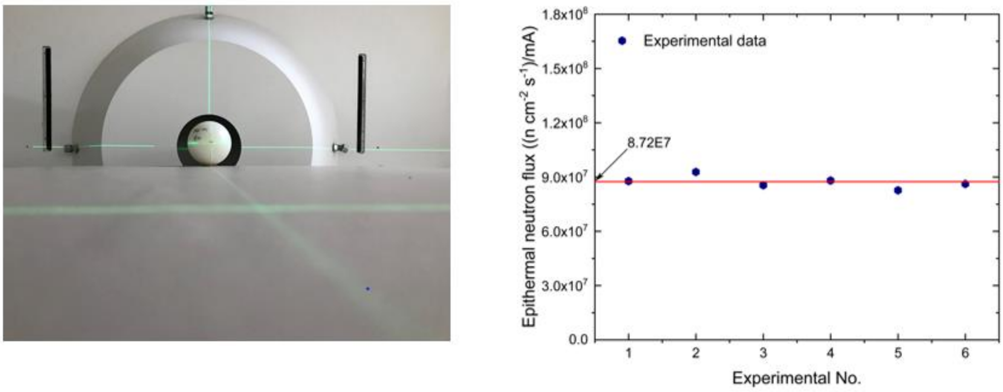

Fig. 6. Preliminary experiment results, epi-thermal neutron flux detector (left) and unit proton flow strength ultra-hot neutron dose at beam outlet

super-thermal neutron beam of $1\times10^9 n/cm^2\cdot s$.

Proton Therapy Device Based on High-Frequency Linear Acceleration

Traditional large-scale proton therapy equipment faces numerous limitations and challenges in areas such as beam generation devices, dose delivery, and proton planning system algorithms, including high cost, large footprint, impact of respiratory movement, and low efficiency. In response, Ruisk has designed a new type of proton therapy device — High-Frequency Linear FLASH Proton Therapy System that integrates the advantages of FLASH radiotherapy, 3D point scanning, and high output with light capital investment.

The proton therapy system utilizes a more compact high-gradient high-frequency linear accelerator, capable of actively adjusting beam energy with short energy modulation time. The exit energy is 230 MeV, with an energy adjustment step length of 1MeV. It has the characteristics of millisecond-level rapid energy switching and millimeter-level miniature beam bunch structure, which can realize beam expansion through point scanning. The main part of the accelerator consists of an ion source system, a Radio Frequency Quadrupole (RFQ), a Interdigital H-mode Drift Tube Linear Accelerator (IH-DTL), a Side Coupled Drift Tube Linear Accelerator (SCDTL), a Side Cavity Coupled Linear Accelerator (SCL), and a beam transport line. At the treatment end, the high-energy proton beam enters a fixed or rotating treatment room through the beam transport system, where the fixed treatment room includes a fixed treatment head and treatment chair, and the rotating treatment room includes a rotating gantry, rotating treatment head, treatment bed, and movable floor. The treatment of patients is completed with the assistance of a treatment planning system, image guidance, and treatment control system. For dose delivery, both scattering and repeated scanning methods are provided, taking into account regular treatment while meeting the scalability needs of future FLASH treatment.

Figure 7 presents one of the treatment room solutions provided by Ruisk for the proton device, including a gantry treatment room, a horizontal beam treatment bed room, and two rotating chair treatment rooms.

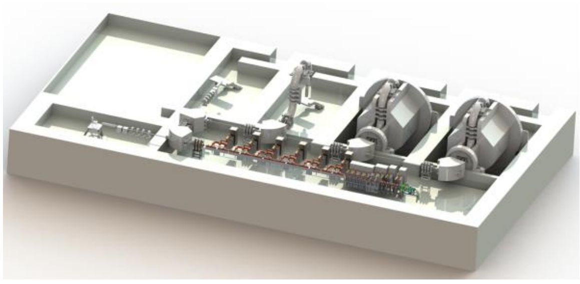

Fig. 7. Layout Model of High-Frequency Linear Proton Therapy Device

The design of the proton therapy system has been completed. We are currently undergoing the processing and performance testing of prototype modules for the accelerator, rotating gantry, and rotating chairs.

Conclusion

Advanced particle radiotherapy technology holds the promise of further improving tumor treatment outcomes. Among these, the boron neutron capture therapy (BNCT) device can be used for the treatment of infiltrative, diffuse tumors, and those that are difficult to operate on. Proton therapy allows for more precise dose delivery, and combined with future FLASH therapy, is expected to improve clinical outcomes for a variety of tumors. Relying on its technical team, Ruisk has developed a BNCT device with fully independent intellectual property rights in China. The device is currently in the commissioning stage, and can subsequently provide an effective means for the clinical research and application of boron neutron capture therapy technology. Looking to the future, Ruisk is developing a proton therapy device based on high-frequency linear acceleration, which has now entered the component-level prototype production and testing stage. This device has the capability of active energy adjustment at the millisecond level, and can expand the single delivery dose. It provides technical assurance for further enhancing the clinical effects of proton therapy.