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(陽電子マンモグラフィを用いた陽子線治療評価フレームワークの開発)
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論 文 内 容 の 要 旨

Chapter 1: Introduction

Cancer is expected to become a more common cause of illness and fatality in most parts of the world. The treatment of cancer includes one or more treatment modalities based on the type of cancer, its location, and stage of progression. Radiotherapy (RT) is one of the most successful treatment options for cancer, alongside surgery and/or chemotherapy. The ultimate goal of radiation therapy is to deliver a certain amount of radiation dose to the targeted organs while not affecting healthy organs and cells. In this regard, the use of high-energy proton beams has garnered significant attention worldwide owing to their low lateral scattering, no exit dose, and high dose deposition in the Bragg peak region. Considering the proton radiotherapy, a major obstacle would be the uncertainties associated with the range of the proton beam, at which largest dose gradient is located. The uncertainties could be due to many factors such as; error in the estimated proton range, unexpected anatomical changes and issues with the patient or accelerator setup. A fully developed non-invasive range verification method could lead to reduced beam range uncertainties and providing a safe volume of dosage of proton therapy. Therefore, a reliable way to verify the range predicted by the treatment planning system, either directly during the treatment or after the treatment, would be highly desirable for achieving the actual benefit of the proton therapy.

Several techniques for proton range monitoring were proposed, that are; proton radiography and tomography, ionoacoustics, Secondary Electron Bremsstrahlung (SEB), and Prompt Gamma Imaging (PGI). Along with these approaches, auto-activation Positron Emission Tomography (PET) is an additional noteworthy technique, mainly explored after the imaging of proton induced positron emitting radioisotopes (such as ^{15}O, ^{11}C and ^{13}N), which would be extremely desirable for realistic clinical applications. There is various configured PET (such as; full-ring, non-ring, slanged angle, dual-head) systems have been tested for practical and accurate proton range verification. Another notable system that has higher spatial resolution and sensitivity compared to previously introduced systems would be the positron emission mammography (PEM) system, which is a dedicated PET system for detecting breast cancer. We have developed a highly sensitive PEMGRAPH (Mirai Imaging Inc., Fukushima, Japan)

that consists of a dedicated dual-head PEM system with Pr:LuAG (Praseodymium-dopped Lutetium Aluminum Garnet) crystal. Because PEMGRAPH is an open system with better spatial resolution and sensitivity, we hypothesized that it would be useful for proton therapy monitoring. The goal of this thesis was to fully exploit the advantages of proton beams and enhance accuracy and precision of proton therapy by reducing range uncertainty. To complete the quality assurance process, more than just a positron emission scanner and a reconstruction algorithm is needed. In order to verify the range of proton, a method for the quantitative determination of proton induced radioisotopes using a spectral analysis approach was applied. The generated positron emitters as a result of proton interaction with major nuclei found in human tissues were quantified using the SA approach; this was investigated from both theoretical and experimental aspects.

Chapter 2: Simulation of positron emitting radioisotopes during proton therapy

A PET scanner detects the coincident gamma-rays emitted when the positron, which is emitted during the decay of these radioactive isotopes, annihilates with an electron. Several protons induced positron emitters such as ^{11}C, ^{15}O and ^{13}N are produced due to nuclear interactions of proton with the patient's tissue. The ^{13}N positron emitting radioisotope, which mostly results from the $^{16}O(p,2p2n)^{13}N$ nuclear reaction and has a low threshold energy of 5.660 MeV close to the proton beam's end of range, is of particular interest in this study. Monte Carlo simulations can be used to create a comprehensive simulation of both radiation interactions and the geometry of treatment hardware and patient anatomy. In this study, we use the PHITS Monte Carlo code to simulate positron emitters during proton therapy. The simulation of positron emitters during proton irradiation in a homogeneous, inhomogeneous slab and MIRD anthropomorphic targets was investigated using the PHITS code. Proton induced positron emitting radioisotopes in the 40 MeV to 250 MeV incident energy range on homogeneous phantom were studied focusing to calculate the offset distance between the distal edge positron emitting radioisotopes and the real Bragg peak. The energy of incident protons was used 80 MeV and 70-80 MeV with 1 MeV interval energy modulation, for obtaining pristine and spread-out Bragg peak (SOBP), respectively. While, to predict the production of positron emitters, the MIRD anthropomorphic phantom was irradiated with monoenergetic 80 MeV energy of incident protons. For both homogeneous and inhomogeneous slab as well as MIRD anthropomorphic phantom the 1D, 2D and 3D profiles of dose deposition and positron emitters with depth along the incident protons beam were calculated. The time-course activity in the time range 15 to 55 minutes for ^{15}O, ^{11}C, and ^{13}N were generated and the spectrum of ^{13}N which has half-life 9.93 minutes was found to be visible at higher depths and stayed detectable up to 55 minutes after the proton irradiation. While the relatively short-lived ^{15}O spectrum which has half-life 2.03 minutes almost vanished entirely before 30 minutes after the irradiation. Moreover, the activity of ^{11}C is the most dominated at the shorter depth due to longer half-life about 20.33 minutes. The simulation results showed the offset distances between the generated ^{13}N peak and the actual Bragg peak with 1 to 2 mm for the homogeneous, inhomogeneous slab and MIRD anthropomorphic phantom studies, respectively.

Chapter 3: Detection of positron annihilation photons by PEM

Protons beam used in cancer radiotherapy have the physical advantage of having a finite range, resulting in a sharp distal dose gradient. As a result, healthy tissue distal to the target is spared from radiation. However, the benefit of the sharp distal dose gradient cannot yet be

fully realized because the beam's end-of-range is uncertain. In this chapter, we present an experimental study using our developed highly sensitive a proto-type dual-head Positron Emission Mammography (PEM) system to verify the range of proton therapy beams. The PEM is a dedicated PET system was initially developed for detecting breast cancer. For the first time, we used the PEM to detect annihilation gamma-rays from any organ of the patient released by proton induced positrons and electrons of the target tissue. The performance of the system was assessed in a water-gel phantom. Following the earlier knowledge of the simulation studies, the phantom was irradiated by a monoenergetic proton beam with 80 MeV energy for 60 s. The proton beam was pencil-like with a beam current of 10.20 nA produced by an azimuthally varying field (AVF) cyclotron at the Cyclotron and Radioisotopes Centre (CYRIC) facility at Tohoku University, Japan. The acquired list mode data were reconstructed to dynamic frames using the 3D iterative maximum likelihood-expectation maximization (MLEM) method. The detected gamma rays produced there are two peaks. In addition to these two peaks, a small tail peak was observed at the end of proton beam path and vanished rather quickly. The results of the experiment indicate a good agreement with the simulated one. A spectral analysis approach will be used to quantify the types of radioisotopes produced, as well as their concentration along the beam path, which could be useful for verifying the range of proton beams.

Chapter 4: Quantification of proton induced radioisotopes using SA approach

In this chapter, the results of dynamic positron emission tomography (PET) of proton beam irradiation were examined and presented utilizing an approach known as 'Spectral Analysis'. In dynamic PET studies, the term spectral analysis indicates a single-input/single-output model used for the data quantification. Spectral analysis (SA) allows the quantification of dynamic data by relating the radioactivity measured by the scanner in time to the underlying physiological processes of the investigated system. The SA was performed based on the "analysis scheme" to the dynamic time-course activity data findings from simulations and experimental studies. For both the simulation studies and experimental measurements the SA technique was applied to the 40 frames (from 15 to 55 minutes; considering 15 minutes after proton irradiation) to quantify the positron emitter radioisotopes. The SA technique was also applied to the time-course dataset (from 15 to 55 minutes after irradiation) to predict the half-life of each positron emitting radioisotopes present in the different regions of interest (ROIs): whole, edge, plateau, and Bragg region. In both simulation and experimental studies, the proposed scheme successfully extracted the 3D spatial distributions of positron emitting radioisotopes, ^{11}C, ^{15}O and ^{13}N, respectively. The half-life of the SA extracted radioisotopes were confirmed by the ROIs analysis. In case of experimental data, the SA analysis confirmed the activity in the distal falloff region of proton induced ^{13}N radioisotopes. The ROIs study also confirmed that the ^{13}N radioisotope makes the highest contribution in the Bragg region.

Chapter 5: Quantitative comparison and proton range verification

A quantitative comparison was carried out in this chapter between SA extracted and MC simulated radioisotopes. The peak positions of the proton induced positron emitting radioisotopes were verified by comparing the SA extracted radioisotope with the MC simulated radioisotope as well as with simulated dose for both the simulation and experimental studies. The results show there is no offset distance at the distal depth region between the SA extracted and the MC simulated radioisotopes along the beam direction. In other words, for example, the peak positions of the SA extracted ^{13}N is completely overlaid on the simulated one. Though,

some discrepancies observed between SA radioisotopes and MC simulated one in the shallow-depth region. It is observed that the offset distances between the SA extracted ^{13}N peak and the actual Bragg peak with 1 to 2 mm, whereas the ^{11}C and ^{15}O peaks are very far away from the real Bragg peaks for the homogeneous, inhomogeneous slab and MIRD anthropomorphic phantom studies which is a good agreement with MC radioisotopes. On the other hand, when compared to the actual Bragg peak for the simulated homogeneous water-gel, the offset distance between the SA extracted ^{13}N peak from the experimental data is 3 mm. The simulated Bragg peak is very sharp, while the experimental ^{13}N peak is rather wide, indicating reasonable agreement with the simulation results. This distinct ^{13}N as well as the offset values could be used as an index for PEM-based proton range verification using SA approach.

Chapter 6: Conclusions and future prospects

For the purpose of proton range verification, we proposed a framework to investigate positron emitting radioisotopes using the simplest and fastest SA approach in simulations and experiments with highly sensitive PEM system. We have developed a series of simulation, experimental, and analysis tools for this purpose and applied them in this experimental campaign for the first time. The results showed the proposed tool with the combination of PEM system and SA approach could be useful for proton range verification. From our simulations and experimental results, we conclude that the SA approach is feasible within clinical beam delivery conditions. However, further investigations involving an animal or human subject study utilizing SA approach will be needed for the robustness of the framework.

別紙１

論文審査結果の要旨及びその担当者

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論文審査結果の要旨

近年、癌の治療法として陽子線治療が注目されている。しかし、陽子線治療の大きな障害となるのは、その飛程に関わる不確かさである。本論文では、陽子線の飛程の検証方法を新たに開発し、飛程の不確かさを低減することにより、陽子線治療における陽子線の利点を最大限に引き出すことを目的としている。本論文は全部で6章からなる。

第1章は序論であり、本研究の背景、目的及び構成を述べている。

第2章は陽子線治療を模擬するモンテカルロシミュレーションについて述べている。

第3章では、陽子線によって作られた陽電子放出核種を検出するための装置、PEM装置に関する説明がされている。

第4章では本研究において陽電子放出核種の検出のために開発されたスペクトラル解析法について解説が行われている。

第5章では、実際の陽子線の到達位置を示すブラッグピークと、PEM装置で検出された窒素13の信号がどの程度近いかをシミュレーションおよび実験で示され、本方法の有用性が確認された。

第6章は本研究のまとめである。

本研究では新しい陽子線治療の評価法を提案し、この方法が臨床応用可能であることが示された。本方法は臨床的な有用性が高く、また、放射線治療における新しい医工学的なアプローチが示されている。よって、本論文は博士（医工学）の学位論文として合格と認める。