FEASIBILITY STUDIES ON THE IN-VIVO EXPERIMENTS AT THE MC-50 CYCLOTRON USING A PROTOTYPE LEPT SYSTEM*

Kye-Ryung Kim#, Myung-Hwan Jung, Seok-Ki Lee, Ji-Ho Jang
PEFP, KAERI, Daejeon, Korea

Tae-Keun Yang
KIRAMS, Seoul, Korea

You-Mie Lee
Kyungpook National Univ., Daegu, Korea

Abstract

A prototype LEPT (Low Energy Proton Therapy) system was developed and installed at the MC-50 cyclotron in 2007. Some of the users of the PEFP (Proton Engineering Frontier Project) have been requiring an in-vivo irradiation system for the utilization in the fields of medical and biological sciences [1]. We are studying on the possibility of in-vivo experiments by using the prototype LEPT system. The developed LEPT system consists of collimators, range shifter, rotating modulator for SOBP (Spread Out Bragg Peak), etc. We added a ridge-filter type modulator, a depth-dose measurement system, a mouse holder, boluses, and a collimator for the in-vivo experiments. The energy and current from the cyclotron was 45 MeV and a few nA. For the in-vivo experiments, accurate control of dose rate and penetration depth range is essential. The other important issue is how we can control the irradiation area and volume with high uniformity and accuracy. We investigated the dose distribution inside a samples using PMMA phantom, bolus, and depth-dose measurement system. The absorbed doses were measured by using ionization chamber and GAF films. The dose rate was 0.2~1 Gy/sec and the penetration depth was 10~15 mm. The first in-vivo experiments for the LLC (Lewis Lung Cancer) inoculated C57 mice by using this system was performed successfully.

INTRODUCTION

Proton therapy is widely acknowledged as one of the most effective methods in the selective destruction of cancer cells. [2] In Korea, a 230MeV cyclotron was imported and installed at the NCC (National Cancer Center) for the proton therapy in 2006 and treatment of patients began in March, 2007. [3] More than 250 patients were treated by using this machine, and the scientists who are interested in proton therapy have been increased continuously. But the experiments for proton therapy were limited to the in-vitro level because there's no dedicated facilities for in-vivo experiments. For this reason, development of the in-vivo experiment was strongly requested by the PEFP's users during last few years. To satisfy users' requirements, we developed in-vivo experiment system and installed it at the MC-50 cyclotron using the prototype LEPT and some components necessary for in-vivo experiments.

DEVELOPMENT OF IN-VIVO EXPERIMENT SYSTEM

LEPT Beamline at the MC-50 Cyclotron

The prototype LEPT system was installed at the MC-50 cyclotron of KIRAMS to support basic and pilot studies on proton therapy in the fields of medical and biological sciences in 2007. It was composed of rotating modulator, range shifter, collimator, etc. For in-vivo experiments, we had to add some components necessary to control and measure the depth-dose profiles inside a tumor mass. The whole system is shown in Fig. 1. As shown in figure,

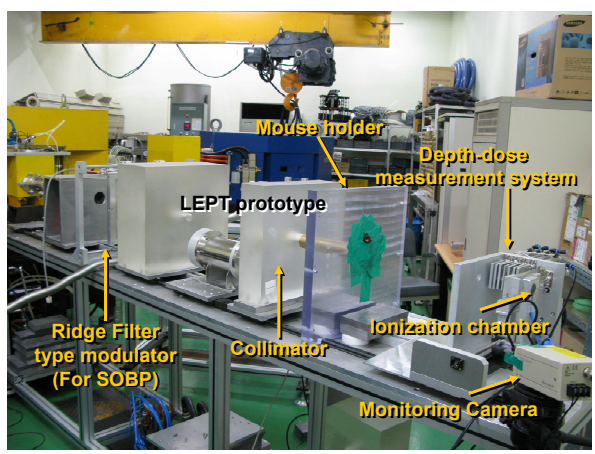


Figure 1: 45MeV PEFP beam line installed at the MC-50 cyclotron of KIRAMS.

* Work was performed as a part of Proton Engineering Frontier Project and supported by the MEST (Ministry of Education, Science and Technology) of the Korean government
# kimkr@kaeri.re.kr

ridge filter type modulator, depth-dose measurement system, mouse holder, and monitoring camera were added.

Ridge-Filter Type Modulator

To deliver uniform dose to the sample volume, beam scanner and modulator combined. When use this kind of method, ridge-filter type modulator is more convenient because of there's no time sharing effect. Uniform dose distribution in depth as well as in lateral and vertical direction can be made unrelated the timing shape of beam scanning instruments. And another unique aspect of this ridge filter type modulator is it can make uniform depth-dose distribution from the surface to the planned depth.

The design of the ridge and processed shape are shown in Fig. 2 with the photograph of the whole system. It was made of pure Al and was designed by using MCNPX code calculation. The maximum thickness of the ridge is 6 mm in consideration of 45-MeV proton beam incidence for the maximum value.

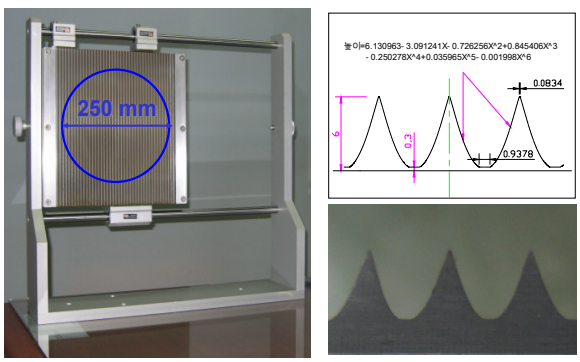


Figure 2: Photograph of ridge-filter type modulator and design drawings.

The depth-dose distribution and lateral dose distribution were shown in Fig. 3, which was realized by combining with wobbler scanning method and energy degrader. The dose distribution had more than 85% uniformity in both directions.

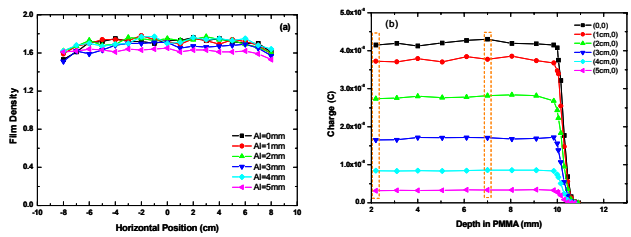


Figure 3: Dose distribution with wobbler scanning method (a) lateral direction and (b) depth.

Depth-Dose Measurement System

There are many kinds of methods to measure the depth-dose profile inside a volume of target. The most general method in hospital is to use water phantom and ionization chamber. But it is not easy to handle and to control because of the big size and water. Another more convenient method is to use film stack made of many sheets of thin radio-chromic films, such as, MD-55, HD-810, and EBT. But it is just for single usage. To make up for these weak points in the current depth-dose measurement system explained previously, we developed a depth-dose measurement system by using plastic phantom and ionisation chamber as shown in Fig. 4.

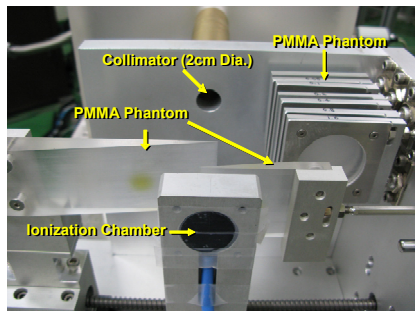


Figure 4: Depth-dose measurement system composed of two-kinds of PMMA phantom and ionisation chamber.

The PMMA phantom consists wedge-shaped and plate-type ones. The PMMA thickness can be controlled in the range from 2.2 ~ 14.8 mm for wedge-shaped phantom. For plate-type phantom, it was composed of six sheets of different thickness, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6 mm. The range of total thickness made by combination of multiple sheets is 0.05 ~ 3.15 mm in step of 0.05 mm. The ionisation chamber was PTW Markus 23343 with 0.055-cm^3 measuring volume and 6-mm aperture. This system was controlled by computer using LabView program. The measured depth-dose distributions are shown in Fig. 5 for 41.7 MeV proton beam.

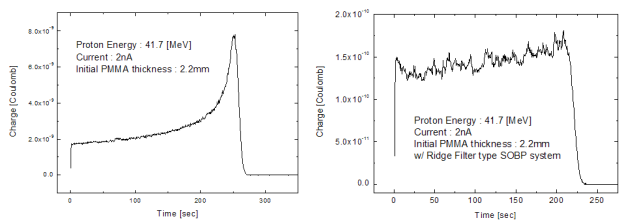


Figure 5: Results of depth-dose Profile Measurement (a) w/o SOBP and (b) w/ SOBP.

Bolus and Mouse Holder

For in-vivo experiments for small animal, mice, mouse holder was manufactured. The mouse holder has 25 mm aperture for proton beam incidence. Inside the aperture bolus and collimator to restrict the proton beam to the tumor volume were inserted. To verify the bolus design, we investigate the proton beam size and range by using PMMA phantom which has sloped aperture as shown in Fig. 6. The beam profile and dose rate were measured by using film stack composed of eighteen 0.1-mm thick HD-810 GAF films and seventeen 0.65-mm thick PMMA sheets. The schematics and results of these measurements are shown in Fig. 7. The results are agreed well with the calculation results as expected. As a result, we conclude that we can control the beam size and range by using the

bolus and collimator. This results was applied to the design of the bolus for the in-vivo experiment to the mice.

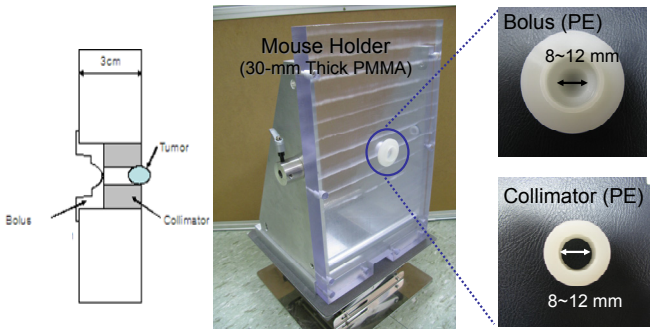
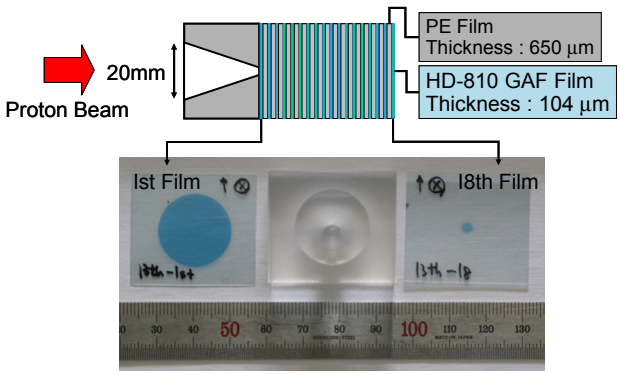
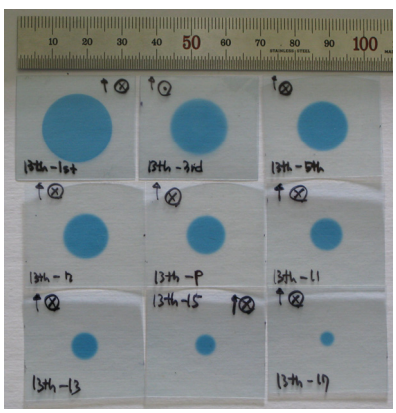


Figure 6: Concept of mouse holder and photographs of mouse holder, bolus, and collimator.



(a) Bouls verification using PMMA phantom



(b) Film images according to the positions.

Figure 7: Results of Bolus verification.

In-Vivo Experiment

The first in-vivo experiment using developed system was conducted by using C57 mice. To investigate the tumor growth suppression effects, we establish C57 xenograft model. The LLC (Lewis Lung Carcinoma) 5310^5 cells inoculated into the mice's flanks. Eight days later, the tumor grew to the 8~10 mm in diameter as shown in Fig. 8. The shapes of tumor were assumed as spheres. After choosing a bolus which has proper diameter matched to the diameter of tumor sphere in the flank of the mouse, we inserted it in front part of the mouse holder's opening. Behind the bolus, collimator with same size of bolus was located. We put the tumor inside the collimator. The dose rate was 0.133 Gy/sec and irradiation time were 150 sec and 300 sec for 20 Gy and 40 Gy, respectively.

Figure 8: LLC inoculated mouse.

During 12 days after proton irradiation, we measured the growth rate of tumor for nine mice. The variation of the tumor's growth rate was displayed in Fig. 9. Compared to the non-treated tumor, treated tumor was grown slowly. And, the growth rate was decreased with increase of the irradiation dose.

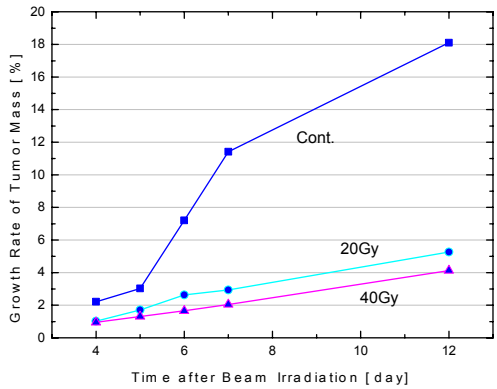


Figure 9: Growth rates of treated and non-treated tumors.

SUMMARY

An in-vivo experiment system was developed and installed at the MC-50 cyclotron of KIRAMS to satisfy the users' requirements in the fields of the medical and biological sciences. Verification of developed system was performed successfully by the application to the C57 xenograft model. As a result, the proton's suppression effect for the tumor growth was confirmed also.

REFERENCES

[1] K. B. Lee, et al., "Low energy proton beam induces tumor cell apoptosis through reactive oxygen species and activation of caspases", Experimental and Molecular Medicine, Vol. 40, No. 1, pp. 118~129, 2008.

[2] Y. Jongen, et al., "The proton therapy system for the NPTC: equipment description and progress report", Nucl. Instr. Meth., Vol. B113, pp. 522~525, 1996.

[3] J. W. Kim, "Status of the Proton Therapy Facility at the National Cancer Center, Korea", J. Korean Phys. Soc., Vol. 52, No. 3, pp. 738~742, 2008.