

**Project on creation of guidance to evaluate medical
devices / regenerative products with emerging
technology**

**Boron Neutron Capture Therapy (BNCT)
Review WG Report**

March 2019

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Foreword

Professor Roentgen discovered X-rays in 1895 and the history of radiation therapy started following year. Radiation therapy was supported by subsequent progress in therapeutic instruments and peripheral equipment as well as advances in radiobiology, which forms its foundation. Radiation therapy is now recognized as one of the three mainstays of cancer treatment, along with surgical therapy and anticancer drug therapy. This treatment is localized similar to surgery, in that it only treats the tumor and the surrounding area. Therefore, ascertaining how to limit damage to the tumor continues to be the largest area of research in radiation therapy. Recent advances in high-precision radiation therapy, such as intensity-modulated radiation therapy (IMRT) and particle beam therapy, have been largely dependent on improvements in dose distribution using physical engineering techniques. However, there are limitations to these technologies. When we say that these techniques have high precision, we mean that they have high precision in the field imaging, and not at the level of cancer cells. These technologies cannot be applied to tumors that cannot be clearly visualized with imaging or tumors that cause microscopic infiltration. Thus, it is essential to shift from “image selectivity” to “cancer cell selectivity” therapy as next-generation radiation therapy.

In principle, boron neutron capture therapy (BNCT) destroys selectively cancer cells using high LET radiation (α ray and lithium nucleus) generated by nuclear reaction between boron (^{10}B) and thermal neutrons without serious damage to the surrounding normal cells. To date, BNCT is reliant on research reactors for its neutron source; however, for it to become general (standard) therapy, a compact accelerator neutron source needs to be developed that can be installed in urban medical facilities. Clinical trials are currently underway using the world’s first BNCT accelerator neutron source on subjects with brain tumors, and head and neck tumors. Thus, we are on the verge of a practical application of this technology. Furthermore, neutron generators and boron carriers were classed under the “*Sakigake* Designation Scheme” by the Ministry of Health, Labor, and Welfare in 2017, thus further accelerating the movement toward the clinical introduction of BNCT accelerators.

This working group has investigated recent trends in the development of accelerator-based BNCT, which is expected to be developed for practical application, centering on the remarkable technological innovation of the “accelerator neutron generator.” Based on the results of the investigation, the working group deliberated on matters that should be noted during the development, manufacture, and installation phases of the accelerator neutron generator and treatment planning system that will be used in combination with the applicable generator, from the perspective of physical engineering, nonclinical and clinical research, and radiation safety management. The findings are summarized into a draft guidance to contribute to expediting the development and approval review of this technology. Accelerator-based BNCT is a new cancer treatment method that Japan can offer to the rest of the world. We therefore hope that the guidance presented in this report provides beneficial information to both the manufacturing industry and regulatory authorities to ensure that people suffering from cancer worldwide can benefit from this technology as soon as possible.

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**Guidance on Evaluation of Accelerator Neutron
Irradiation Device System for Boron Neutron Capture
Therapy (Draft)**

Guidance on Evaluation of Accelerator Neutron Irradiation Device System for Boron Neutron Capture Therapy (Draft)

1. Introduction

Boron neutron capture therapy (BNCT) is radiation therapy that is based on the nuclear capture reaction that occurs when the ^{10}B compound is irradiated with thermal neutrons to yield alpha particles and lithium nuclei to selectively destroy the cancer cells.

The track ranges of the two emitted particles within the body are extremely short at approximately 10 μm , and this distance is not greater than the diameter of the cancer cell. The emitted particles thus destroy only the nuclei of the cancer cells and do not reach normal cells, even those immediately adjacent to the cancer cells. The two particles used for therapeutic effect are heavy ions, and hence, have a potent cytotoxic effect on cancer cells. Therefore, in principle, damage is suppressed to normal cells, which do not uptake boron, while selectively destroying the cancer cells. BNCT is expected to have significant therapeutic effects against invasive cancers with unclear margins, such as malignant brain tumors and cancers resistant to radiation therapy. In addition, because there is limited radiation effect from the neutron beam on normal tissue, it can also be used as an indicator of for recurrent cancer after conventional radiation therapy.

Japan is the world leader in the field of BNCT. Since the world's first BNCT accelerator began operating in the country in 2010, BNCT has been rapidly transforming from clinical studies using research reactors, and now faces a significant turning point. An accelerator-based BNCT phase I clinical study on brain tumors and cancer of the head and neck has been completed, and research is progressing to phase II clinical studies. It is important to set signposts for evaluation to contribute to expedited approval review to enable the delivery of this cutting-edge therapeutic equipment to patients as soon as possible. The major point of difference between BNCT, conventional radiotherapy and particle beam therapy is the use of boron agents and neutron beams. A variety of technologies are also available to generate neutron beams, including research reactors, and accelerators using nuclear reactions. Therefore, during the clinical application of BNCT, it will be necessary to extract characteristics that differ from those of conventional radiation therapy and evaluate this technology based on a consideration of the associated technological issues and limitations.

Considering the above background, this working group investigated the research and development, usage trends, and standards related to BNCT accelerator neutron irradiation device and treatment planning device both in Japan and overseas, and created a draft guidance to enable appropriate and expedited evaluation of the efficacy, safety, and quality of this therapy on scientific grounds.

2. Scope

The targets of this guidance are compact accelerator-based neutron sources for BNCT and the treatment planning device used in combination with the applicable device.

3. Role of This Guidance

This guidance has presented items considered important at present, based on the consideration that it pertains to the development of important device. The guidance will be revised based on future technological innovations and amassed knowledge and does not have binding force over the content of approval applications. The flexible application of this guidance is essential when evaluating products subject to it. The evaluation must reflect full understanding of the characteristics of the given product and be based on reasonable scientific basis. Referencing other, related guidelines both in Japan and overseas should also be considered in addition to using this guidance. It is also necessary to comply with the

various laws related to radiation safety (Atomic Energy Basic Act, Act on Prevention of Radiation Hazards, Industrial Safety and Health Act, etc.).

4. Points to Consider in Evaluation

(1) Basic items

- 1) Clearly show the developmental background, development product specifications, development product and usage status of similar products in Japan and overseas, the equipment design and system principles (including algorithms), standard usage methods, etc.
- 2) Stipulate and evaluate evaluation items required for overall system installation and operation, referencing the following items:
 - (i) Software (including OS: operating system and algorithms)
 - (ii) Installation conditions
 - (a) Weight (load-bearing conditions required for the floor where equipment is used)
 - (b) Dimensions (including when housed)
 - (c) Anti-tip measures
 - (iii) Target material
 - (a) Physical and chemical safety of the target material and methods of handling
 - (b) Deterioration due to charged particle irradiation and neutron generation of the target material (blistering, etc.), safety measures for damaged material (measures for dust and evaporation of the material, etc.) and replacement frequency
 - (c) Procedures for replacement of target material
 - (iv) Noise and vibration
 - (v) Maintenance inspections and details thereof
 - (vi) Measures for activation of apparatus and incidental equipment
 - (a) Maintenance methods for activated equipment (Hands on, use of specialized jigs)
 - (b) Replacement frequency of activated parts and replacement method
 - (c) Safe waste disposal methods
 - (vii) Necessity of training plans and details thereof
 - (viii) Documentation of user operating manuals, etc., and details thereof
 - (ix) Methods for patient monitoring during irradiation
 - (x) Troubleshooting protocols (measures for dealing with sudden changes in patients and removal of patients from the apparatus, radiation problems, leakage of coolant into the target vacuum box, measures for power outages, and measures for emergency stop)
 - (xi) Software life science process (See: JIS T 2304)
 - (xii) Risk management (See: ISO 14971)

It is essential to examine measures based on the worst-case scenario, where this examination is not limited to equipment risks, but also includes accidents during treatment. Refer to the appendix for other main points to note regarding the targets of this evaluation index.
- 3) Equivalence of final product and testing apparatus

When nonclinical and clinical studies are implemented using the test equipment, evaluate equivalence with the final product.

(2) Nonclinical studies

These include the conduct-appropriate evaluation of the safety and efficacy of the system as a whole, and of the safety and efficacy of the neutron irradiation field through the bench tests and biological studies shown below. When necessary, the performance and quality of the patient irradiation system, the radiation measurement monitor in the treatment room and the treatment planning device that comprise the treatment system are also evaluated according to related guidelines and industry standards.

1) Safety evaluation of accelerator neutron irradiation device

- (i) Electrical safety (See: JIS T 0601-1)
- (ii) Electromagnetic compatibility (See: JIS T 0601-2)
- (iii) Radiation safety (See: JIS T 0601-2-64)
- (iv) Mechanical safety (See: JIS T 0601-1)
 - (a) Alarm
 - (b) Interlock
 - (c) Emergency stop mechanism
 - (d) Excess irradiation prevention mechanism
 - (e) Incorrect operation prevention mechanism
 - (f) Other necessary mechanisms
- (v) Biological safety (See: JIS T 0993-1)
- (vi) Safety for exposure by leakage radiation besides the beam port

Because high intensity neutron beam is generated and used for treatment, there is a possibility that radiation (neutron beams, gamma rays and residual gamma rays) leak from the equipment or the walls outside the beam port. Whenever possible, therefore, take note of the following matters, with reference to JIS T0601-2-64:

 - (a) Ascertain the characteristics of the leaking radiation (type of radiation, dose rate, etc.). Assume an operational history of approximately 10 years for the residual gamma rays.
 - (b) Ensure that the disadvantage to the patient through exposure outside the treatment area is sufficiently smaller than the advantages of treatment.
- (vii) Safety for exposure of medical staffs (including equipment maintenance worker) to residual radiation due to activated equipment (See: Act on Prevention of Radiation Hazards)

Residual radiation may be emitted from the accelerator and the neutron irradiation device with the activated components even when the accelerator is stopped and neutron beams are not generated. Thus, the following points must be noted:

 - (a) Ascertain the characteristics of the residual radiation (dose rate, spatial distribution, and temporal change). Assume an operational history of approximately 10 years.
 - (b) Ensure that the exposure of medical staffs is sufficiently small compared with the limit value stipulated by law (conduct appropriate exposure management).
- (viii) Safety for exposure of worker from the activated components such as target during maintenance and inspection of the therapeutic device.

Ensure that the equipment is designed so that the exposure of radiation worker involved in the operation and maintenance management of the equipment is sufficiently small compared with the limit value stipulated by law.

2) Performance evaluation of accelerator neutron irradiation equipment

- (i) Stability, reproducibility, and feasible and continuous operating time of the energy and current of the charged particle beam generated and accelerated in the accelerator

- (ii) Operational stability of charged particle beam charge monitor
- (iii) Soundness of target material (cooling system, temperature monitoring, etc.)
 - (a) Safety measures should be adopted to prevent adverse reactions caused by unanticipated excessive beam irradiating to the target material.
 - (b) Measures should be adopted to prevent blistering.
 - (c) Safety measures should be adopted in consideration of such events as when the cooling of the target material stops, or when there is leakage of the coolant (including on the vacuum side).
 - (d) Safety measures should be adopted for events such as the leakage of the target material when using a liquid target material like liquid lithium.
- (iv) Stability and reproducibility of characteristics of the neutron beam emitted from the beam port
- (v) Stability and reproducibility of characteristics of the gamma ray mixed in the neutron beam
- (vi) Feasibility of irradiation

Output the results implemented according to the irradiation schedule.
- (vii) Safety and reproducibility of the methods for observing and controlling the neutron beam and mixed gamma rays during irradiation
 - (a) When directly measuring the generated neutron beam and mixed gamma rays in real time
 - reliability and stability of measurement monitor
 - (b) When indirectly observing or controlling the generated neutron beam based on charged particle output (current value)
 - uniformity of characteristics of the neutron beam generated relative to the current of the charged particle
 - methods for ascertaining soundness of target material
 - method for estimating the characteristics of the neutron beam generated during treatment when there is a large change in the characteristics of the beam relative to the current of the incident charged particle, and neutron flux may change compared with that immediately before treatment
- (viii) Size of irradiation field of neutron beam, treatable depth, and irradiation time

Present the equipment's performance such as the treatable range and depth, neutron flux, mixed gamma ray rate, and the targeted irradiation time for each irradiation case. The dose distribution and irradiation time for each case is determined by the physical characteristics of the beam generated by the equipment and can change depending on the boron concentration in each tissue. When presenting these performance values, also show the boron concentration value used for calculation, the relative biological effectiveness (RBE) value, and the compound biological effectiveness (CBE) value.
- (ix) Change in position of patient and focus during treatment

If the position of the patient and the focus change during neutron beam irradiation, there may be fluctuation in the dose delivered to the patient. In principle, thus, the position of the patient must not be changed.

When the position of the patient and the focus are allowed to change during irradiation, monitor the position of the patient and the focus, and demonstrate that it is possible to control the irradiation by considering the effect of such elements as the change in dose caused by the change. In addition, demonstrate the stability and reliability of the monitor measuring positional changes of the patient and the focus.

- (x) The method of calculation used to evaluate the dose of the neutron beam and the dose effect in human body

When using calculation methods for dose evaluation related to the neutron beam and in human body based on the Monte Carlo method, present the calculation method (calculation code, nuclear data used for transport calculations, dose conversion factor, etc.).

3) **Safety and performance evaluation of treatment planning device**

Unlike conventional radiation treatment, BNCT uses continuous energy (white) neutrons, and the dose from mixed gamma rays and secondary gamma rays generated by the reaction of the body tissue and neutrons must be evaluated. The factor (RBE value) to convert from the absorbed dose to gray-equivalent (Gy-Eq) dose changes depending upon the kind of tissue and organ, and also on neutron energy. Basically, Monte Carlo method is used for dose evaluation of BNCT, furthermore a display function is also necessary to show the dose distribution to the tumor and normal tissue. BNCT is also characterized by the use of boron drug and the treatment is completed with a single irradiation. It is also necessary to consider settings of the patient's irradiation position, possibility of respiratory movement, and changes in irradiation conditions during irradiation, and the activation of the patient and building.

Evaluate the treatment planning device by considering these matters that are unique to BNCT, as well as taking note of the following: When the device has functions other than calculating the dose in human body, clearly state the principles used to achieve these functions and the performance.

- (i) Purpose of use, principles, etc.
 - (a) Purpose of use
 - (b) Principles, algorithms
 - (c) Function, performance
 - (d) Usability
- (ii) Performance evaluation
 - (a) Contour creation function
 - Able to perform region-splitting process by thresholding CT (computed tomography) values.
 - Setting function for region of interest, such as the focus site, and organ, where dose evaluation is performed using CT imaging etc.
 - (b) Geometric parameter display function
 - Superimposed display function for radiation irradiation angle and range on 3D patient models and medical imaging
 - Display to use for position matching at the time of irradiation (beam's eye view, digitally reconstructed radiograph (DRR), etc.)
 - (c) Dose distribution computation function/dose distribution display function
 - Able to calculate dose distribution of the range of irradiation using geometric parameters relating to irradiation, using irradiation equipment used for treatment. The calculated items include neutron flux, photon flux, absorption dose generated by the reaction between the neutrons and ^{10}B , absorption dose generated by the reaction between neutrons and elements comprising the body tissue (hydrogen, nitrogen, etc.), and the gamma ray absorption dose.
 - (d) Evaluation of dose-computing algorithm

- The results of dose calculation are within the range of the design standard value when tested based on methods stipulated by the manufacturer during development.
- (e) Dose distribution analysis function
- Able to display the equivalent dose and 3D distribution based on the calculated physical dose (each absorption dose).
 - Able to conduct general statistical processing, including the maximum dose, minimum dose, mean dose, and deviation of the dose delivered to the focus and each region of interest.
 - Able to display the dose volume histogram (DVH) for the focus and each region of interest.
 - Able to compare the dose distribution delivered to the focus and the normal tissue against the same medical imaging slice.
- (f) Irradiation dose parameter calculation/setting function
- Calculate or set the irradiation time or neutron fluence and generate the charged amount of charged particles to deliver the prescribed dose.
- (g) Radiation treatment parameter optimization function
- Find the combination of geometric parameters (position of incident beam, angle, irradiation range, etc.) to ensure that dose distribution to surrounding important organs can be reduced while delivering as high a dose as possible to the focus, considering the set focus and the surrounding organ.
- (h) Re-planning function
- Assist in the creation of new radiation treatment plans by calling up the contours and parameters of already created radiation treatment plans on different medical images.
- (iii) Safety evaluation
- (a) Distance and length dimensions
 - (b) Radiation dose
 - (c) Date and time format
 - (d) Preventing use by unauthorized personnel
 - (e) Data limiting value
 - (f) Protection from unauthorized changes
 - (g) Accuracy of data transmission
 - (h) Coordinate system and scale
 - (i) Temporary storage and archiving of data
 - (j) Soundness
 - Confirm that the calculated dose value is within an acceptable range of accuracy for the computing time assumed for clinical use and the simulated system.
 - Ensure that the region of interest (ROI) and dose distribution display match the coordinates of the Digital Imaging and Communications in Medicine (DICOM) images.
 - Linkage with external computing software and nuclear data library
Confirm reproducibility when dose distribution calculations are outsourced.
Confirm versions of computing software and nuclear data library to be externally outsourced.

4) **Biological effect**

Confirm that biological effect is expressed through neutron beam irradiation after exposure to BNCT boron drugs in BNCT tests. Reports on this testing system have been published in literature on the *in vitro* cytotoxicity effect and *in vivo* tumor proliferation suppression effect. Therefore, construct the system by referencing these cases. In addition, evaluate the biological effect (adverse events) of irradiation using neutrons alone.

5) **Animal studies**

Animal studies are to be appropriately evaluated, taking note of the following items:

- (i) Animal studies
 - (a) Extrapolability of animal species to humans (anatomical and biological characteristics, sensitivity to radiation, etc.)
 - (b) Consideration comparing the procedures on animals with those in clinical practice, and extrapolability to humans
- (ii) Study protocol
 - (a) Endpoint, evaluation criteria, evaluation method, evaluation period, and evaluator
 - (b) Measurement data (physiological, mechanical and electrical data, radiation intensity, etc.)
 - (c) Setting number of cases
- (iii) Points to note for evaluation
 - (a) Treatment achievement status (gross pathological observation of the treated area and histopathological evaluation, etc.)
 - (b) Treatment status (level of achievement of treatment targets)
 - (c) Extent and frequency of adverse events on the body
 - (d) Equipment defects relating to items confirmed in animal studies
 - (e) Differences between results obtained in animal studies and simulations

(3) **Clinical studies**

The concepts of setting the target sample size in clinical studies, endpoints to assess the efficacy of the obtained results, and the evaluation of adverse events may be implemented by referencing clinical studies on conventional radiation therapy device, in line with each disease and irradiation site. However, it is also necessary to conduct separate evaluations of adverse events caused by the concurrent use of boron agents, as an item specific to BNCT.

In BNCT, the cytotoxic effect on tumor cells and adverse effects on normal tissue derive from the irradiation effect of two heavy particles with track ranges of 10 μm or less. It is necessary to formulate treatment plans based on a scientific examination of nonclinical results from the perspective of efficacy and safety assurance in humans. Specifically, it is essential to evaluate the tumor size reduction (response) effect and the effects to the normal tissues would be affected by the microscopic distribution of the boron agent on these tissues.

Conduct appropriate evaluation of clinical studies on BNCT by referencing the following:

1) **Treatment protocol**

Specifically, this can be created in the same manner as clinical trial / study protocols for conventional radiation or medical therapy. However, set efficacy and safety endpoints that consider concepts and processes specific to BNCT.

If the treatment planning system has functions other than *in vivo* dose calculations, and if the efficacy of these functions cannot be properly evaluated with nonclinical studies alone, provide an explanation on the propriety of implementing the clinical study.

(1) Indicated diseases/sites

Explain the theoretical background for being able to anticipate that the effect is not inferior to or surpasses that of conventional treatment methods and explain the results of previous clinical studies that have applied BNCT to the respective diseases/sites as grounds for setting the indicated diseases/sites.

(2) Setting endpoints

Set appropriate endpoints (survival rate, tumor response rate, palliative effect, etc.) depending on the indicated diseases/sites based on the results of boron agent distribution in the tumor verified in nonclinical studies. Set appropriate endpoints for adverse effects on normal tissues based on the microscopic distribution of the boron agent in normal tissue and the intra/extravascular distribution ratio verified in nonclinical studies.

(3) Grounds for setting the method of boron agent administration, irradiation timing, and neutron fluence during irradiation

Determine the method of boron agent administration and timing of irradiation based on data on the cytotoxic effect and adverse effects on normal tissue due to the microscopic distribution of the boron agent in the tumor and normal tissue, and the intra-/extracellular and intra-/extravascular distribution ratios in nonclinical studies. In addition, explain the grounds for setting these items.

The neutron fluence irradiated to the patient is expected to differ depending on the boron agent, target disease, and irradiation site. Thus, scientifically explain the grounds for setting the parameters (boron concentration value and tolerable dose for normal tissue) based on the results of nonclinical studies (RBE and CBE values) and the findings of conventional radiation treatment.

(4) Treatment plan

The above evaluation items should be appropriately reflected in the treatment plan.

2) Accuracy of irradiation of neutron beam

(1) Evaluation of irradiation accuracy

The irradiation neutrons are more significantly affected by changes in patients position (example: slope of the neck) during irradiation compared with X-rays and particle beams. Therefore, describe the method for evaluating differences in the irradiation position on the treatment plan and at the start of treatment (set-up error). And also, describe the method for evaluating changes in irradiation positions during irradiation (intra-fractional error) because an irradiation session lasts approximately 30 minutes to one hour.

(2) Verification of irradiation neutron fluence

It is preferable to describe methods for evaluating safety based on previous nonclinical studies and clinical studies, as well as the grounds for determining the prescribed dose for normal tissue or the tumor for the neutron fluence irradiated to the patient.

3) Defect (See: 4. (1) 2) (xii) Risk Management)

Evaluate the details, frequency, and seriousness of the defects. Explain the safety measures adopted for defects.

Concept of risk management

– Reference information –

Matters relating to risk management are as follows, based on current technological limitations and constraints:

- (1) Measurement of neutron beams and gamma rays
 - (a) When directly measuring neutron beams and gamma rays: Regularly calibrate the value displayed on the measuring equipment and reduce risk by confirming that the measurements have been conducted accurately.
 - (b) When not directly evaluating measurement of neutron beams and gamma rays: Check the correlation between the output (current value) of the charged particles and the generated neutron flux, and indirectly monitor and control the generated neutron beam. In this method, the risk is reduced by performing the irradiation to confirm the correlation between the generated neutron flux and the output of charged particles, and performing measurement experiments to confirm the soundness of the target material before and after irradiation. This method can also be applied for the direct measurement of neutron flux described in (a), thus further reducing the risks of the direct measurement method.
- (2) Evaluating measurement of the dose applied to the patient

There is a possibility that the risk can be further reduced by setting and irradiating an integrated/nonpower-based radiation detector such as activated foil and thermoluminescent dosimeters (TLD) around the radiation field of the patient. However, the measurement values of these methods can change depending on such conditions as the measurement position and may be associated with significant errors. Thus, it must be understood that these data should be used only as an auxiliary method and not be applied for absolute dose control.
- (3) Soundness of target material

When it is difficult to directly confirm the conditions of the target material during treatment, indirect monitoring is performed as much as possible by combining information, such as the temperature of the cooling water of the target material and the extent of vacuum in the accelerating tube. In addition, risk is reduced by setting an interlock that can stop irradiation immediately when an anomaly is detected.
- (4) Leaked radiation outside the beam port

The results of measurement evaluations using gold foil and TLD have been reported in clinical research on reactors¹⁾. No serious effects have been generated by leaked radiation in the results of clinical studies to date^{2~5)}.
- (5) Exposure by residual gamma rays after the irradiation by activation of the device

Manage and reduce the exposure dose by limiting the time to enter the irradiation room, taking a distance from the beam port, combining equipment that remotely removes the patient from the beam port, etc.

 - (a) For the patient, the dose delivered during irradiation is quite higher, and the dose delivered by residual gamma rays after irradiation is negligible.
 - (b) Manage the exposure dose for medical staffs such as doctors according to facility management based on the related laws and regulations.
- (6) Exit criteria

Examine the activation of patient as needed, referencing guidelines from related societies.

(7) Changes in patient position during irradiation

Basically, measures will be taken to suppress the movement of the patient as much as possible using a fixing shell. Install a monitor that enables the sequential monitoring of the condition of the patient during irradiation. Adopt measures that enable immediately stop irradiation when the patient's position changes significantly relative to the irradiation condition.

(8) Dynamics of boron during irradiation

Control the dose using a boron concentration estimation method that is as accurate as possible. A post evaluation of boron concentration and neutron fluence during irradiation will be performed to confirm the final given dose.

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