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Radiation dose assessment for radiation workers during 18F-FDG synthesis and dispensing activities in hot cells: a proposal to improve the safety of radiation protection measures for workers

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ABSTRACT

Background*:** Hot cells are used in the production of radiopharmaceuticals to provide radiation workers with a safe environment in which to work. This study was conducted to measure the radiation dose that leaks through the walls of a hot cell. ***Materials and Methods*:** For this study, hot cells of five big hospitals (≥ 1000 beds) in South Korea were selected. To calculate the radiation exposure outside the walls of the hot cell (i.e., the external dose) during fluorine-18 fluorodeoxyglucose (^{18}F-FDG) synthesis and dispensing activities, exposure rates were measured with a Geiger Muller counter (GM counter) at five locations around the hot cells (10 measurements per each measurement point). Based on the measurements, operating conditions of the hot cells of the five hospitals were conservatively considered to calculate the effective dose. The radiation exposure inside the hot cell (i.e., the internal dose) was estimated considering the operating conditions of the hot cells of five large hospitals as well as international guidelines. ***Results: The Based on the experimental results, the impact of the internal dose was found to be negligibly low during ^{18}F-FDG synthesis and dispensing activities (less than 0.21 mSv/y); however, the radiation leakage exhibited levels requiring caution in all directions, with a radiation leakage of up to 19.5 μSv/h measured on the lead glass windows of the hot cells in some hospitals. ***Conclusion:*** The conclusion is that radioisotope manufacturers operating radiopharmaceutical synthesis and dispensing hot cells should implement various improvements. Strengthening the shielding of the lead glass windows on the front and sides of cells, implementing real-time dosimetric monitoring, setting dose limits for radiopharmaceutical production processes, and regular worker rotations are needed.

Keywords: *^{18}F-FDG, hot cell, radiation worker, external dose, internal dose.*

INTRODUCTION

Positron emission tomography (PET) is widely used in nuclear medicine imaging, and has become increasingly popular because it allows not only the three-dimensional observation of bodily organs, but also facilitates the evaluation of physiological (functional) metabolisms within tissues in the body. Fluorine -18 fluorodeoxyglucose (^{18}F-FDG) is the

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radiopharmaceutical most commonly used for PET imaging [1]. The basic principle of PET imaging is as follows. When a positron (i.e., an antiparticle to an electron) within an atom is ejected from the nucleus, it bonds with an electron. This positron-electron pair is annihilated, thereby emitting two gamma rays with equal energies of 0.511 MeV in opposite directions (i.e., 180 degrees apart from each other). By employing radioisotopes capable of emitting positrons, the corresponding 0.511 MeV gamma ray energy that is emitted in opposite directions can be measured via a circularly arranged detector centered on the location where the positron-electron annihilation occurred, and the target organ and lesion can be visualized in the resulting radionuclide image [2]. Radioisotopes (radionuclides) such as C-11, N-13, O-15, and F-18 are used to obtain PET tracers for imaging. Among these, F-18 is the one most commonly used in PET imaging as its half-life (110 min) is useful in clinical applications and its energy can easily be detected.

Synthesis is the process of incorporating deoxyglucose into F-18, after which the synthesized radioactive isotopes are transferred to a separate dispensing module. Because the work area is exposed to high dose rate radiation during this operation, it is performed in a heavily sealed space called a hot cell, which is shielded by a lead housing of specified thickness and equipped with an air exhaust and a triple filtration system. In other words, a hot cell is a chamber that isolates the radiation source from the outside environment to minimize the exposure of workers to ionizing radiation. Given that the synthesis and dispensing modules usually contain radionuclides amounting to hundreds of GBq during ^{18}F-FDG synthesis, the walls of hot cells have thick lead shielding (~100 mm) in all directions that is designed to prevent the escape of radiation from the hot cell.

The purpose of this study is to assess the safety of hot cell radiation shields by measuring the radiation released from the inside to the outside of a hot cell during ^{18}F-FDG synthesis and dispensing activities, and to determine the proportions of external and internal exposures relative to the total radiation exposure by calculating the internal dose while taking into account the operating conditions, such as the maximum daily production, expected daily dispersion rate, and annual consumption ^{18}F-FDG. Few studies have been conducted on the radiation exposure caused by the radiation released to the outside of a hot cell (hereinafter referred to as the "external dose") and the radiation exposure caused by radionuclides dispersing within a hot cell (hereinafter called the "internal dose") during ^{18}F-FDG synthesis. Although such a radiation assessment is essential when setting up or improving radiation protection plans for radiation workers, no study has been performed for the big hospitals in South Korea yet. Therefore, we performed the radiation assessment for the hot cells by utilizing data from the five big hospitals in South Korea in this study. The results can be used as a strong rationale for the need to strengthen radiation protection measures in relation to radiopharmaceutical production in a comprehensive manner while taking into account the current operations and management system and the shielding facilities.

MATERIALS AND METHODS

The external and internal doses for radiation workers involved in ^{18}F-FDG synthesis and dispensing activities in the hot cells of five large hospitals (≥ 1000 beds) in a major city in South Korea were assessed based on the maximum daily production of ^{18}F-FDG.

Maximum daily production of ^{18}F-FDG by hospital

The maximum daily production of F-18 of Hospital A, B, C, D, and E were 494 GBq. 814 GBq, 185 GBq, 296 GBp, and 370 GBp, respectively.

Sizes and specifications of the evaluated hot cells

The ^{18}F-FDG synthesis device in a hot cell can be observed through a lead glass window in the front shield, and is customized in terms of its

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size and specifications to the production characteristics of each hospital, as shown in table 1. If a hospital operates multiple hot cells for ^{18}F-FDG production, the one with the highest daily production rate was selected for assessment in this study.

Radiation dose measurement

External dose

Radiation workers usually face the front of the hot cell during radiopharmaceutical synthesis and dispensing activities because the hot cells themselves are mounted along the wall. However, in this study, radiation doses were also measured in the rooms adjacent to the hot cell room (e.g., the upstairs floor and the walls to the sides and rear of the hot cell) in order to determine the level of radiation in adjacent rooms used by non-radiation workers, such as machine rooms, waste storage rooms, and storerooms.

Doses were measured during ^{18}F-FDG synthesis and dispensing activities at measurement points located at the center of the lead glass window in the front opening, and at points on the front, sides, rear, and top of the shielding walls on their respective extended lines from the ^{18}F-FDG synthesis and dispensing devices. A total of ten measurements were made at 5-min intervals at each of the positions shown in figure 1. The bottom part was excluded from dose measurement because the hot cells were located on the bottom-most floor in all five hospitals investigated. When calculating the expected effective dose p.a. received by radiation worker based on the dose assessment results, the total number of operating hours was set based on two hours a day, five days a week, and 50 weeks per year.

The radiation detector used to measure the external dose was a GM counter (RadEye B20, Thermo Scientific, Germany) that had been calibrated by a laboratory that specializes in the field that was certified by the Korea Laboratory Accreditation Scheme (KOLAS) and accredited by the International Laboratory Accreditation Cooperation.

Internal dose

In this study, the internal doses were not directly measured with the whole body counter or samples such as blood and urine, but estimated by calculations using factors of the working environment in order to evaluate internal exposure of workers conservatively.

In this study, only the internal dose of F-18 was measured because it is the most commonly used radionuclide in cyclotron-based radiopharmaceutical production facilities and is the radionuclide with the longest half-life (110 min). As a liquid-state radionuclide with chemical properties similar to those of I-131, F-18 is classified into Group 2 of the classification in table 2 proposed by Takada *et al.* [3], which is used by nuclear operators and nuclear safety commissions in radiation protection inspection plans for unsealed radiation sources. The table 2 presents the dispersion rate and correction factors necessary for estimating the internal radiation dose depending on the method of manipulating unsealed radiation sources and the dispersion rate, which varies depending on the radionuclide, physical state, and manipulation method. The table 2 was used for calculating the maximum atmospheric dispersion rate in the hot cell room, the maximum expected atmospheric concentration, and the expected internal dose.

Given the fact that ^{18}F-FDG synthesis is performed in an automated synthesis module within a hot cell equipped with an air exhaust system and a triple filtration system (pre-filter, HEPA filter, and charcoal (carbon) filter) designed to provide isolation and negative pressure, the leakage of contaminated air from inside the hot cell is precluded. Moreover, all chemical reactions throughout the synthesis process, including the heating and evaporation steps, occur in reactor vials. The possibility of dispersion can also be precluded because the reactor vial is sealed and its state is inspected via leakage or pressure checks during the calibration prior to each operation of the automated synthesis module. Accordingly, the dispersion rate was calculated assuming common manipulation (×1) for the exhaust test, and assuming the following synthesis and dispensing work conditions for the internal dose measurement. The average air intake of a

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radiation worker was set at 1.1 m^3/h, as specified in the International Commission on Radiological Protection (ICRP) 103 [4].

1) Total number of operating hours: 2 h/day = 10 h/week = 500 h/year
2) Average air intake of a radiation worker: 1.1 m^3/h
3) Hot cell exhaust air: 100 m^3/h
4) Proportion of F-18 diffused into the hot cell from the vials and the synthesis module: 1%

Internal doses in the working conditions described above were measured using Eqs. (1)–(5) together with the dose conversion factor 9.3 × 10^{-11} Sv/Bq specified in ICRP 68 [5].

Expected dispersion rate = 10^{-4} (Group 2) × 1 (liquid) × 1 (common manipulation) (1)

Indoor dispersion rate (Bq/day) = Max. production (Bq/day) × 10^{-4} (expected dispersion rate) × 0.1 (indoor spread rate) (2)

Average atmospheric concentration (Bq/m^3) = $\frac{\text{Expected indoor dispersion rate}}{\text{Exhaust} \times \text{work hours}}$ (3)

Annual intake (Bq/y) = Average atmospheric concentration × 500 h × 1.1 m^3/h (average air intake for an adult) (4)

Expected internal dose = Annual intake × Dose conversion factor (5)

Table 1. Specifications of the hot cell shielding by hospital.

Hospital			Size (mm) (all sizes in W × L × H)	Shielding	
				All side wall	Lead glass window
A	Synthesis	Outside	2450 × 1190 × 2500	75 mm Pb	75 mm PbEq
		Inside	1000 × 850 × 900		
	Dispensing	Outside	2480 × 1140 × 2400	60 mm Pb	60 mm PbEq
		Inside	1050 × 850 × 900		
B	Synthesis	Outside	1310 × 1190 × 2500	75 mm Pb	75 mm PbEq
		Inside	970 × 875 × 870		
	Dispensing	Outside	1650 × 1166 × 2400	75 mm Pb	75 mm PbEq
		Inside	880 × 700 × 700		
C	Synthesis	Outside	1080 × 1251 × 2300	100 mm Pb	60 mm PbEq
		Inside	700 × 700 × 700		
	Dispensing	Outside	1330 × 1287 × 2300	75 mm Pb	60 mm PbEq
		Inside	700 × 700 × 650		
D	Synthesis	Outside	2140 × 1190 × 2500	75 mm Pb	60 mm PbEq
		Inside	850 × 875 × 870		
	Dispensing	Outside	1540 × 1490 × 3030	75 mm Pb	75 mm PbEq
		Inside	1280 × 930 × 1160		
E	Synthesis	Outside	1040 × 1170 × 2480	75 mm Pb	75 mm PbEq
		Inside	720 × 710 × 635		
	Dispensing	Outside	1270 × 1220 × 2680	75 mm Pb	75 mm PbEq
		Inside	920 × 820 × 670		

Table 2. Dispersion rates and correction factors depending on the radionuclide and manipulation method.

Radionuclide		Dispersion rate/day	Physical state	Correction factor	Manipulation method	Correction factor
Group 1	H-3, C-14, S-35, Se-75	10^{-3}	powder	× 10	Heating	× 100
Group 2	As-77, Ru-103, Sb-125, I-123, I-125, I-131, Cs-137, Hg-197	10^{-4}	Liquid	× 1	Chemical reaction, Machining, Animal testing	× 10
Group 3	Na-22, Na-24, P-32, Ca-45, Cr-51, Fe-59, Ga-67, Mo-99/Tc-99m, In-111, Pm-147, Au-198, Tl-201	10^{-7}	Solid	× 0.1	Usual manipulation	× 1
					Storage	× 0.1

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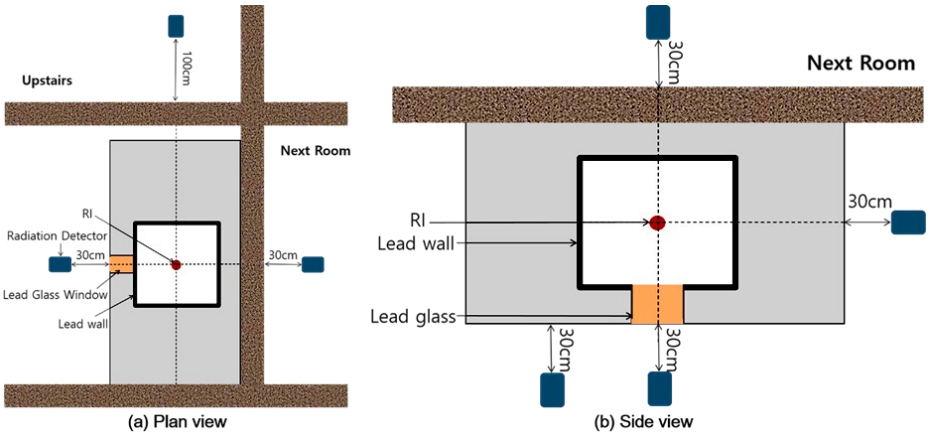


Figure 1. Dose measurement points on the hot cell surfaces: **(a)** plan view, and **(b)** side view.

RESULTS

Table 3 outlines the results of the external doses measured during ^{18}F-FDG synthesis and dispensing activities as well as estimated effective doses. Table 4 summarizes the measured external doses during dispensing activities and corresponding effective doses. The table shows the average of 10 measurements taken at each measurement point. In the case of the Hospital B, the hot cell was located below ground level and the rear was filled with soil, no measurements were performed in that region. During synthesis, external doses at the window or front (from 0.26 μSv/h to 19.50 μSv/h) were generally higher than the others except for the Hospital E. For the Hospital E, the external dose at the rear (7.74 μSv/h) was the highest. The external dose of the Hospital A showed the highest external dose of 19.50 μSv/h at the window. Similarly, during dispensing activities, external doses at the window or front (from 0.39 μSv/h to 14.40 μSv/h) were generally higher than the others except for the Hospital E. For the Hospital E, the external dose at the rear (7.23 μSv/h) was the highest. The external dose of the Hospital A showed the highest external dose of 14.40 μSv/h at the front. The external doses were found to be significantly higher in some hospitals especially for the Hospital A. In some hospitals, radiation exposure levels in excess of the dose limits for non-radiation personnel were measured in the rooms situated immediately over and next to the top, sides, and rear of the hot cell.

Table 5 outlines the results of the estimated internal dose during ^{18}F-FDG synthesis and dispensing activities. The internal dose during ^{18}F-FDG synthesis and dispensing activities was found to range between 0.047 and 0.208 mSv/y.

Table 3. Measured external doses and estimated effective doses during ^{18}F-FDG synthesis.

Hospital	Evaluated point	External dose (μSv/h)	Effective dose (mSv/y)
A	Front	3.54	1.77
	Window	19.50	9.75
	Side	3.13	1.57
	Rear	0.72	0.36
	Top	0.84	0.42
B	Front	13.93	6.97
	Window	10.01	5.01
	Side	12.55	6.28
	Rear	-	-
	Top	2.14	1.07
C	Front	0.26	0.13
	Window	8.91	4.46
	Side	0.30	0.15
	Rear	0.22	0.11
	Top	0.00	0.00
D	Front	2.31	1.16
	Window	3.11	1.56
	Side	2.22	1.11
	Rear	2.58	1.29
	Top	0.97	0.49
E	Front	6.19	3.10
	Window	6.55	3.28
	Side	5.33	2.67
	Rear	7.74	3.87
	Top	1.51	0.76

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Table 4. Measured external doses and estimated effective doses during dispensing activities.

Hospital	Evaluated point	External dose (μSv/h)	Effective dose (mSv/y)
A	Front	14.40	7.20
	Window	12.30	6.15
	Side	12.00	6.00
	Rear	4.82	2.41
	Top	0.75	0.38
B	Front	13.45	6.73
	Window	10.11	5.06
	Side	12.16	6.08
	Rear	-	-
	Top	2.04	1.02
C	Front	0.39	0.20
	Window	7.99	4.00
	Side	0.32	0.16
	Rear	0.36	0.18
	Top	0.00	0.00
D	Front	2.43	1.22
	Window	3.59	1.80
	Side	2.66	1.33
	Rear	1.97	0.99
	Top	0.71	0.36
E	Front	6.05	3.03
	Window	5.81	2.91
	Side	5.02	2.51
	Rear	7.23	3.62
	Top	1.44	0.72

DISCUSSION

The results of the present study demonstrated that the radiation workers are exposed to a significant amount of radiation during ^{18}F-FDG synthesis and dispensing activities, and this is predominantly due to the external dose. The external doses measured in some hospitals were alarmingly high, and this may be due to two facts: 1) shielding defects due to manufacturing errors in the hot cell shielding design, i.e., deliberate or inadvertent design mistakes in the lead thickness and content; and 2) the synthesis and dispensing of radiopharmaceuticals exceeding the limits of the hot cell shielding performance. It is recommended to set appropriate dose limits for radiopharmaceutical synthesis and dispensing activities in hot cells and to monitor the working

Table 5. Estimated internal doses.

Hospital	Indoor dispersion rate (Bq/day)	Average atmospheric concentration (Bq/m^3)	Annual intake (Bq)	Internal dose (mSv/y)
A	494,000	2,470	1,358,500	0.126
B	814,000	4,070	2,238,500	0.208
C	185,000	925	508,750	0.047
D	296,000	1,480	814,000	0.076
E	370,000	1,850	1,017,500	0.095

hours of each radiation worker so that workers that have exceeded or are about to exceed the dose limit can be immediately shifted to non-radiation related tasks. At the same time, shifts of workers should be implemented to shorten the time individual workers are engaged in radiation related tasks. In addition, sufficient shielding should be provided for the lead glass window by increasing the design thickness, adjusting the size and position of the lead glass window, and using additional mobile lead glass shields of sufficient thickness. Work environments should be improved by installing real-time monitoring systems that emit a warning sound when a worker is at risk of exceeding the dose limit.

The long-term exposure of a human body to F-18, due to its relatively high energy (0.511 MeV), puts it at higher risk of experiencing the harmful effects of radiation exposure [6]. The exposure during ^{18}F-FDG synthesis can be reduced by allocating a group of radiation workers to perform the work in turns instead of allocating one radiation worker to conduct the entire operation. The expected annual effective dose in an extreme case of this study was up to 9.75 mSv under the assumption that one radiation worker works throughout the year, which corresponds to about the half of the annual average of 20 mSv of the 5-year dose limit set for a radiation worker (100 mSv) [4] and about 10-fold the dose limit set for non-radiation workers (1 mSv/y) [4]. Even though the annual dose limits for radiation workers have not yet been exceeded, considering the repetitive long-term exposure during radiopharmaceutical synthesis and dispensing processes to ensure continuous

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production, the radiation workers involved in radiopharmaceutical production are at higher risk compared with those in other fields.

In some hospitals, radiation exposure levels in excess of the dose limits for non-radiation personnel were measured in the rooms situated immediately over and next to the top, sides, and rear of the hot cell [4]. These rooms were used as equipment rooms, waste storage rooms, storerooms, etc. However, since potential harmful effects are only expected after a multi-hour stay in these rooms, personnel entering them for only a short time are not expected to be at any significant risk.

All activities involving radiation should be conducted in compliance with the as low as reasonably achievable (ALARA) principle [7-9]. Adherence to this principle should be applied not only to the protection of radiation workers, but also to reducing the unnecessary exposure of non-radiation workers. To this end, it is recommended that measures must be taken to minimize the exposure of radiation worker during the synthesis and dispensing of all radiopharmaceuticals, including ^{18}F-FDG. With the rapidly increasing use of radioisotopes in the treatment of various diseases [9], coupled with increases in the demand for radiopharmaceuticals, the number of radiation workers engaged in radiopharmaceutical synthesis and dispensing activities for longer periods of time will increase, as will the number of radiopharmaceutical manufacturers. To ensure radiation medicine remains a valuable asset in combating disease and ill health, the first priority is to ensure the safety of radiation workers that are directly engaged in radiopharmaceutical production. Therefore, when allocating radiation workers to conduct radiopharmaceutical synthesis and dispensing activities in hot cells, it is essential that additional customized radiation protection measures are adopted that have been optimized for each healthcare institution by taking into account a variety of factors, such as the daily production, shielding performance, working hours, shift intervals, and real-time monitoring requirements.

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***Conflicts of interest*:** *Declared none.*

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