Personalized ^{18}FDG Dose Synthesis Using BG-75 Generator: 1st Year Experience at JCI Accredited Tertiary Care Hospital in Pakistan

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ABSTRACT

Background: Compact cyclotrons are getting popular to fulfill enormous current demands of PET tracers. Aga Khan University Hospital, Karachi, Pakistan has acquired the first smallest footprint of BG-75 Generator for ^{18}FDG-based PET/CT clinical imaging. We are sharing our experience of BG-75 in the first year (December 2015-November 2016) after commissioning.

Material and Methods: BG-75 Generator (ABT, USA) was installed in available space without major design modification. It has a self-shielded mini-cyclotron (7.5 MeV proton beam, positive ion with current < 5µA) to produce [^{18}F]F-, an automated card-based radiochemistry module to produce ^{18}FDG and automated QC module to perform tests upon each batch of ^{18}FDG. Data were collected for yields of [^{18}F]F-, ^{18}FDG, QC and radiation safety parameters.

Results: Total 545 runs in 167 days (3±01 runs/day) were made. Average yield with 60 minute bombardment using 4.5 µA current was 37 mCi and 21 mCi for [^{18}F]F- and ^{18}FDG, respectively. Total 29 runs had chemistry or QC failures and were discarded. Remaining 516 batches were used to perform imaging upon 1370 patients (8±03 patients/day). Radiation dose in BG-75 suite and effective doses to 02 operators were within statutory limits.

Conclusion: BG-75 Generator provides safe, dependable and sustainable supply of ^{18}F-Fluoride for ^{18}FDG and other low-volume clinical PET imaging. Its compactness and automation need minimal space and manpower. Radiation dose rate in cyclotron suite and personal dosimetry were also found within safe limits. Its Dose-on-Demand workflow offers a new concept of Personalized Dose Preparation which is currently not possible with a conventional cyclotron.

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Keywords

Cyclotron ● Positron Emission Tomography Computed Tomography ● Fluorodeoxyglucose ^{18}F

Introduction

Positron emission tomography with computerized tomography (PET/CT) is considered as one the most innovative inventions in the healthcare of current century. In the last 20 years, ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-based PET/CT has become standard of care for diagnosis, staging, restaging and therapeutic monitoring of many common cancers [1]. In recent years, ^{18}FDG PET/CT has also en-

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tered from research laboratories into clinical neurology and cardiology arenas. There has been a robust growth in installation of PET/CT scanners and also cyclotrons in both developed and developing countries. Majority of installed medical cyclotrons are being used for the production of ^{18}FDG due to its established clinical role in oncology and relatively longer half-life of ^{18}F (110 minute). However, humongous cost of infrastructure required for its synthesis like cyclotron, radiosynthesis, quality control and dispensing units are the primary factors favoring centralized supply (by ^{18}FDG vendors) to other PET/CT facilities without an on-site cyclotron [2]. In developed countries, this strategy has been successful to provide a sustainable ^{18}FDG supply to facilities within the distribution grid. Although, healthcare facilities in remote areas have to send their patients to facilities having an on-site cyclotron or lying within the distribution grid of vendors. However, in Pakistan this centralized model of ^{18}FDG supply despite 03 functioning cyclotrons could not be materialized primarily due to logistic issues. Due to these reasons and lack of space required for a conventional cyclotron in the proposed PET/CT facility, Aga Khan University Hospital (AKUH), Karachi, Pakistan acquired a Dose-on-Demand Biomarker Generator (BG-75) developed by ABT Molecular Imaging, USA in December 2015. AKUH is the first PET/CT facility of country which acquired this smallest footprint mini-cyclotron; in this paper we share our experience regarding performance, reliability and safety of BG-75 Dose-on-Demand generator producing ^{18}F- and ^{18}FDG in the first 12 months after commissioning.

Material and Methods

Study Duration and Data Collection

This study was conducted at PET/CT Imaging Services, Department of Radiology, Aga Khan University Hospital, Karachi, Pakistan. AKUH is the first Joint Commission International Accreditation (JCIA) healthcare facility of Pakistan since 2009. The data was collected from December 2015 till November 2016 about number of cyclotron runs/day, ^{18}F-Fluoride yield, ^{18}FDG produced/run, QC of each batch and number of patients being performed during the study period. In addition, we also collected the data regarding radiation survey monitoring of cyclotron plus radiochemistry module for secondary neutron, gamma radiation and also personal dosimetry of radiation workers involved in operating cyclotron, radiosynthesis and QC modules.

Biomarker Generator (BG-75)

This Dose-on-Demand Biomarker Generator (BG-75, ABT Molecular Imaging, Knoxville, TN, USA) was installed in the basement level-2 of oncology services in 1 of 3 purpose-built bunkers for linear accelerators and became operational in December 2015. It consists of a self-shielded mini-cyclotron and a fully automated, aseptic card-based dose synthesis and quality control modules.

Mini-Cyclotron

The cyclotron has 7.5 MeV proton beam, positive ion with an internal beam current of $\leq 5\mu A$, three non-simultaneous internal targets and a 1.2 Tesla magnet to generate a magnetic field (1.8 T_{max}). The physical dimension of the shielded cyclotron is 2.39 m in diameter (unshielded: 1.25 m) and a height of 1.63 m (unshielded: 0.37 m). The self-shielding of BG-75 is composed of high density boronated concrete and polyethylene with 0.64 cm outer steel exterior.

Microchemistry Module

The microchemistry component of BG-75 is a compact, programmable and fully automated module which greatly simplifies the chemical processes for biomarker radiolabeling, which otherwise would require a hot chemistry lab, dispensing unit and a dedicated 6-8 members team of cyclotron operator, technician, radiochemist and radio-pharmacist. The self-shielded (2.5cm lead walls) micro-chemistry mod-

ule was housed in a separate room adjacent to cyclotron vault. Once ^{18}F-Fluoride (^{18}F-) is generated in the cyclotron, it is pushed to the microchemistry system loaded with a disposable Dose Synthesis Card (DSC) for a single run and a reagents kit containing chemicals for radio-labelling reaction (one kit for 8 runs). When the cycle (mean: 27 minute) is complete, synthesized dose of ^{18}FDG in 3 cc liquid is delivered to a tungsten shielded vial or syringe ready for patient injection, and a small sample (180 µl) is delivered to the automated QC system for qualification testing.

QC Module

This module is a very compact, integrated and automated system which was also housed in radiochemistry room as well. It uses embedded methods, micro-sensors and small scale analytics (HPLC, radiation detector, pH meter) to perform pH, filter integrity, residual volatile organics and radiochemical purity tests as required by US pharmacopeia and FDA standards to qualify radiopharmaceuticals for human injection and clinical applications. Few manual tests were performed for endotoxins, sterility and radionuclide purity. The whole QC process took about 20 minute and system generated a QC report for each batch of ^{18}FDG.

Production of ^{18}F- and ^{18}FDG

^{18}F- was produced through ^{18}O(p,n)^{18}F nuclear reaction by bombarding 95% enriched [^{18}O]H_2O target (280 µl) with a 7.5 MeV proton beam with an average current of 4.5 µA for 60 minutes using Tantalum target. However, on some days we also had runs with shorter bombardment times (30-40 minute to accommodate unscheduled 1-2 patients at the end of day) or longer bombardment time (>60 minute in initial phase only). At the end of bombardment (EoB), the [^{18}F]F- containing [^{18}O] water was transferred to a reaction vial placed within the DSC in the radiochemistry module. Using nucleophilic substitution of mannose triflate precursor, ^{18}FDG was synthesized and followed by acid hydrolysis [3]. The product was purified by cartridge-based solid phase extraction, then passed through 0.2 µm filter and delivered into a sterile tungsten-shielded syringe or vial.

QC of ^{18}FDG

An aliquot of each batch of ^{18}FDG was used for performing automated QC tests including pH, radiochemical identity/purity, Kryptofix 2.2.2, residual solvents (acetonitrile and ethanol) and filter integrity test. Manually performed test upon each batch included physical appearance, radionuclidic purity (using multichannel analyzer), endotoxin and sterility tests. The average duration of QC run was 20 minutes. After 20, the system generated a detailed QC report of each ^{18}FDG dose. Once all QC parameters (automated and manual, except sterility test which takes 14 days to get result) of ^{18}FDG batch were found within US pharmacopeia and FDA guidelines [4], it was released to be administered to patients.

Radiation Safety and Monitoring of Radiation Workers

The cyclotron suite was inspected by Pakistan Nuclear Regulatory Authority (PNRA) after a scrupulous and tedious testing process, approved the facility for clinical use in December 2015. The secondary neutrons around the cyclotron shield in the cyclotron room were monitored with a calibrated Neutron Meter 12-4, Ludlum Measurements, Inc., Sweetwater, TX). The gamma dose level around cyclotron shield and radiochemistry unit was measured using survey meter (Inspector Exp+, SE International, Inc, Summertown, TN, USA). These measurements were acquired for the first and last runs of cyclotron on every functional day. Personal dosimetry of radiation workers operating cyclotron and radiochemistry unit was performed with optically stimulated luminescent (OSL) dosimeter. We have a team of 02 qualified members to run cyclotron suite. One operator is having more than 5 years of experience in working on a conventional cyclotron

and the other is having 20 years of experience in working in radiopharmacy and has had hands-on training upon another ABT facility in Varna, Bulgaria.

Statistical Analysis

Data was analyzed using commercially available statistical package for social sciences (SPSS version 17; SPSS Inc., Chicago, Illinois, USA). Continuous variables were described by mean ± SD and respective ranges were needed. Scatter plots were analyzed to determine the trend of ^{18}FDG doses and ^{18}F-Fluoride yield against number of cyclotron runs, respectively.

Results

During study period, we scheduled to perform ^{18}FDG PET/CT imaging and CT-based radiotherapy planning using the same scanner (Celesteion, Toshiba, Japan) on alternate day basis (3 days for PET/CT imaging and 2 days for CT planning). Total number of functional days for PET/CT imaging was 167 for which BG-75 Dose-on-Demand generator was operational. In these 167 operational days, 545 cyclotron runs were performed (Table 1).

BG-75 Yield of ^{18}F Fluoride

During 167 functional days, 545 runs were done with an average of 03 ±01 runs/day. Overall, we did a 60-minute bombardment of [^{18}O] H_2O with a beam current of 4.5 µA. However, longer bombardment time (about 90 minutes) was tried in early study period (1st two months for few runs) and shorter runs (30-40 minute) for 5th and 6th runs infrequently to accommodate unscheduled 1-2 patients. The average yield at EoB (Minimum - Maximum) of [^{18}F] Fluoride (in mCi) for 1st to 6th runs was 31.34 (12 - 52), 38.89 (15 - 58), 39.82 (19 - 59), 38.06 (14 - 60), 34.15 (23 - 44) and 23.82 (22 - 26; only 02 runs.), respectively (Figure 1). This is to mention that the trend of minimal yield was dominant in the first 20 functional days. These yields were lower than vendor's specification of 1 mCi/minute. In the early phase of study period (2nd month after commissioning), target was ruptured twice on two consecutive days. First rupture was due to the use of a beam current of 5.5µA which was higher than vendor's recommendation and longer bombardment time (>60 minute). Target was rebuilt but ruptured during the very first bombardment due to inadequate placement. However, after subsequent rebuild, no further rupture of target happened during study period.

[^{18}F]FDG Synthesis

At EoB, [^{18}F] Fluoride was transferred to DSC placed in radiochemistry module for an aseptic and fully automated ^{18}FDG synthesis using necleophilic substitution of mannose triflate precursor. The median synthesis time was 27 minute when an average 21.34 ±5.75

Table 1: BG-75 Dose-on-Demand generator: Technical data of one year.

Technical Variables	Values
Total number of functional Days	167
Total number of Patients performed	1370
Total runs of cyclotron in 167 days	545
QC/chemistry failures in 545 runs	29 (05%)
Functional runs of cyclotron in 167 days (545-29)	516
Average run of cyclotron/day	03 ± 01
Average number of patients' FDG doses / day (mean ± SD)	08 ± 03
Average number of patient's FDG doses / run cyclotron	03 ± 01
Average FDG yield /run in mCi (mean ± SD)	21.34 ± 5.75
Average patients' dose in mCi/run (mean ± SD)	8.28 ± 2.54

SD= Standard Deviation

QC=Quality Control

FDG=Fluorodeoxyglucose

mCi=Milli Curie

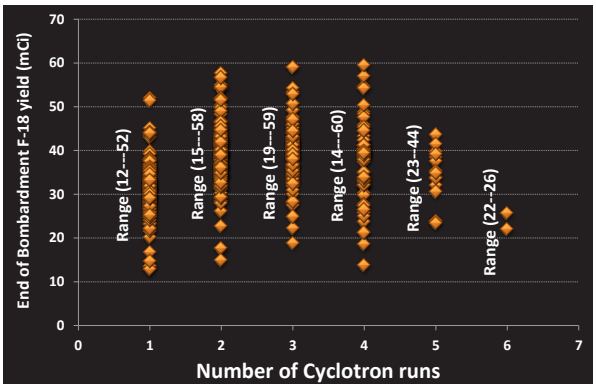

Figure 1: Scatter plot of End of Bombardment (EoB) yield of F-18 against numbers of runs of cyclotron during study period.

mCi of ^{18}FDG in 3 ml volume was shifted into a tungsten-shielded vial or syringe. The first ^{18}FDG dose of the day was released at 107th minute from the start of the first bombardment till the end of radio-synthesis and QC in a tandem fashion. But subsequent doses were available after an average of 60 minutes due to the start of next bombardment in cyclotron with ongoing radiosynthesis of previous production in a synchronous fashion (Figure 2).

QC and Chemistry Failure

During the study period, 29 (5.3%) runs were found unsuccessful due to either chemistry failure [15 (2.7%)] or QC failure [14 (2.6%)] (Table 1). The most common cause of chemistry failure was evaporation of activity to gas trap in the early phase of study. The common reasons for QC failure were higher acetonitrile (08/14) and Kryptofix 2.2.2 (11/14) concentrations found on system generated QC reports of each ^{18}FDG batch. These batches were not released and discarded.

Radiation Exposure and Personal Dosimetry

During study period, no measureable secondary neutron detection was found on neu-

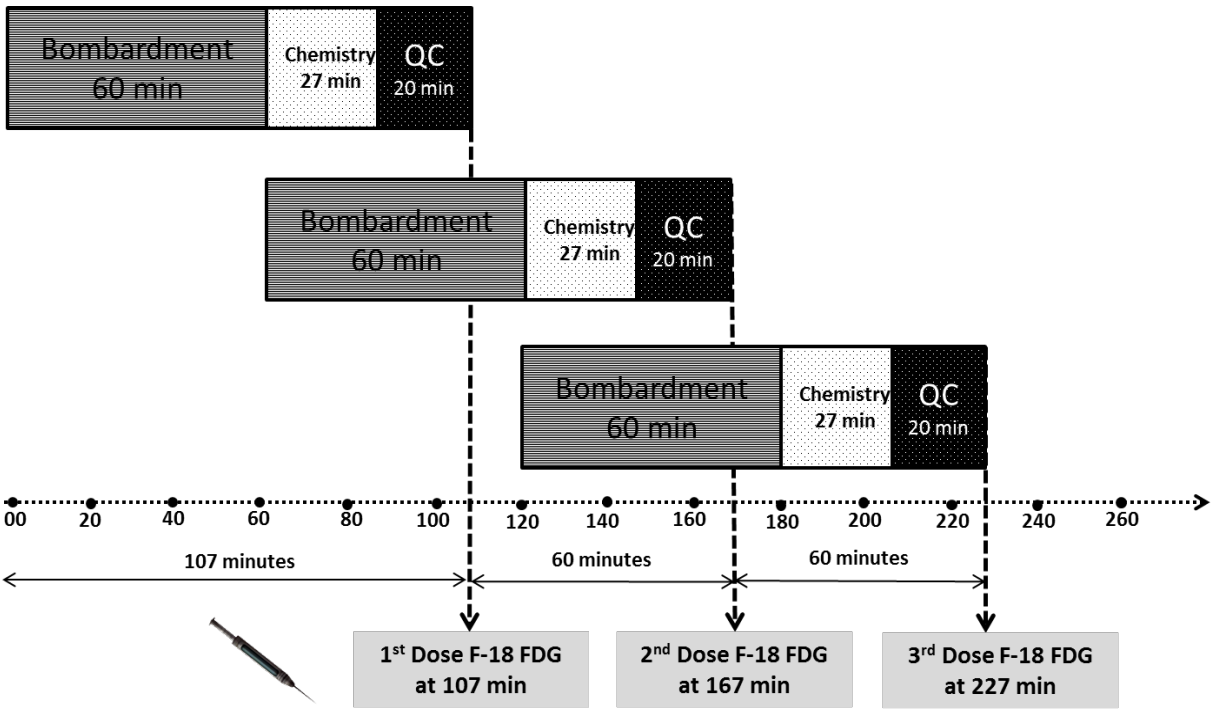

Figure 2: Workflow of cyclotron from bombardment, radiochemistry and quality control of final ^{18}FDG production for three successive runs of the cyclotron.

tron detector. The gamma ray dose rate at 1 meter around shield during bombardment was in the range of 1.35 - 2.9 µSv (0.135-0.29 milli-Roentgen/hour). These values were well below the vendor's specification of 1 mR/h. The cumulative effective doses received by two operators during study period using OSL badges were 1.18 and 0.96 mSv/12 months.

Clinical Imaging

During study period, 516 batches of ^{18}FDG out of 545 cyclotron runs (29 batches were not released due to chemistry and QC failures) were released for clinical use. Total 1370 patients underwent clinical imaging with released batches of ^{18}FDG (Table 1). As per EANM guidelines, we administered 0.08 - 0.14 mCi/kg of ^{18}FDG to these patients [5]. The average administered dose of ^{18}FDG/patient was 8.28 ±2.54 mCi. Average number of patients' ^{18}FDG doses per run and per day was 03 ±01 and 08 ±03, respectively (Table 1 and Figure 3).

Discussion

PET/CT imaging is considered as the most important landmark in the medical imaging which has stepped into the clinical arena from research laboratories and now considered as a standard of care for many cancers,

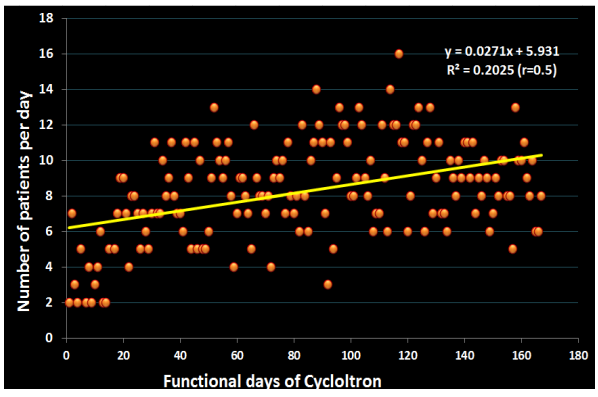

Figure 3: Scatter plot for number of patients performed with ^{18}FDG doses against functional days of cyclotron.

dementia and coronary artery diseases. Due to the shorter half-lives of positron emitters, either an on-site or off-site cyclotron within the distribution grid is mandatory. However, cost, space and manpower integrated with a conventional cyclotron facility are enormous. Due to this single fact, we see thousands of PET/CT installations, but about 1200 cyclotrons installations worldwide [6]. Therefore, low cost, small footprint cyclotrons with integrated radiochemistry unit needing minimum manpower are very much required to mitigate this gap and to ensure a dependable and sustainable supply of PET tracers worldwide.

AKUH, Karachi is the first JCIA healthcare facility of Pakistan which installed the first Dose-on-Demand BG-75 Generator of country to support the clinical ^{18}FDG-based PET/CT imaging. The small footprint of BG-75 cyclotron is due to the configuration of a positive ion beam of 7.5 MeV with an internal target. Use of card-based synthesis of ^{18}FDG ensures compactness of radiosynthesis unit. Due to this overall compactness and effective shielding, BG-75 system was easily accommodated in our proposed bunker without major civil work and significant cost. This was not feasible for a conventional cyclotron which would have required space to house cyclotron, hot cell, radiochemistry, QC laboratory and dispensing units. The workflow of BG-75 from bombardment to synthesis of ^{18}FDG is fully automated and starts with a push of button and ends with a prepared ^{18}FDG dose in a shielded vial or syringe. The major QC tests are performed in an automated mode with minimal human input for radio-nuclidic purity, sterility and endotoxin. Only 1-2 operators are required to perform the entire process in contrary to a team of 6-8 operators required for a conventional cyclotron facility. This again has contributed to a huge saving under the head of annual running cost.

The average EoB yield of [^{18}F] Flouride was less than vendor's specification of 1 mCi/minute bombardment. Cyclotron yield is depen-

dent upon beam energy, beam current, bombardment time, purity of enriched water and target material [7]. The reason for lower yield in current study was use of a beam current 4.5 μA, while vendor's specified yield was at a beam current of 5 μA. In early study period (first 02 months after commissioning), we tried few runs with longer bombardment time (> 60 minute) using a beam current of 5.5 μA, but that ended up in target rupture. This caused transient suspension of services and radiation exposure to engineers involved in target rebuild process. Therefore, during remaining study period, we decided to use a beam current of 4.5 μA and did not have further target rupture in the study period. Our findings are in concordance with Awasthi et al, who also had yields of 0.92 and 0.61 mCi/min for beam current of 5 and 3.8 μA, respectively during optimization process [8]. The average yield of 1st run was lower than 2nd -5th runs, and this was also observed by Awasthi et al. [8] and most likely due to the stabilization of beam current in subsequent runs. The average yield of 6th run (only 02 runs) was the lowest among all runs which was due to shorter bombardment time to accommodate unscheduled patients at the end of a functional day. However, Awasthi et al. [8] reported a higher yield in later phase of their study which could be due to the use of different beam energies and beam currents.

The chemistry and QC failure rate during study period was 5.3% (29/545 runs) which was much frequent in early phase after commissioning. Our frequency is much smaller than that reported by Awasthi et al. [8] (overall 13%; 71% of which is related to DSC failures). The reason for lower frequency in current study is most likely due to the modification in design by the vendor. According to a recently published study by a commercial FDG production site, authors have reported a dispensing failure of 3% of total 2286 synthesis over a 9-year period [9]. We strongly feel that higher QC and chemistry failures were teething problems as these have reduced later phases of study.

Shielding of cyclotron and radiosynthesis unit was found effective in keeping radiation level within permissible limits by the statutory body during its inspection. Furthermore, daily area monitoring during bombardment (average 1 hr bombardment time and beam current up to 5.5 μA) and radiosynthesis for secondary neutron and gamma rays were also within permissible limits. This was also reflected by personal cumulative effective doses received by two operators during study period (1.18 and 0.96 mSv/12 months). This is smaller than average effective dose of 1.64 ±0.014 mSv/yr received by chemist group worked at cyclotron facility in Islamic Republic of Iran [10].

Since the radiosynthesis module uses prepackaged and certified DSC and reagent kits followed by a battery of QC tests upon each ^{18}FDG batch, national nuclear regulatory authority found the end product meeting current good manufacturing practice (cGMP) [11]. During study period, we had done 1370 patients with various malignancies by complying EANM dose recommendations (0.08 – 0.14 mCi/kg or 3-5 MBq/kg)[5]. We found that an average of 3 ±01 runs/day was adequate to complete imaging of 8 ±03 patients. The quality of imaging was found excellent and comparable to other imaging sites using a conventional cyclotron. Most importantly, the acquisition of BG-75 system provided a safe, sustainable and dependable supply of PET tracer for clinical imaging. Its uniquely small footprint cyclotron with fully automated radiosynthesis and QC modules was the best fit for available space without need for major modification in our facility design. The unique shielding of cyclotron and radiosynthesis module ensured exposure rate within cyclotron suite and effective doses received by operators well below the permissible limits. This Dose-on-Demand workflow enables the user to prepare ^{18}FDG doses once patient arrives and found eligible to undergo imaging. In case of no-show or rescheduling of appointment, a

futile run could be saved which is not possible with conventional cyclotron. Similarly, in case of abrupt PET/CT scanner failure, further cyclotron runs can be avoided to save the cost which is again impossible with conventional cyclotron which makes 10-25 doses of ^{18}FDG in a single run. Furthermore, ^{18}F-Fluoride produced by BG-75 can also be used to label low volume but highly specific PET probes like fluoromisonidazole (FMISO) and Prostate Specific Membrane Antigen (PSMA).

Conclusion

We conclude that ABT BG-75 provides a safe, dependable and sustainable supply of ^{18}F-Fluoride and ^{18}FDG for clinical imaging. Its compact design, shielding and fully automated workflow ensures minimal space and only 1-2 operators to run the production facility. Radiation dose rate in cyclotron suite and personal dosimetry were also found within safe limits. It also provides a cost effective supply of ^{18}F-Fluoride for low volume PET tracers like FMISO and PSMA. Its Dose-on-Demand workflow offers a new concept of Personalized Dose Preparation which is currently impossible with a conventional cyclotron.

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Conflict of Interest

No financial or institutional conflict of interest.

References

1. Avril NE, Weber WA. Monitoring response to treatment in patients utilizing PET. *Radiol Clin North Am*. 2005;**43**:189-204. PubMed PMID: 15693656.
2. Uz Zaman M, Fatima N, Sajjad Z, Zaman U, Tahseen R, Zaman A. 18FDG synthesis and supply: a journey from existing centralized to future decentralized models. *Asian Pac J Cancer Prev.* 2014;**15**:10057-9. PubMed PMID: 25556425.
3. Hamacher K, Coenen HH, Stöcklin G. Efficient stereospecific synthesis of no-carrier-added 2-[18F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine*. 1986;**27**:235-8.
4. United States Pharmacopeial C. The United States pharmacopeia. the national formulary. 36th revision 31st ed. Rockville: United States Pharmacopeial Convention; 2013.
5. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging*. 2015;**42**:328-54. doi: 10.1007/s00259-014-2961-x. PubMed PMID: 25452219; PubMed Central PMCID: PMC4315529.
6. Goethals PE, Zimmermann RG. Cyclotrons used in nuclear medicine world market report & directory. 2015th ed; 2015.
7. Radioisotopes I, No RS [Internet]. Cyclotron Produced Radionuclides: Guidance on Facility Design and Production of [18F] Fluorodeoxyglucose (FDG). [cited 2017 June 12]. Available from: http://www-pub.iaea.org/mtcd/publications/pdf/pub1515_web.pdf
8. Awasthi V, Watson J, Gali H, Matlock G, McFarland A, Bailey J, et al. A "dose on demand" Biomarker Generator for automated production of [(18)F]F(-) and [(18)F]FDG. *Appl Radiat Isot*. 2014;**89**:167-75. doi: 10.1016/j.apradiso.2014.02.015. PubMed PMID: 24650573.
9. Gaspar L, Reich M, Kassai Z, Macasek F, Rodrigo L, Kruzliak P, et al. Long-term quality assurance of [(18)F]-fluorodeoxyglucose (FDG) manufacturing. *Am J Nucl Med Mol Imaging*. 2016;**6**:154-65. PubMed PMID: 27508102; PubMed Central PMCID: PMC4965520.
10. Zargan S, Ghafarian P, Monfared AS, Sharafi A, Bakhshayeshkaram M, Ay M. Evaluation of radiation exposure to staff and environment dose from [18F]-FDG in PET/CT and cyclotron center using thermoluminescent dosimetry. *Journal of biomedical physics & engineering*. 2017;**7**:1.
11. Schwarz SW, Dick D, VanBrocklin HF, Hoffman JM. Regulatory Requirements for PET Drug Production. *J Nucl Med*. 2014;**55**:1132-7. doi: 10.2967/jnumed.113.132472. PubMed PMID: 24914057.