Productivity of [18F] PSMA in relation to initial [18F] activities: A Preliminary Cyclotron-Based Study

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ABSTRACT

Prostate cancer is becoming clinical concern in Bangladesh, raising the need for advanced imaging for accurate diagnosis and patient management. [^{18}F] PSMA-1007 is an attractive PET radiopharmaceutical because the longer half-life of ^{18}F (Fluorine-18) supports centralized cyclotron-based production and distribution to nearby PET centres.

A preliminary comparison was performed using two production runs carried out under high- and moderate-activity conditions at EOB. In the first run, the EOB activity was 4648 mCi. Despite the higher starting activity, the final product activity was only 95 mCi, with a decay-corrected activity of 126.99 mCi and a decay-corrected radiochemical yield (RCY) of 2.7%. In the second run, the EOB activity was lower at 2300 mCi, yet the final product activity increased to 1200 mCi, with a decay-corrected activity of 1604 mCi and a decay-corrected RCY of 69.75%.

These findings indicate that higher starting activity does not necessarily result in successful [^{18}F] PSMA-1007 production. Rather, excessive starting activity may adversely affect the radiolabelling process. In contrast, a moderate starting activity may provide more favourable conditions for efficient labelling and product recovery. This preliminary study highlights the importance of optimizing EOB activity to achieve reliable cyclotron-based production of [^{18}F] PSMA-1007 for routine prostate cancer imaging services in Bangladesh.

Keywords: Prostate cancer, [^{18}F] PSMA-1007, End of bombardment; Radiochemical yield, Cyclotron.

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INTRODUCTION

Prostate cancer is one of the most common malignancies in men and has become increasingly important in both diagnostic imaging and treatment planning. In Bangladesh, the disease may still receive less attention than some other major cancers. This cancer is diagnosed at advanced stages, leading to much poorer survival than other malignancies in Bangladesh. Though in a limited-resource diagnostic facility, more concern should be given in the diagnosis of these malignancies (1, 2). Prostate-specific membrane antigen (PSMA)-targeted positron emission tomography and computed tomography (PET-CT) imaging has become the gold standard for diagnosis, staging, and restaging of prostate cancer. [^{18}F] PSMA PET-CT has shown better lesion detection than the commonly used [^{18}F] FDG PET-CT scan, particularly in recurrent disease and in patients with low PSA levels. Although ^{68}Ga (Gallium)-labeled PSMA radiotracers are widely used, their generator-based production has limited batch capacity. For this reason, there has been strong interest in radiofluorinated PSMA ligands, especially [^{18}F] PSMA-1007. Because fluorine-18 has a longer half-life and is cyclotron-produced, it is more suitable for larger batch production and regional distribution. In addition, [^{18}F] PSMA-1007 shows minimal urinary excretion, which is particularly helpful for detecting lesions in the pelvis and prostate bed (3, 4). Beside this, [^{18}F] PSMA-1007 PET-CT scan has improved clinical patient management. In patients with biochemical recurrence after radical prostatectomy, it detects meaningful observation even at low PSA levels. Men with biochemical recurrence, confirmed by [^{18}F] PSMA-1007 PET-CT scan, can directly influence treatment plans. Therefore, access to a reliable PSMA radiopharmaceutical is not only a technical matter but also an important clinical issue for personalized prostate cancer care (5).

As a developing nation with limited medical resources, [^{18}F] PSMA-1007 PET-CT scan has special practical significance. The first reported synthesis and quality control assessment of [^{18}F] PSMA-1007 at NINMAS showed that local production is feasible, meeting European Pharmacopoeia-related quality requirements for clinical use. This was an important milestone for the country because centralized cyclotron-based production can support not only on-site patient imaging but also distribution to nearby PET-CT centers (6). However, for such a system to function smoothly in routine service, production must be reproducible, efficient, and stable from batch to batch. Regular synthesis of [^{18}F] PSMA-1007 depends on several technical and chemical factors. Precursor quality, cassette and tubing material, purification procedures, synthesizer performance, etc. can all influence yield and product quality (7).

Among these, the starting activity of ^{18}F at end of bombardment (EOB) is especially important. In principle, a higher starting activity might be expected to produce a higher final activity. In practice, this linearity is not observed. Low and medium starting activities produced radiochemical yields of about 52%, whereas high starting activity reduced yield to about 40%, with no proportional gain in the final available activity. This concluded that increasing the starting 18F activity does not necessarily improve final [^{18}F] PSMA-1007 output and that an intermediate activity range may offer the best balance between beam time, yield, purity, and number of available doses (8).

This study is highly relevant for medical cyclotron facilities where radiopharmaceuticals are distributed to all nearby PET-CT centers. Excessive starting activity may create an unfavorable radiochemical environment and may increase losses during labeling, purification, and formulation (9). Optimization of EOB activity is a key step in establishing dependable cyclotron-based production of [^{18}F] PSMA-1007. In a country like Bangladesh, where radiopharmaceutical production must be efficient enough to support growing clinical demand, identifying the most suitable starting activity is essential for improving reliability, reducing failed batches, and strengthening prostate cancer imaging services. This study aimed to evaluate how different starting ^{18}F activities at EOB influence the final product activity and decay-corrected radiochemical yield of [^{18}F] PSMA-1007, with the goal of identifying a more suitable production condition for routine clinical use.

METHODS

This study was carried out at the Cyclotron facility of the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Bangladesh Medical University (BMU) Campus, Shahbag, Dhaka. The study was based on regular production runs of [^{18}F] PSMA-1007 performed using a fully automated, cassette-based synthesis module (Synthera®). [18F] Fluoride was produced in a medical cyclotron (18/9 MeV IBA Cyclone, Belgium) and used for automated radiosynthesis of [^{18}F] PSMA-1007 by direct labeling of the PSMA-1007 precursor (Huayi Isotopes Co.). The irradiated target solution is passed through a Quaternary Methyl Ammonium (QMA) cartridge (Huayi Isotopes Co.), and ^{18}O (Oxygen) water is recovered. The trapped ^{18}F is eluted in the reaction vial and undergoes one-step radiofluorination with the PSMA-1007 precursor (Huayi Isotopes Co.). The final [^{18}F] PSMA-1007 is purified by solid-phase extraction cartridges (C18ec, SCX column, Huayi Isotopes Co.) and collected in collection vial.

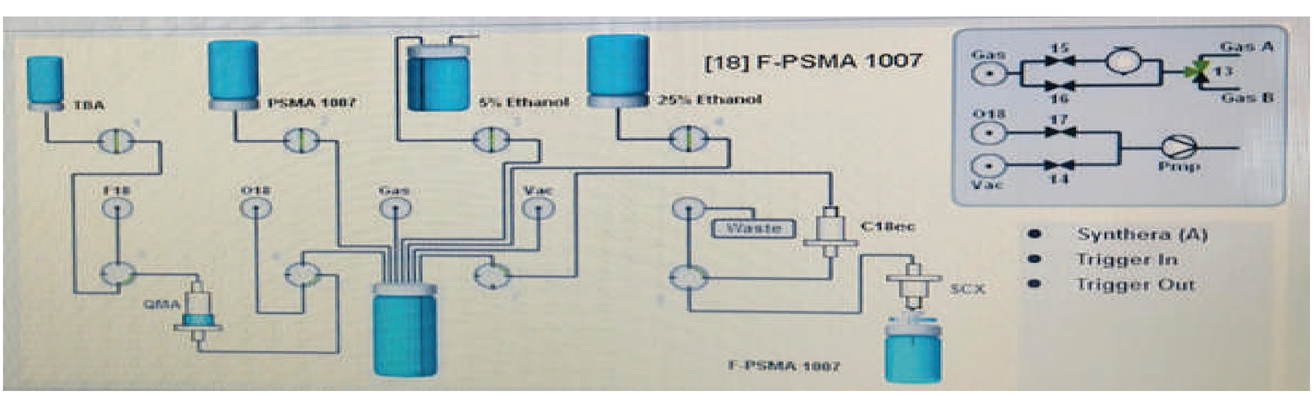

Figure 1: The schematic diagram of [^{18}F] PSMA-1007 synthesis unit by using Synthera®

For the present study, two separate runs were performed under routine regular conditions at two different activities at the end of bombardment (EOB). One was 4648 mCi, considered a high activity condition, and another was 2300 mCi, considered a moderate activity condition. Aside from the difference in starting EOB activity, the synthesis workflow, production parameters, and general processing conditions were kept as the same as possible in order to find the influence of starting activity on the final production outcome. The decay-corrected final activity and decay-corrected radiochemical yield (RCY) were also calculated for these two different productions.

RESULTS

Two production runs of [^{18}F] PSMA-1007 performed under separate starting ^{18}F activities at EOB showed a remarkable difference in final product activity and production efficiency.

Table 1: The schematic diagram of [^{18}F] PSMA-1007 synthesis unit by using Synthera®

Parameter	High-activity run	Moderate-activity run
Activity at EOB (mCi)	4648	2300
Final product activity (mCi)	95	1200
Decay-corrected final activity (mCi)	126.99	1604
Decay-corrected RCY (%)	2.7	69.75

In the first run, the activity at EOB was 4648 mCi which was representing the high-activity condition. Despite this high starting activity, the final produced [^{18}F] PSMA-1007 activity was only 95 mCi. After decay correction, the final activity was 126.99 mCi, and the decay-corrected radiochemical yield (RCY) was 2.7%. In the second run, the activity at EOB was lower, at 2300 mCi, representing the moderate-activity condition. However, in contrast to the first run, the final produced [^{18}F] PSMA-1007 activity was 1200 mCi. The decay-corrected final activity was 1604 mCi, and the decay-corrected RCY reached 69.75%.

A direct comparison of the two runs showed that the moderate-activity condition produced substantially better results than the high-activity condition. Although the second run started with approximately 50.5% lower EOB activity than the first run, it produced about 12.6 times higher final activity and about 12.6 times higher decay-corrected final activity. Most importantly, the decay-corrected RCY in the moderate-activity run was about 25.8 times higher than that of the high-activity run. Higher starting activity at EOB did not result in higher final [^{18}F] PSMA-1007 production under the present operating conditions. Instead, the moderate starting activity was associated with markedly superior product recovery and radiochemical yield.

DISCUSSION

The present study showed an inverse relationship between starting 18F activity at EOB and the final production performance of [^{18}F] PSMA-1007. This finding is vital because it represents that, under routine cyclotron production conditions, a higher starting activity does not automatically translate into a higher final product output. Instead, an excessive starting activity may significantly compromise labeling efficiency and product recovery (10).

This observation is similar to previously published production studies of [^{18}F] PSMA-1007 with low, medium, and high activity at EOB. For low activity at EOB, the yield was 52%, whereas for high activity at EOB, the yield was decreased to 40%. Intermediate activity range as the most practical option for balancing yield, purity, beam time, and number of deliverable doses (8). Similarly, one-step GMP-compliant production of [^{18}F] PSMA-1007 could achieve radiochemical yields in the range of 25-80%, while the initial NINMAS report described a radiochemical yield of 46.85% with a 40-minute synthesis time. In this context, the 69.75%

decay-corrected RCY observed in the moderate-activity run of the present study is well within, and even toward the upper side of, the yield range, whereas the 2.7% yield of the high-activity run is clearly far below expected routine performance (3, 6, 11).

Excessive starting activity resulted in a poor production outcome in the present study. This is probable because of the high radioactive burden during the labeling phase, which may create an unfavorable radiochemical environment that promotes side reactions, precursor degradation, and finally, incomplete labeling (12). It was found that the final [^{18}F] PSMA-1007 product did not show radiolysis up to 8 hours after the end of synthesis; this does not exclude the possibility that transient radiolytic stress occurred earlier during the reaction, purification, and formulation stages when activity concentration was highest. Therefore, the present findings are similar to the idea that high starting activity may adversely affect the reaction system before the final product is stabilized. In this study, radiolysis, precursor instability, and process-related loss were not directly measured, so these mechanisms should be considered probable explanations rather than proven causes (9, 13). Another important point is that [^{18}F] PSMA-1007 production is also sensitive to multiple technical variables other than starting activity alone. It was found that cassette material, tubing type, and precursor significantly influenced activity yield and radiochemical purity. Fluoro-elastomer tubing increased non-radioactive PSMA-1007 contamination and reduced molar activity, whereas the use of silicone tubing together with an acetic acid salt precursor improved overall production performance. It also found that the automated synthesis platform itself can influence [^{18}F] PSMA-1007 output, with one module producing a substantially higher decay-corrected radiochemical yield than another under otherwise comparable conditions. These findings strongly suggest that the poor result observed in the high-activity run of the present study may not have been caused by activity alone but by interaction between high activity and process limitations such as cassette behavior, purification losses, precursor condition, module-specific performance, etc. (14).

Smooth and regular production of [^{18}F] PSMA-1007 is vital for Bangladesh. The main practical cause of ^{18}F-labeled PSMA tracers is that they are well suited to centralized cyclotron production and regional distribution, unlike generator-based approaches that have more limited production capacity. It is established that [^{18}F] PSMA-1007 can be produced in batch sizes sufficient not only for on-site use but also for supply to nearby PET-CT centers. This advantage is especially important in a country like Bangladesh where access to advanced prostate cancer imaging is still emerging and where smooth radiopharmaceutical production can directly expand patient management. The first successful synthesis and quality control report from NINMAS already established that [^{18}F] PSMA-1007 production is feasible in Bangladesh. The present study adds an important operational message that reliable service expansion depends not simply on producing the highest possible activity at EOB but on identifying an activity range that preserves labeling efficiency and minimizes batch failure (15, 16).

The discussion of clinical relevance is strengthened by the growing importance of [^{18}F] PSMA-1007 PET-CT in patient management. Several studies showed high detection efficacy with relatively low PSA levels in recurrent prostate cancer and changed management in more than half of men with biochemical recurrence. These clinical advantages mean that production optimization is not only a radiochemistry problem but also a patient-care issue. A failed or poor-yield batch may reduce scan availability, delay diagnosis, and limit appropriate staging or restaging in patients who may benefit from PSMA-targeted imaging. Therefore, improving radiochemical reliability at the production level has direct downstream importance for oncology service delivery (4, 17).

LIMITATIONS

This study has several limitations. First, it is based on only two production data points, so the findings should be interpreted as a preliminary operational observation rather than a definitive optimization study. Second, no direct measurement was performed for precursor degradation, cartridge retention, residual activity in waste, or reaction-phase radiolysis, all of which could have helped identify the exact reason for the very low yield in the high-activity run. Future studies should include a larger number of syntheses across several predefined EOB activity ranges, with simultaneous recording of beam time, synthesis duration, cartridge-associated losses, radiochemical purity, stability, precursor condition, and module performance.

Despite these limitations, the present study provides a practical and clinically meaningful message that [^{18}F] PSMA-1007 production is highly sensitive to operational conditions and that moderate starting activity may provide a more favorable balance between chemical efficiency and final product recovery than excessively high activity. For a medical cyclotron facility aiming to establish dependable routine service, the goal should not be maximum EOB activity alone but optimum EOB activity. In this preliminary experience, the moderate-activity condition clearly performed better and appears to be a more suitable starting point for reliable cyclotron-based production of [^{18}F] PSMA-1007 for prostate cancer imaging.

CONCLUSION

Successful synthesis of [^{18}F] PSMA-1007 is not determined by high starting 18F activity, which was observed in this study. The run performed with moderate EOB activity produced a remarkable higher final product activity and a much higher decay-corrected radiochemical yield than the run performed with high EOB activity. These findings reveal that elevated starting activity may negatively affect labeling efficiency and overall product recovery, whereas a moderate activity range may provide a more favorable condition for reliable synthesis. This observation is highly important for medical cyclotron facilities, especially in developing countries like Bangladesh, where smooth and regular radiopharmaceutical production is vital for meeting the demand of PET-CT imaging services. Optimization of the starting activity of ^{18}F at EOB may improve batch success, reduce production failure, and support more consistent availability of [^{18}F] PSMA-1007 for prostate cancer imaging. Although this study is based on a limited number of production runs, it provides an important operational insight and a useful basis for larger future studies aimed at defining the optimum production window for routine clinical use.

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