Nuclear Medicine and Molecular Imaging (2019) 53:102–107
https://doi.org/10.1007/s13139-019-00590-1

PERSPECTIVE

ISSN (print) 1869-3482
ISSN (online) 1869-3474

Theranostics in Bangladesh: Current Status, Challenges, and Future Perspective

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Received: 11 February 2019 / Revised: 21 February 2019 / Accepted: 22 February 2019 / Published online: 2 April 2019

Abstract

Background and Current Status of Theranostics Therapeutic nuclear medicine (NM) in Bangladesh began in the early 1980s with the application of radioactive iodine for treatment of thyroid cancer and primary hyperthyroidism. Since then, NM practice has remarkably developed in the country with the advancement of instrumentation, radiopharmacy, and information technology. The government took the initiative to establish four PET-CT centers at different NM centers, including one at the National Institute of Nuclear Medicine and Allied Sciences (NINMAS). A further development is the installation of a cyclotron center (18-MeV cyclotron) at NINMAS by the government's fund. Currently, NM is providing good health services to oncology patients throughout the country. More than 20 NM centers are functioning in different parts of the country, and therapeutic NM has an important place. However, conventional radioactive iodine still remains the major theranostic application.

Challenges and Future Perspective The expansion and development of therapeutic NM for other cancers have been limited due to a number of challenging factors. A brief overview of the history and current status of NM in Bangladesh is presented here with an examination of factors that pose as obstacles to the introduction and development of new therapeutic technologies. Finally, future perspectives are discussed with ways to mitigate existing problems and challenges.

Keywords Theranostics · Bangladesh · Radioactive iodine therapy · Bangladesh atomic energy commission · National Institute of Nuclear Medicine and Allied Sciences

Brief History and Current Status of Nuclear Medicine in Bangladesh

Years before nuclear medicine (NM) became a popularly recognized medical field in Bangladesh, it existed as "radioisotope center," which was set up by the Pakistan Atomic Energy Commission (PAEC) in 1958 at the Dhaka Medical College Hospital premises. Later in 1962, the center was officially inaugurated as the Nuclear Medicine Centre, Dhaka, but its activity remained more or less quiescent [1–3]. After independence war of 1970, Bangladesh Atomic Energy Commission (BAEC) was formed in 1973, and NM became a daughter organization of BAEC. However, the actual significance of the field of NM became recognized after the Institute of Nuclear Medicine now renamed as National Institute of Nuclear Medicine and Allied Sciences (NINMAS) was established in 1980 at Bangabandhu Sheikh Mujib Medical University (BSMMU) Campus. Since then, the growth and popularity of NM continued at an exponential rate with high demand for both diagnostic and therapeutic NM services. At present, more than 20 NM centers together with a national institute, i.e., NINMAS are functioning in different parts of country. More centers are also being under establishment and planned for the near future (Fig. 1) [4]. NINMAS however remains the apex referral center for NM procedures in Bangladesh, and the Institute continues to take the lead in establishing new technologies and in setting the goals.

Recently, the government took the initiative to establish four PET-CT units at different NM centers of the country, including two at the NINMAS. A further development is the installation of a cyclotron (18-MeV cyclotron) at NINMAS by the government's own fund.

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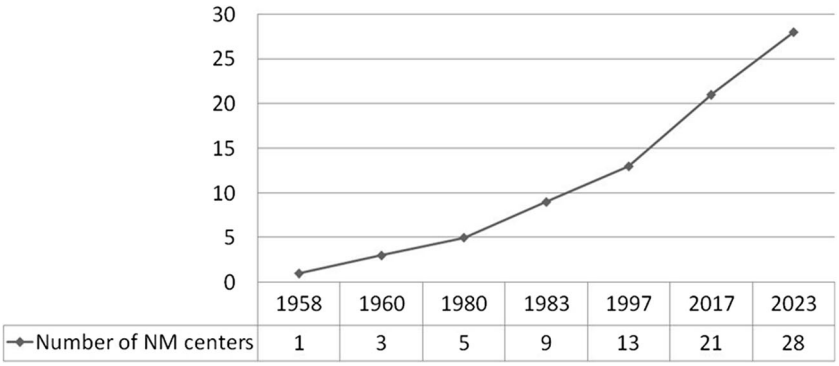

Fig. 1 Increasing number of nuclear medicine facilities/ institutes with time in Bangladesh

Therapeutic NM in Bangladesh began in the early 1980s with the application of radioactive iodine (^{131}I) in thyroid cancer and primary hyperthyroidism. The first radioactive iodine therapy (RAIT) for thyroid cancer was given at NINMAS in 1980 (NINMAS records), and it soon became a routine procedure in the management of differentiated thyroid cancer (DTC) and primary hyperthyroidism both at NINMAS and other NM centers in the country [5, 6].

Another radionuclide that was used for therapy at NINMAS was the reactor-produced ^{32}P with a physical half-life of 14.3 days. In the early years after the establishment of the Nuclear Medicine Institute, this pure beta-emitting radionuclide was used regularly for the treatment of myeloproliferative diseases, such as polycythaemia vera and essential thrombocythaemia. It was a simple convenient form of therapy with a fixed orally administered dose ranging from 2 to 5 mCi. After therapy, blood counts were checked every month to assess response and exclude significant myelosuppression. In the absence of adequate response, the treatment was repeated. Unfortunately, the results of the patients treated could not be published due to loss of the documented data, but subjective evidence of good response with improved quality of life was reported in all the elderly patients who received treatment. This therapeutic approach was subsequently discontinued at NINMAS due to the apprehension of potential leukemic transformation in patients who received the radionuclide.

Brachytherapy with strontium-90 (^{90}Sr) applicator is the other form of therapy offered at NINMAS. The ^{90}Sr applicator is used in ocular diseases; for pterygium, a benign ocular condition and in ocular malignancy, such as superficial conjunctival squamous cell carcinoma. In pterygium, the β emitter is used within 24 h of surgical excision of the lesion and is applied in fractional doses over a few days. Data before 2007 is not available; but since January 2007, a total of 404 patients were treated for pterygium, and the follow-up results showed low recurrence rate of pterygium and no major complications. In superficial conjunctival squamous cell carcinoma, the ^{90}Sr source on a stand-off eye applicator is used to deliver a single dose (30 Gy) to the surgical bed within 2 days of surgery. Data available till 2007 (NINMAS records) showed about 30 patients who received the therapy at NINMAS with subsequent optimal disease control [7].

However, conventional radioactive iodine for imaging and therapy still remains the major theranostic application. Since 1980 until December 2018, a total of 6376 patients have received ^{131}I therapy for primary hyperthyroidism and 5876 patients for DTC at NINMAS. The weekly therapeutic disposal of NINMAS is about 10–20 patients for DTC and about 10–12 patients of primary hyperthyroidism. The NM facilities are mostly (more than 80%) located outside the capital city of the Dhaka. However, Figs. 2 and 3 reflect a centripetal flux of patients to the capital from all over the country with high patient loads in the NINMAS and Institute of Nuclear Medicine & Allied Sciences (INMAS), Dhaka. The percentages of given RAIT for DTC from NINMAS and INMAS, Dhaka are 50.3 and 15.57% compared with the other NM centers of the country.

The first official protocol for the management of DTC and primary hyperthyroidism with RAIT was formulated through a workshop organized by the Society of Nuclear Medicine, Bangladesh (SNMB) in 2001 and which was published in the Bangladesh Journal of Nuclear Medicine (BJNM) in 2002 [8]. Since then, a large number of patients were treated following the protocol, and huge information and experiences were obtained resulting a need to further upgrade the protocol. In 2014, the national guideline for RAIT of DTC and primary hyperthyroidism was proposed through a national conference of SNMB, which was approved, and after approval in 2015, the national guidelines were published in BJNM [6, 9].

Examination of Existing Facilities and Challenges at NINMAS

As mentioned above, NINMAS has been the forerunner in the country for introduction of new NM procedures.

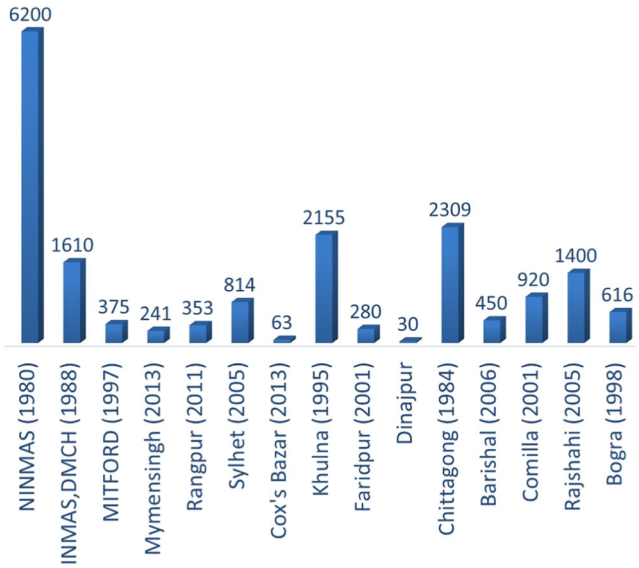

Fig. 2 Radioiodine treatment status of primary hyperthyroidism patients at NINMAS and INMASes till July 2018. Year in parenthesis indicates time point since data were available. A centripetal flux of patients to the capital from all over the country is apparent

However, with regard to theranostic medicine, radioiodine has been and is still the radiopharmaceutical that is used for therapy and imaging in thyroid diseases. Whereas the use of theranostic agents has been consistently increasing around the world, therapeutic NM in Bangladesh with regard to therapy has been very conventional to date. Reasons for the sluggish advancement in therapeutic NM in Bangladesh are manifold. Adedapo et al. have published a list of common challenges generally encountered in NM departments in developing countries [10]. Using a similar approach, we have attempted to re-examine here each of these challenges in context to Bangladesh.

Technical Challenges in Obtaining Radioisotopes

The technical challenges regarding the availability of radioisotopes are somewhat eased by local production of ^{99m}Tc generators and radioiodine, but sometimes, the local supply falls far short of the actual requirements due to the worldwide crisis/shortage of fission molybdenum (Mo). To meet these challenges, BAEC has taken the initiative to upgrade the existing TRIGA Mark II research reactor. Moreover, cold kits are always imported from abroad. Even though due to the bureaucratic processes and customs clearing issues, the timely smooth supply of kits are disrupted.

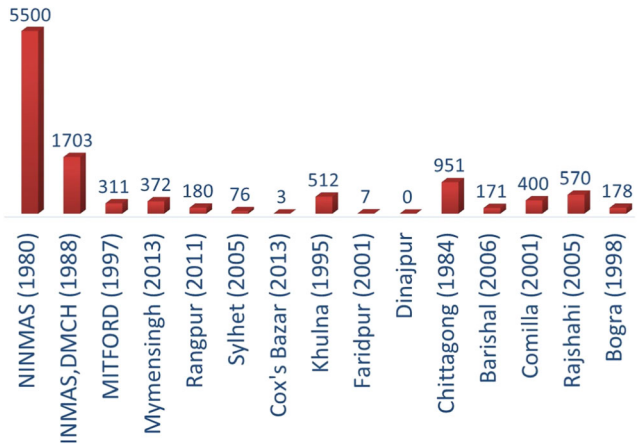

Fig. 3 Radioiodine treatment status of DTC patients at NINMAS and INMASes (till July 2018). The years since data were available are given in parenthesis. The percentage of given RAIT for DTC from NINMAS and INMAS, Dhaka, are 50.3% and 15.57% comparing to the other nuclear medicine centers of the country

Regarding PET radiopharmaceuticals, the only including PET radiopharmaceutical till now is ^{18}F-FDG, which is obtained locally from a cyclotron and radiopharmaceutical facility at a private center in Dhaka. However, NINMAS will soon have PET tracers from its own 18-MeV cyclotron and radiopharmaceutical center established by Bangladesh government fund under the supervision of BAEC and Ministry of Science & Technology (MOST).

Cyclotron operation and radiopharmaceutical production involve the participation of multi-disciplinary professionals. As a new user, the proficiency development of cyclotron operator, radiochemist, physicist, radiopharmacists, and engineers is very necessary to run the facility. With an 18-MeV cyclotron ^{18}F, ^{11}C, ^{15}O, and ^{13}N-labeled PET radiopharmaceuticals can be synthesized. Considering the importance of ^{18}F-FDG, the first priority is to produce ^{18}F and to synthesis ^{18}F-FDG to serve the patients. Synthesis of ^{18}F-NaF for the diagnosis of metastatic bone disease, ^{18}F-FLT, and ^{13}N-NH3 is also in the primary consideration. Synthesis of ^{11}C-acetate, ^{11}C-methionine, and ^{11}C-choline is also in the active consideration. With the development of solid target radiochemistry laboratory, we also have future plan to produce ^{124}I, ^{89}Zr, and ^{64}Cu. Hence, to make the best use of the cyclotron and to synthesize more specific tracer for carcinoma diagnosis, dedicated and expertise manpower with the intense knowledge on the components of cyclotron and working principle, hot cell customization, target and radioisotope delivery systems, synthesis chemistry, designing of synthesis chemistry module, radio pharmacy equipment, regularly requirements, radiopharmaceuticals quality control, and good manufacturing practices (GMP) are highly required.

Local production facilities with the assistance of the International Atomic Energy Agency (IAEA) TC project for the production of ^{177}Lu from ^{176}Lu in the research reactor and ^{90}Y from ^{90}Sr/^{90} Y generator are yet to be installed [11].

Electricity Supply

An interruption in the national power supply was a constant issue in Bangladesh. However, recently, the scenario has changed. NINMAS has installed an uninterrupted express line of power supply and also has full back-up generator to ensue uninterruptible power supply during functioning of the equipment.

Infrastructure and Equipment

In Bangladesh, currently, almost all NM centers are equipped with one or more SPECT or SPECT-CT cameras. NINMAS has been particularly strengthened recently with new SPECT, SPECT-CT cameras, and two PET-CT through an upgradation of government project. However, the existing number of facilities identified is inadequate in comparison with the large number of population in need of service [1, 12].

Information Technology

Telemedicine communication between doctors in the capital city and doctors/patients remote centers in Bangladesh has been developed and functioning. But NM practice has not yet been incorporated into telemedicine. Moreover, the picture of archiving and communication system is currently unavailable. So, there is much room for improvement in this field. Recently, under Asi@Connect Project of Korea and Seoul National University KOICA project, national and international network connections have build up communication in the country to enhance academic, clinical and research excellences, and remote seminars in the partner countries: Korea, Indonesia, and Vietnam.

Medical Physics Equipment

There are few limitations in the country like the unavailability of basic equipment (phantom, radiation sources) for quality control, radiation protection, and monitoring. The opportunities of research in the medical physics fields are also very limited.

Radiation Safety and Regulatory Clearance

Radiation safety is a challenge in NM practice. In Bangladesh, personnel monitors to all the occupational radiation workers are provided by the Bangladesh Atomic Energy Commission Regulatory Authority (BAERA) [13].

Commencement of a NM facility for administration of novel nuclear theranostics is at the custody of BAEC and MOST. The proposed facility like any other nuclear installation within Bangladesh should pass and remain under the scrutiny of BAERA. Current regulation of Directorate General of Drug Administration (DGDA) has detailed guideline for good clinical practice for trials on pharmaceutical products. However, no mention can be identified about radiopharmaceuticals or radionuclide therapeutic agents [14, 15].

Radiopharmacy

Basic radiopharmacy practice is available at NINMAS, but it is yet to reach a standardized level. With the installation of the cyclotron and PET radiopharmaceutical center, there will be

recruitment of more radiochemists, radiopharmacists, and optimized training programs in this field.

Human Resource

Human resource challenges in Bangladesh are similar to other developing countries as mentioned by Adedapo et al. [10]. With regard to referring physicians, there is always the problem where clinicians are unaware of the scope and limitation of a NM procedure. For example, the modus operandi for radioiodine therapy in DTC is often unknown to the primary physicians so the management of patients becomes somewhat complication. These can however be overcome by forming multidisciplinary groups and regular interdisciplinary meetings. At NINMAS, initiative has been taken for multidisciplinary collaborations. For NM physicians, physicists, radiopharmacist, and technologist, education and training are undisputed components. Proper training is an absolute prerequisite in order to render safe and reliable service to the patients. NINMAS has formal training and post-graduate courses only for doctors. Currently, there is very limited formal education or training system for NM technologists. The NM technologists are seemingly overoccupied by the patient load.

Future Perspectives

In Bangladesh, theranostic application in oncology other than thyroid cancer has not been developed as yet. Given the existent basic infrastructure at NINMAS, there is capacity for expansion of NM therapy to include the emerging new science of theranostics. Both immuno-PET and immuno-SPECT imaging can be done with the existent facilities. Histiochemistry laboratory for biomarker profiling is an absolute necessity. NINMAS has a good working relationship with the Histopathology Department in the BSMMU Hospital for this work. However, other molecular therapy-related laboratory facilities are required to establish at NINMAS with international collaboration for technology transfer.

Last but not least, quality training programs are indispensible to develop skill and competency. NINMAS would endeavor to form a core group of selected radiochemists, radiopharmacists, NM physicists, NM physicians, and technologist who can dedicate themselves to this specialized therapy in NM. This would enhance the practice of therapeutic NM in order to improve the quality of life of oncology patients.

The future perspective at NINMAS is therefore to work towards transition from conventional radionuclide to more personalized targeted therapy.

Conclusion

The NM physicians in Bangladesh are aware of the value of therapeutic NM in oncology. For years, they have been providing good health services to oncology patients throughout the country. However, conventional radioactive iodine for imaging and therapy remained the major application. It is time now for expansion of NM facilities to include the emerging new approach of theranostic in oncology. Since NINMAS is situated within a post-graduate medical university, it is surrounded by flourishing clinical, oncology, and laboratory facilities. Thus, there is good opportunity to introduce the new technology at this institute, which has the entire basic NM infrastructure. Once established, theranostic can be used in the management of particular oncological conditions in a more precise and cost effective way.

Acknowledgements The authors would like to thank the Thyroid Division of NINMAS and all Institutes of Nuclear Medicine and Allied Sciences (INMASes) under BAEC.

Compliance with Ethical Standards

Conflict of Interest Shamim MF Begum, Lutfun Nisa, and Azmal K. Sarker declare that they have no conflict of interest. There is no source of funding.

Ethical Approval This is a perspective article describing the summation information on the basis of retrospective data from different nuclear medicine institutes. Data were obtained with the consent of the institutes. Institutional basic data contain human participant involvement in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants during collection of the basic data in individual institute.

This article does not contain any studies with animals performed by any of the authors.

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