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COUNCIL OF NUCLEAR MEDICINE SCIENCE AND TECHNOLOGY, INDIA

NUCLEAR MEDICINE PHYSICISTS ASSOCIATION OF INDIA
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NEWSLETTER

REINVENTING FOR NEW MOMENTUM

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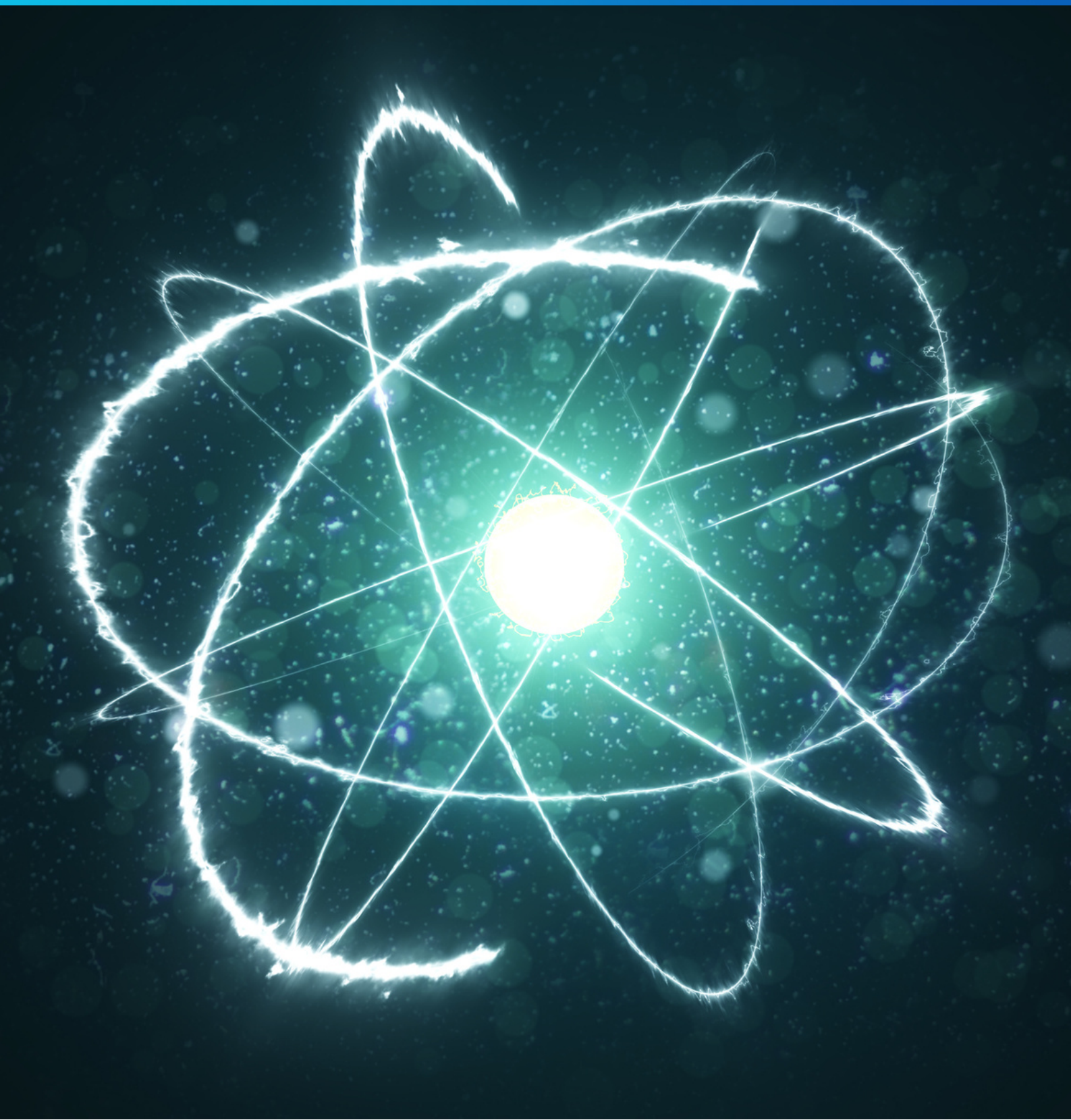

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Nuclear Medicine Physicists Association of India was established in the year 2007 to promote, protect and safeguard the interests and future of the Nuclear Medicine Physicists/Technologists fraternity and fulfil its duties towards the society. As of now, we have more than 400 members in the Society. The Society is managed by a team comprising of a President, Secretary, Treasurer and six Executive Committee members, who are elected by the life members of NMPAI once in two years.

The Society takes pride in completing fifteen years since inception and seek to grow leaps and bound academically and socially in the near future with continuous efforts of our eminent members/scientists and colleagues.

MR. SACHIN TAYAL
SECRETARY, NMPAI

ABOUT CNMST

The field of nuclear medicine is gradually evolving into molecular imaging and therapeutics. It is therefore inevitable that future training programs will have to place an even greater emphasis on technology, both in clinical and research settings. In order to advance healthcare in India, the Council's primary function is to establish and maintain standards of training and education that render nuclear medicine services to the people. By certifying individuals through psychometrically sound examinations, CNMST also promotes quality healthcare in the country.

The beginning is coming together, the progress is staying together, and the success is working together. CNMST is committed to bringing this all together.

DR. AMIT NAUTIYAL
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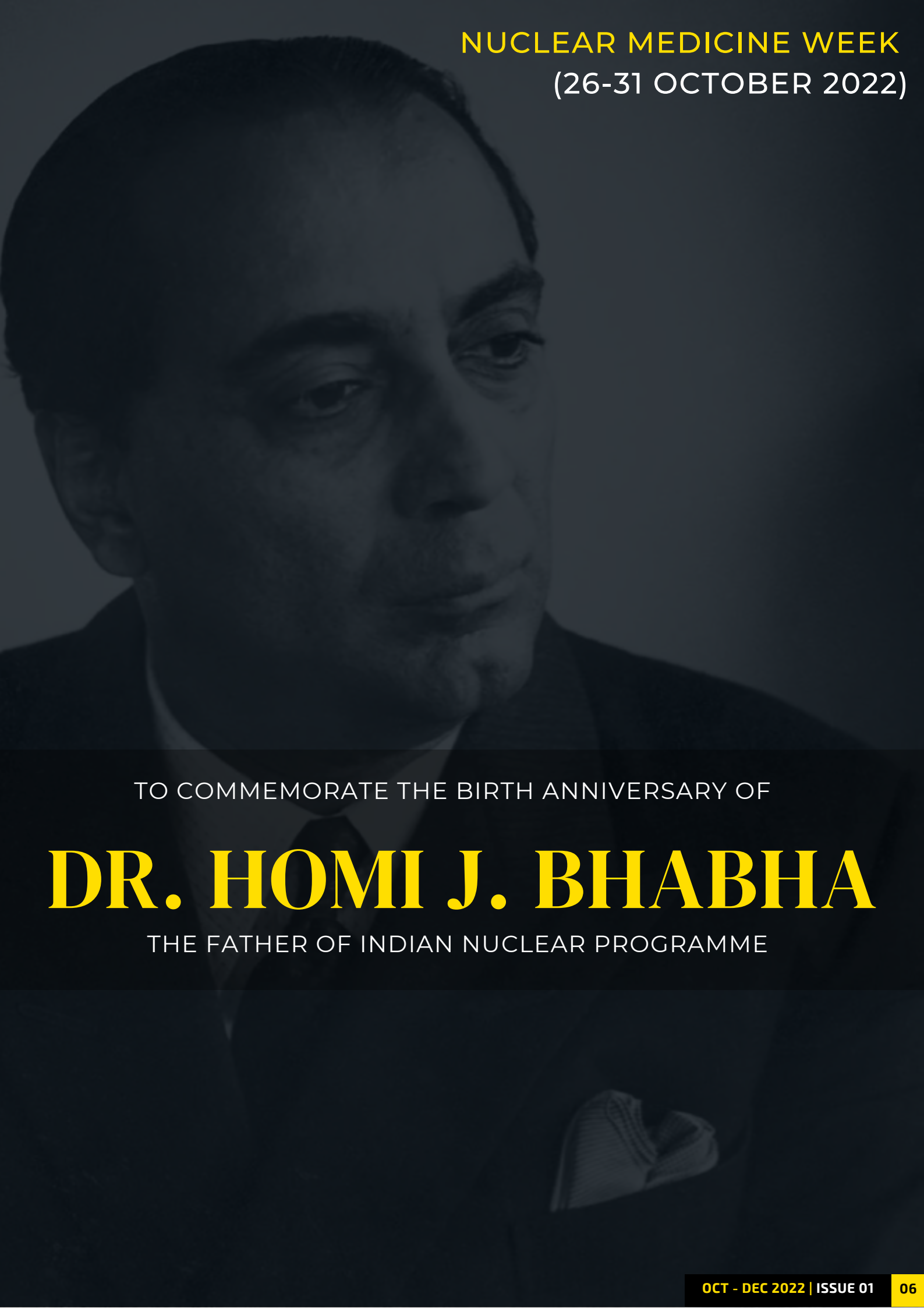

NUCLEAR MEDICINE WEEK
(26-31 OCTOBER 2022)

TO COMMEMORATE THE BIRTH ANNIVERSARY OF

DR. HOMI J. BHABHA

THE FATHER OF INDIAN NUCLEAR PROGRAMME

NUCLEAR MEDICINE WEEK (26-31 OCTOBER 2022)

Dr. Homi J Bhabha was an Indian physicist, The father of the Indian nuclear program. He was born on 30th Oct 1909 to a rich aristocratic family in Mumbai.

LIFE OF BHABHA

EDUCATION

At the age of 18, a young Homi joined Cambridge University to study mechanical engineering in accordance with his father's and uncle Dorab Tata's wish. But his strong interest in Physics made him extend his stay at Cambridge to complete another degree in the field. He received his doctorate in nuclear physics after his first scientific paper, **'The Absorption of Cosmic Radiation'**. **'Bhabha scattering'**, based on another one of his papers that explained electron-positron scattering, was named after him.

REORGANIZATION AND FOUNDATION OF INSTITUTES

He was the founding director of Tata Institute of Fundamental Research (TIFR) in 1945 and Trombay Atomic Energy Establishment (later renamed Bhabha Atomic Research Centre, by Prime Minister Indira Gandhi, in his memory). Bhabha was also a painter and a classical music and opera enthusiast, besides being an amateur botanist

In 1955, he was elected as the president of the first international conference on the Peaceful Uses of Atomic Energy, which was organized by the United Nations at Geneva.

DEATH

Homi Bhabha died in the Air India Flight 101 crash on January 24, 1966. Miscommunication between the Geneva Airport and the flight's pilot about the aircraft's position near the Mont Blanc mountain is the official reason of the crash. Several theories have been proposed for the air crash, including a conspiracy theory claiming that the Central Intelligence Agency (CIA) was involved in order to paralyze India's nuclear program -- but none have been proven.

To pay our homage to the father of Indian nuclear program, we celebrate the Nuclear Medicine week in the last week of October.

Dr. Ankit Watts
Secretary HQ SNM - India

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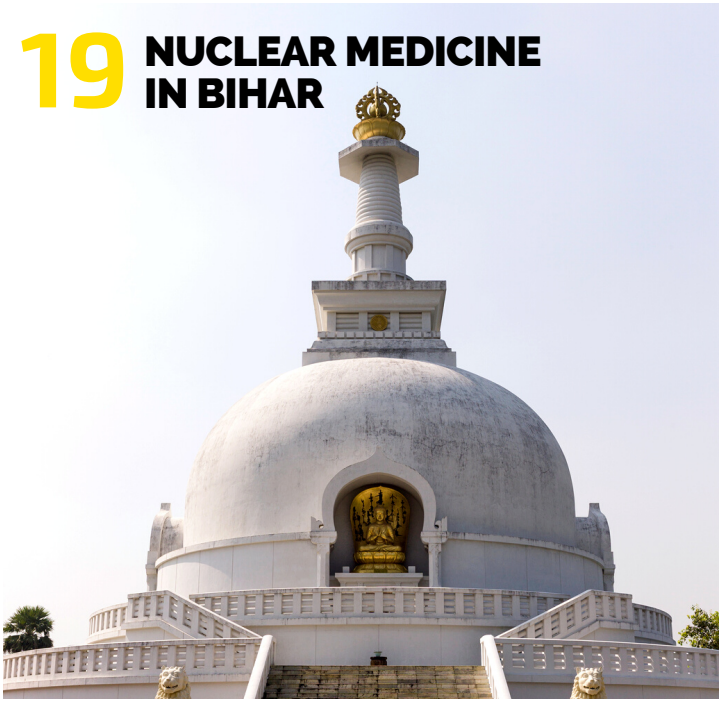

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Statistical Parametric Mapping (SPM) analysis of FDG-PET studies in Autoimmune Encephalitis

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INTRODUCTION

Autoimmune Encephalitis (AIE) is an immune-mediated response triggered by tumors, infections or it may be cryptogenic and is associated with the presence of antibodies against cell surface antigens (CSAab), synaptic antigens (SyAab) or intraneuronal antigens (INAab), also known as onconeural antibodies [1].

The diagnosis of non-infectious, autoimmune-mediated encephalitis is generally based on clinical symptoms, detection of specific anti-neuronal antibodies on serum and/or cerebrospinal fluid (CSF) sampling, electroencephalography (EEG), cerebral magnetic resonance imaging (MRI) and F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) [2].

FDG-PET is used to visualize neuronal glycolytic metabolic activity, which increases during brain inflammation or decreases in specific regions of the brain due to neuronal dysfunction. In AIE, a mixed pattern of basal ganglia hypermetabolism with cortical hypometabolism has been described [3].

Statistical Parametric Mapping (SPM) (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running on a MATLAB (MathWorks) platform can be used to analyze and compare cortical and subcortical brain metabolism to a healthy control group at a voxel level [4], thus providing voxel based image statistics.

SPM serves as useful diagnostic aid along with visual interpretation of FDG-PET in AIE, especially when MRI is normal [5] or in supporting clinical and MRI findings while antibody results are awaited.

It also has potential to evaluate response to therapy and for monitoring suspected disease recurrence.

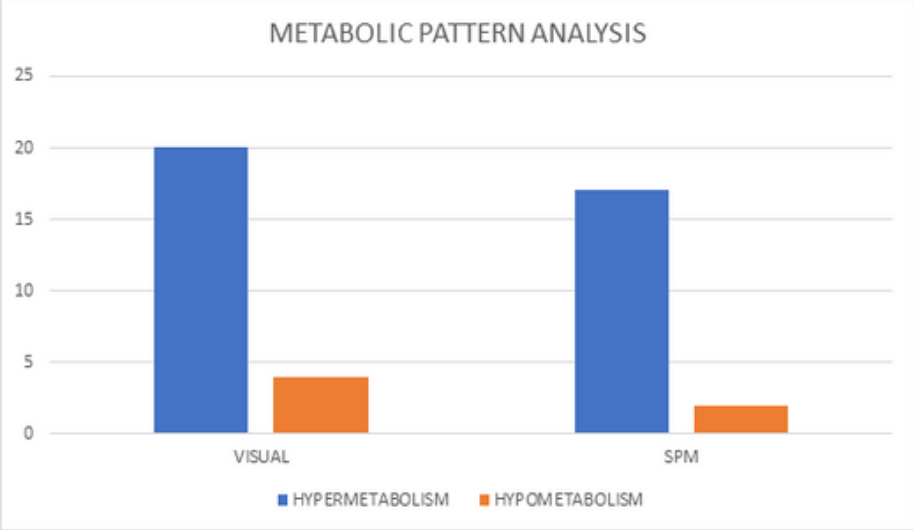
Thus, computer-supported SPM reading may be especially useful to support the qualitative findings in AIE.

METHODOLOGY

Each patients PET dicom files were retrieved from MMWP work station (Siemens). The dicom images were converted to NIfTI-1.1(.nii) format using SPM-12 (Functional Imaging Laboratory, Wellcome Centre for Human Neuroimaging, University College London, UK). The images were spatially normalized and smoothed by an isotropic 10-mm full width half maximum filter. SPM analysis using general linear model was undertaken and each patient was compared statistically to the reference group of 28 healthy control subjects using a two-sample t-test. The measurements were assumed to be independent and have unequal variance between levels. Proportional scaling to the global mean was used to minimize inter subject variability. Proportional scaling basically scales each image according to a reference count, which is the global brain activity to a physiologically realistic value of 50 ml/dl/min. Hence, single-case SPM analysis essentially compares regional differences in relative glucose metabolism. At the end, the SPM.mat file containing the specified design matrix was generated. Using this file, contrasts were defined, thus providing a map of voxels with statistically significant ($p < 0.05$) higher (hypermetabolism) or lower (hypometabolism) activity in comparison to the control group are mapped using summer or winter colours respectively. These t-maps were overlayed onto the MRI template in SPM and these canonical maps were be displayed for interpretation which is very objective and robust [6]

RESULTS

A total of 39 patients with clinical suspicion of AIE were included for this analysis with mean age 38.4 ± 21.6 years with a median age of 30 years (range: 9 – 75 years).
Metabolic patterns were documented from visual analysis and SPM. The areas of cortical and subcortical hypermetabolism and hypometabolism were compared for visual and SPM analysis of FDG-PET scans in AIE (Bar graph).



BAR GRAPH 3: METABOLIC PATTERNS OF BASAL GANGLIA IN THE AIE PATIENTS.

Cohen's Kappa statistic for concordance between visual and SPM evaluation of FDG-PET images in AIE is shown below [7].

Table 1: Visual and SPM analysis for metabolism.

BASAL GANGLIA	CONCORDANCE %	KAPPA COEFFICIENT	AGREEMENTS
HYPERMETABOLISM	92.30	0.84	Almost perfect
HYPOMETABOLISM	94.87	0.64	Substantial

Hypermetabolism was seen predominantly in the basal ganglia and hypermetabolism and hypometabolism detected on SPM (17/39 cases and 2/39 cases) showed almost perfect and substantial concordance between visual analysis.

CONCLUSION

SPM analysis showed good concordance with visual analysis for demonstrating basal ganglia hypermetabolism and cortical hypometabolism in AIE. Though visual evaluation is most commonly performed in the routine clinical setting for the reporting of FDG-PET scans in AIE, objective evaluation using voxel-based, data driven robust techniques would definitely enhance interpretation.

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Transferring Medical Imaging data to cloud - Future of data storage

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INTRODUCTION

Medical imaging data is very important and must be stored in a safe and accessible manner. Initially, images were stored in the form of hard copies. Later on due to massive technological advancements over the last few years, several options for storing medical images became available which include magnetic tape, optical media, spinning disks and solid state drives. [1]
Healthcare service providers need to store and retrieve medical imaging data as and when required for viewing and analysis purpose. This data, if required needs to be shared with other institutions. Furthermore, the data must be accessible for remote viewing. [2]
Institutes usually invest heavily while purchasing new medical imaging equipment with all the latest possible features, but at the same time, they do not show much interest to go for the latest and upgraded data storage and retrieval system. [3]

PACS : Picture archiving and communication systems (PACS) is one of the most commonly used storage device system which provides convenient access to medical imaging data and is cost effective.A PACS usually consist of four major components: A) Imaging Device B) A secure network to transmit data C) A reliable storage media D) Workstation for viewing and analysis.PACS are generally used by individual departments. However if there is network of hospitals or even a large institution having various departments, it becomes difficult to have multiple logins and viewing multiple windows across all the system. [4]

VNAs (Vendor Neutral Archive) : Similar to PACS, VNAs also use DICOM-based storing of medical images. The added advantage of VNAs is, they allow organizations to integrate the viewing and storage of digital health data regardless of vendor restrictions. [5]

Cloud for storage of medical imaging data : Traditionally, most of the Institutes prefer data storage facilities at their own place but with the advancement of technology, nowadays many institutions are using cloud data storage. Cloud storage is basically a cloud computing model in which data is stored on remote servers and accessed over the internet or through a dedicated secure network connection. It reduces maintenance costs and enable the access of data at any given place and time. [6]

Cloud-based storage systems are considerably less expensive compared to onsite PACS systems, as they don't require storage hardware or physical servers. They have higher storage capacity that can be increased at any time. Cloud based data storage has lower risk of losing data as compare to onsite PACS system, where the patient information is vulnerable to any hardware damage.

Despite these advantages, majority of healthcare institutes still hesitate to move on the cloud based storage, as the data servers not available locally so there is always fear of data confidentiality or data theft and secondly there is always the chance of potential performance issues due to network issues.[7]

Cloud with Local host- a Hybrid approach : The problem of local server has been overcome with Hybrid approach, where a user uses a local server that communicates with the cloud storage. Local server stores the most frequently accessed data to provide faster access while communicating with cloud storage. [8]

Future Prospects : The Medical Imaging field has been known for itsinnovation, improvement and continuous development. Cloud based storing of Medical imaging data can be used toditalize patient' health records that can be accessed from anywhere leading to better patient management care.Hence the Cloud based storage of Medical imaging data is the key to future.

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Is low activity 18F-FDG whole Body PET/CT feasible in Lymphoma patients with conventional PET/CT?

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INTRODUCTION

Lymphomas are heterogeneous group of malignancies that arise from clonal proliferation of B-cell, T-cell and natural killer (NK) cells [1-3]. It is a form of cancer that develops in the lymphatic system. Broadly, it is categorized into two types: Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL) [2-4]. HL is detected in the lymph nodes of the neck and mediastinum frequently and around 5% appears in extranodal sites. However,about 30% of NHL is found in extranodal sites. NHL is the more frequent of the two and accounts for 85% of all lymphomas [1,5]. The main etiological features of the lymphoma are: Helicobacter pylori (MALT lymphoma), Borrelia burgdorferi, Chlamydia psittaci, Campylobacter jejuni, human T- cell lymphotropic virus (adult T- cell leukemia/lymphoma), hepatitis C (lymphoplasmacytic lymphoma, diffuse large B-cell lymphoma and marginal zone lymphoma), human herpes virus 8 (primary effusion lymphoma & Castleman disease) [6-8].

As per GLOBOCAN 2020 statistics, worldwide, the age standardized incidence rate of HL was 0.43% while for NHL, the age-standardized incidence rate was 2.8%. In India, the occurrence of HL in the population was 5,677 & 2,938 per 100,000 for males and females respectively, while for NHL was 15,884 & 7,918 per 100,000 for males and females, respectively [9]. Histopathology is the gold standard for the diagnosis of lymphoma [10, 11]. The anatomical modalities (CT & MRI) are less potent in identifying bone marrow involvement due to a lack of functional information, which may influence the disease staging [5].

18F-FDG PET/CT plays a pivotal role in the detection of lymphoma. PET/CT has the capacity to detect metabolic changes in malignant cells even before there are any evident structural abnormalities [12]. In general, the imaging with 18F-FDG is routinely done at least 60 minutes after intravenous injection of standard activity of 370MBq (10mCi) with a scan time of 2-3 minutes per bed for at least 8–9 beds. High radiation exposure to radiation-sensitive populations such as infants, children, and adolescents, as well as in patients who need repeated scans to monitor treatment response, the general public, and radiation personnel, is our main concern [13]. Also, there are certain places having scarce availability of 18F-FDG due to non-availability of cyclotron and space constraints. This study is aimed to develop a new protocol by using low-activity 18F-FDG in lymphoma patients without compromising the image quality and scan information and thereby decreasing the radiation exposure to the radiation worker and general public.

METHODOLOGY

The scans were performed on GE Discovery 710 PET/CT scanner (Boston, Massachusetts, USA).A PET/CT acquisition was performed after an intravenous injection of 111-185MBq (3-5mCi) of 18F-FDG. A CT scan acquisition was performed first. After the CT scan, PET acquisition was acquired for 5 minutes per bed position for at least 8 to 9 beds depending on the height of the patient. Image analysis was done for the evaluation of the median, range, and standard deviation of SUVmean of the liver, SUVmean, SUVmax of the blood pool, SUVmax, and tumor to background ratio (TBR) of the lesion. Images were quantitatively and visually analysed by two nuclear medicine physicians with at least 3 years of experience in PET/CT reporting. A five-point Likert scale was used for assessing the subjective image quality and evaluating the concordance and discordance between the readers. The readers suggested the image score ≥3 had acceptable image quality and was useful for patient diagnosis.

RESULTS

A total of 10 patients (6 men; 4 women) were enrolled prospectively in this study, with a mean age of 41.60 ± 15.81 years and a body mass index (BMI) of 21.64 ± 3.09kg/m2. The mean activity of 18F-FDG administered was 149.11 ± 14.61MBq (4.03 ± 0.39mCi) and acquired the PET/CT scan with 5 min per bed position at 60 min post-injection.

The median SUVmax and SUVmean of lesion were 2.74 (range 0.30-23.73) and 1.18 (range 0.30-6.25), respectively. The median TBRmax and TBRmean of lesions were 2.24 (range 0.30–20.45) and 1.87 (range 0.34-5.79), respectively. A five-point Likert scale was used for the subjective scoring of the PET/CT images. Table 1 shows the values of the subjective image quality scores.

Table 1. Subjective image quality scoring

Subject	Reader 1 scoring	Reader 2 scoring
1	3	5
2	3	4
3	4	5
4	3	4
5	3	4
6	3	4
7	4	4
8	3	4
9	3	5
10	3	4
Mean ± SD	**3.20 ± 0.40**	**4.3 ± 0.45**

Table 2. Reader's image quality scoring

Image quality score	Score 1 Very poor	Score 2 Poor	Score 3 Average	Score 4 Good	Score 5 Excellent
Reader 1	0	0	8	2	0
Reader 2	0	0	0	7	3

The above table 1 mentioned that the subjective scoring was concorded only in a single patient (patient 7, table 1 and figure 1) and had discordance in 9 patients (figure 2). Table 1 suggests the mean score of 3.20 ± 0.40 by reader 1 and 4.3 ± 0.45 by reader 2. Most of the image quality scores were ≥3 points, thus meeting the needs of clinical diagnosis. Further, the readers suggested the image score ≥3 had acceptable image quality and was useful for patient diagnosis.

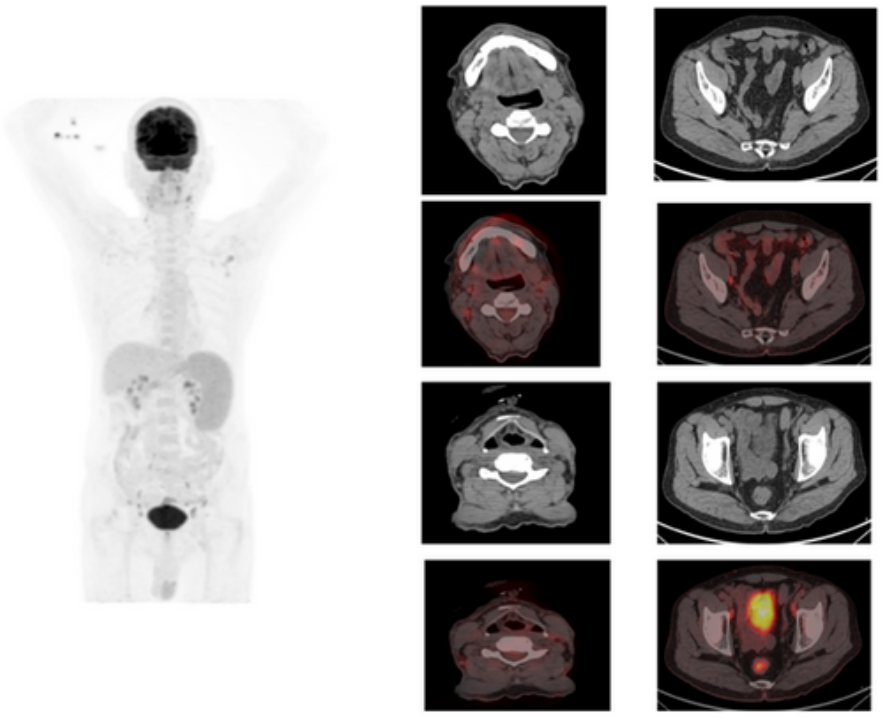

Figure 1A : 66-year-old male with histopathologically confirmed mantle cell lymphoma with chief complaints of loss of appetite. Low activity [162.8MBq (4mCi)] whole body 18F-FDG PET/CT imaging performed at 60 minutes post-injection with 5 minutes per bed position showed metabolically active bilateral cervical, axillary, inguinal, and external iliac lymph nodes along with splenic involvement. Both readers gave a subjective score ≥3, which suggests good image quality.

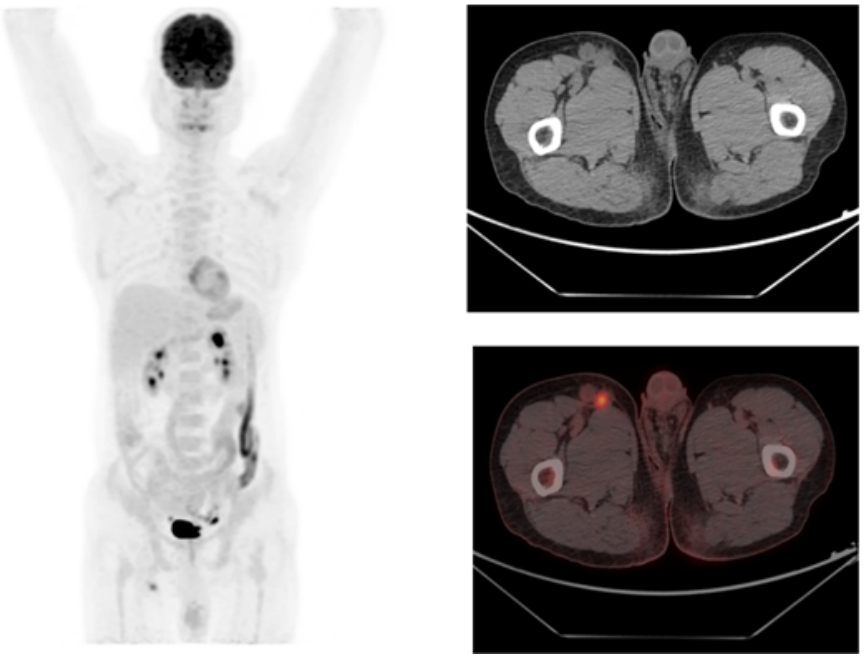

Figure 2A : 40-year-old male with histopathologically confirmed follicular lymphoma with post-3 cycles of chemotherapy. Low dose [148MBq (4mCi)] whole body 18F-FDG PET/CT imaging performed at 60 minutes post-injection with 5 minutes per bed position showed a metabolically active right inguinal lymph node (Deauville 4). A Likert score ≥3 was given by both readers, suggesting good image quality.

Thus, the results suggested a sufficient and acceptable imaging quality of whole-body PET/CT with low-dose 111-185MBq (3-5mCi) 18F-FDG in lymphoma could be achieved in our above-described protocol for PET/CT scan and is feasible for clinical application.

CONCLUSION

Our study can be used effectively in diagnostic centres with a lower patient load. Hence, we can improve image quality by increasing the imaging time. Therefore, our study is supposed to develop a new protocol by using low-activity 18F-FDG in lymphoma patients without compromising the image quality and lesion detectability in lymphoma patients and might reduce the radiation exposure to the patient, general public, and personnel.

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Expansion of Nuclear Medicine in Bihar

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Nuclear Medicine is a branch of medicine that deals with the use of artificially produced radioisotopes for research, diagnostic, therapeutic and investigative purposes. The equipments used in nuclear medicine department mainly consists of planar gamma camera, single photon emission computed tomography (SPECT-CT), positron emission tomography (PET-CT), medical cyclotron, radiochemistry modules, thyroid uptake probe, dose calibrator, area monitor, portable survey meter, pocket dosimeter. Nuclear Medicine is one of the most emerging branches of medical science. It is flourishing just like explosion in almost all parts of India including Patna, an eastern city of India.

Patna the capital of Bihar accounts for ~2% of total state population (2,529,478 vs 12,4,900,000). So there is a huge demand of department of Nuclear Medicine at Patna. Previously, people had to go to other distant cities like Delhi/Mumbai for the nuclear medicine facilities, but the scenario has been changing in recent past. At present there are dedicated 5 cancer treatment centres at Patna, catering not only the need of patients from Bihar state but from the other neighbouring state as well. The city has 4 SPECT-CT/gamma cameras and 5 PET-CT in working condition and one more PET-CT facility is upcoming.

Indira Gandhi Institute of Medical Sciences (IGIMS) was established on 19th November 1983, as an autonomous organisation on the pattern of All India Institute of Medical Sciences, New Delhi. The objective was to provide super specialty medical facilities in Bihar. It is having multidisciplinary and super-speciality treatment modalities which include conventional as well as modern treatment system.

State Cancer Institute, IGIMS, Patna

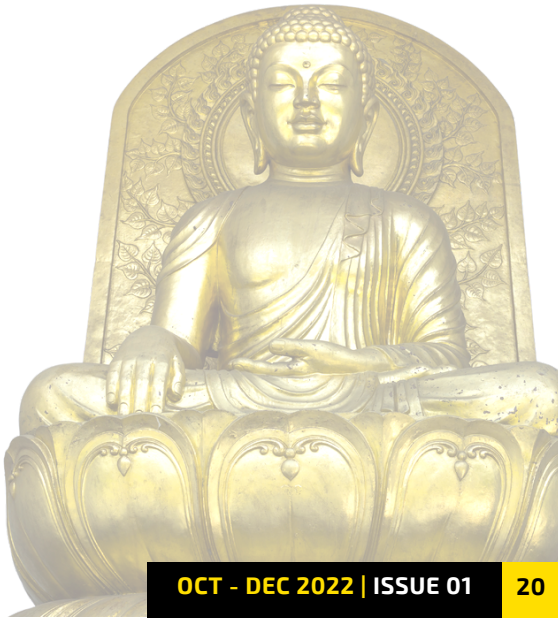
For the benefit of patient suffering from cancers, State Cancer Institute (where all cancer treatment facilities and with all modalities including 'State Of Art' equipment) is serving the purpose under one roof. It is situated within the premises of IGIMS campus, near Emergency and Trauma center. State cancer institute is having following Department of Radiation Oncology, Department of Surgical Oncology, Department of Gynaecological Oncology, Department of Medical Oncology, Department of Medical Physics, and Department of Nuclear Medicine. The distance between IGIMS and Patna airport is about 2.5 kms and from Patna Junction railway station is around 7 kms.

The nuclear medicine department is functional and serving critical role in the management of cancer patients. Presently here we have only single PET-CT equipment and planning to have all the necessary equipment and accessories needed for full-fledged department. The department is purposed to have medical cyclotron, radiochemistry modules, gallium radiochemistry module, two PET–CT scanners, PET-MRI scanner, two SPECT-CT scanners, and two planar gamma cameras. There is also a provision for low and high dose Radioiodine-131 (131I) therapy, Lutetium-177 and Actinium-225 therapy.

Along with the equipments, for the department to be fully functional many posts have also been proposed including 5 clinical and 2 non-clinical faculty, 6 medical physicists, 5 senior residents, 1 pharmacist, and administrative staff. Most of the proposed posts have been approved. In upcoming years, we also have the vision to start the post graduate academic courses in nuclear medicine including MD and M.Sc. Nuclear Medicine.

Team Nuclear Medicine

The first PET-CT installed in the premises of the State Cancer Institute, is the only government sector PET-CT of Bihar and Jharkhand. It is mainly serving to the oncology patients. We also have huge demand of PET-CT procedures from the other departments. Almost 50 % of the PET-CT procedures are done free of cost (with the help of Bihar government and Ayushman Bharat) to facilitate the poor patients suffering from cancer. Presently, we are using only 18F-FDG and doing all indicated cases of 18F-FDG PET-CT. The permission for gallium labelled pharmaceuticals has already been obtained from the Atomic Energy Regulatory Board (AERB) and very soon we will have the facility for diagnosis of neuroendocrine tumour and prostate cancer. This will again help the concerned physicians and the needy patients.



Innovations, inventions, and entrepreneurship: Extended role of Nuclear Medicine health professionals

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The modern Nuclear Medicine offers a unique, non-invasive view into intracellular processes and enzyme trafficking, peptide, receptors, and gene expression forming the theoretical and applied foundation for personalized molecular nuclear medicine. The contributions of nuclear medicine are creating the possibility for a future of personalized medicine, in which treatments and medications will be based on an individual's unique genetic profile and response to disease processes using sophisticated tools and techniques.

Innovations and inventions in nuclear medicine encourage interdisciplinary collaboration. Collaborations should continue to encourage between basic chemistry, physics, computer science, molecular biological science, imaging science, and laboratory science. Innovations and Inventions grew leaps and bounds, as multi-disciplinary centers focused on nuclear medicine technology development and application, to stimulate the flow of new ideas for the development and translation of next-generation radiopharmaceuticals development, production, logistics supply chain, imaging instrumentation, quality service deliverables. The role of the industry should be considered and mechanisms developed that would hasten the technology development process.

Change in technological practices (process) or technological physical embodiment (products) leads to innovation and invention along with the intellectual property right (IPR) as a source of revenue generation in terms of commercial value, enriching nation's economy to become an academic entrepreneurship. These inventions in terms of patents can be scaled to marketable processes and products which will bring significantly visible changes in medical radioisotope productions, distribution, supply chain, applications, patient quality care and nuclear medicine community service utilities and delivery.

The entrepreneurship capacity building among the nuclear medicine technology specialists is to ignite the young minds, to acquire hard and soft skills, ideas and managerial abilities, capacities of self-employment, to become employment generator in the specific venture rather than being employed for time-bound limited salaried income.

Innovation, Invention and Entrepreneurship is going to open the new career pathway to become a technopreneur of self-sustained and self-reliant leader. It will open new extended role for the nuclear medicine graduate health professionals towards Operational management, Organizational management, product management, strategic leadership qualities for the societal development and more over strengthening Indian economy by becoming self-reliant leaders.

Intellectual entrepreneurship is an authentic foundation for higher education reform. Entrepreneurial attitude therefore, is the extent of one's positive valuation of inventing and starting a novel business in terms of start-ups to bridge the market demand-supply gap. Intention is the best predictor of behavior, thus it can predict the process of venture creation. Venture creation is not likely to take place without intention. Attitudes, subjective norms and perceived behavioral control are described as the antecedents of intention. Among university students Entrepreneurial Intentions need to be ignited, rejuvenated and revitalized. Innovation, entrepreneurship training and education, family support, government support program, social entrepreneurship, women's participation, individual entrepreneurial characteristics, participation of micro, small and medium enterprises, youth empowerment, collaboration of government-university-industry link are the key tools for entrepreneurship development.

Thus attitude-shift in teaching-learning can influence the entrepreneurial intention and behavior for venture creation of the future ready radiation health professionals too, in nuclear medicine physics practice, radiopharmaceutical production, Logistics, supply chain of medical radioisotopes, intellectual business consultants, franchisee business models and nuclear medicine community service deliverables.

"ALARA" in routine practice

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What is ALARA?

"As Low as reasonably achievable" is a principle on which Radiation safety considerations are made to minimize the exposure levels to the maximum possible extent. The population of concern can be any group who is within the radiation area, be it the patients, public, staff, or any other biota. This principle has to be ingrained in the mind of every radiation worker, especially during duty time.

As we are aware, one: Minimum Time with; two: maximum possible distance from; three: optimum shielding for protection from the radioactive source are the three "Golden rules" of Radiation Safety.

Along with these, every Medical professional should also keep in mind, "Justification, Optimization and Dose limitation" as the three important considerations when a radioactive procedure is being planned for a patient. This judicious application of the precious radioactive source has to be critically discussed and planned by both, the referring doctor and the Nuclear Medicine Physician.

Let us understand the concept of ALARA from the point of view of different professionals.

"ALARA" from the view point of :

Radiological Safety Officer (RSO)

RSO, himself/herself, acts as a "SHIELD" to protect one and all from the organization, even visitors of the organization for variety of purposes , along with the environment , from the risk of unwanted radiation exposure.

Every recommendation provided by RSO to the Management and training given to the newly joined radiation worker voices out the principles of ALARA. Every team member has to be educated for radiation safety considerations and application of the principle of ALARA, so that it becomes the habit or style of radioactive work in the organization.

RSO has to plan and stay updated about every development in safe practices in Radiation area. And faithfully transfer the same to the team members about the radiation safety considerations. Every radioactive source that is being planned for procurement, should be scrutinized by RSO for its benefit risk ratio and the permission from competent authority like AERB in our country, assures and authenticates it safe use. The benefit risk ratio should be more than 1 for the application of the new radioactive source.

Illustratively, an RSO has ALARA in mind, when he :

- Checks for the efficacy of the decontamination procedure, using a contamination monitor and
- Raises a request for the tungsten syringe holder for FDG injections in a very busy PET CT department.

Technologist

A technologist has to avoid patients over exposure by administering minimally required dose, which stands as an example for safety of the patient as well as himself /herself, along with all those team mates, who will handle that patient.

When a "dummy/dry run" practice for any radioactive procedure for the newly joined radiation worker is planned by a Senior staff/ RSO , the underlying principle is to achieve ALARA exposure to the new staff in his profession.

Good manufacturing practices like handling the radioactivity with proper PPE, while preparing radiopharmaceuticals, Quality Control tests before injecting a radiopharmaceutical, especially in the developmental stage/whenever in doubt, can prevent the patient from getting unwanted radioactive exposure, due to poor quality radiopharmaceutical, and keeping an absorbent pad to prevent contamination are the examples of practice based on the principle of ALARA .

The storage of "just arrived" radioactive package in access controlled storage area with restricted entry, till it is being used shows the ALARA conscience, put into practice.

The daily QC of the imaging equipment assures (when it passes) and warns (if it fails) the technologist before the administration of the quality approved radiopharmaceutical.

Hence, the technologist, who performs the QC procedures, has ALARA principle in mind, to avoid the unwanted exposure to the patients, where "Benefit risk" ratio becomes "0"

Nuclear Medicine Physician (NMP)

NMP has the right to restrict the radioactive procedures for a patient, referred by the treating doctor.

It is the NMP, who can see the brighter and darker sides of the procedure; the pros have to outweigh the cons to accept the case for a nuclear medicine procedure.

The good quality interpretable image and targeted therapy are the desired goals of a nuclear medicine physician and these aspects of the procedure, should match with the needs of the patient, the time available and the referring doctors' perspective, along with the non radioactive procedures available for the patient, at that point of time.

A very unbiased and critical analysis should be made by comparing all these alternatives, maintaining transparency with the referring doctor.

Justification to accept or reject the application of nuclear medicine procedure for a case should be based on the principle of ALARA.

Management

The management is the resource provider and the facility built for the radioactive procedures should display the principle of ALARA, that is the entry point should have minimal or negligible radioactive work and the innermost area should be identified for the highest radioactive work, for example, the “Hot lab” should be the innermost room, almost hidden to the public (to reduce their accidental entry).

The wall thickness, the lead glass windows, wherever possible, installation of CCTV cameras in the radioactive patient waiting areas and the Delay tanks as per the AERB specifications to handle liquid radioactive effluents from High dose therapy facilities (in a cordoned section of the institute and identifiable with Radiation symbols) are the examples of ALARA principle being applied by the Management, as per the recommendations of the RSO and the Radiation Safety Committee members of the organization.

Following the AERB guidelines strictly, when the Nuclear Medicine Facility, during its gestational stage, is sufficient to implant the principles of ALARA.

Merging the needs, “Optimization” as the key:

Optimization of any resource means determining the right amount for maximum utilization, the same rule is applicable to use the powerful source of radiation in Nuclear medicine:

"**Neither too much(which is potentially hazardous) nor too less (which can be useless)"**

The management favors the minimum expenditure too and this minimization can be easily extrapolated to the radioactivity procurement. However, the “minimum” should not lose the utility value and the final goal of interpretable images and targeted therapy have to be reached.

Being reasonable, still safe:

When a pediatric or a non ambulatory case undergoes a radioactive procedure, it is quite reasonable to permit an attendant along with the patient, as a caretaker. The patient safety has to be prioritized for co operation and successful completion of the procedure. If possible, the attendants(obviously after confirmation of no pregnancy and preferably older age group) can take turns ,if there are more than one attendants available, so that the exposure levels are divided.

If possible, the attendants(obviously after confirmation of no pregnancy and preferably older age group) can take turns, if there is more than one attendant available, so that the exposure levels are divided.

When a radioactive patient weighing 90 kg has fallen down, it is quite unreasonable for a staff weighing 45 kg to show his/her benevolent gesture of helping the patient alone. Asking for urgent help from the teammates becomes a reasonable and safe action. The time taken to handle the radioactive source is definitely reduced.

I have a double dose, remaining in the vial and more doses can reduce the scanning time, does it mean, I can give a larger dose to the patient? The safety lies in giving just the right dose to the patient and letting the remaining dose decay in the vial inside the lead shield behind the lead bench.

I have lesser than half of the recommended dose. The patient needs the report urgently. Shall I inject the patient and acquire the scan for a longer period?

The interpretable quality of the scan may become questionable. In such a case, it is reasonable to convince the patient for an appointment, the next day or direct the patient to that hospital with the NM department, having a sufficient dose.

Finally, every patient comes with a sincere hope to get treated and invests a substantial amount of his or her resources: time, energy, and money.

Giving due respect to this hope based on ALARA principle by optimum radiation exposure to meet this need **ALARA** is the key to successful professionalism.

Is Occupancy factor a major point of consideration in minimizing radiation exposure from low dose iodine therapy patients to family members/comforter?

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Low dose radioiodine-131 (131I), less than 30 mCi is given to patients to treat hyperthyroid on outdoor patient basis. While the radioactive iodine is beneficial for these patients, it is a potential source of radiation exposure to their comforters and family members which needs to be minimized. As per NCRP Report Number 37, the occupancy factor (OF) is defined as the fraction of the time a person is close to the patient, with the distance during this time assumed to be an average of 1 meter. In this present study we tried to find out the total a cumulative exposure (TAE) to the family members/ comforters from the patient treated with low dose iodine therapy (LDIT) using OF of 0.25.

LDIT was administered to a total of 51 hyperthyroid patients based upon clinical history, TFT values and thyroid scan uptake. Depending upon the activity given to the patient, they were divided into 2 Groups: Group A included 31 patients with activity administrated 5-15 mCi and Group B included 20 patients with activity administrated 16-29 mCi. Radiation exposure rate for each patient was measured at a distance of 1 meter from the patient immediately after LDIT dose administration using ionization chamber-based survey meter. Mean radiation exposure rate was then calculated for both Group A and B patients. TAE for complete decay at a distance r from the patient was calculated using this formula

$$D(\infty) = \frac{34.6\,\Gamma Q_o TE}{r^2}$$

where, Γ is the specific gamma ray constant in (mSv cm2 MBq-1hr-1) at 1 cm, Q_o is the initial activity in mCi, T is the physical half-life in days, r is the distance in cm from the activity to the point of interest and E is the OF (0.25).

The mean activity administered in Group A and Group B was 9.45 mCi and 23.6 mCi, respectively. The total accumulated exposure was observed to be 1.43 mSv for Group A and 3.59 mSv for Group B. This when correlated with OF and to comply with the comforter dose constraint of 5 mSv during the period of patient's treatment as per AERB guidelines, **CODE NO. AERB/RF-MED/SC-2 (Rev. 2)**, the comforter could stay at 1 m distance from the patient for maximum 21 h/day in Group A. However, this time interval significantly reduces to 8.3 h/day in Group B.

Thus, OF clearly needs careful consideration by the hospitals that treats such patients, since a default of 0.25 at 1meter might be difficult in patients of low socioeconomic background an alternative arrangement might needed in order to minimize the radiation exposure to family members/ comforters in patients treated with LDIT.

Dosimetric aspects in TARE

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Over the past decade, the management of disease in patients with hepatocellular carcinoma (HCC) has evolved to a wide variety of therapeutic options, including systemic and locoregional techniques. Selective internal radiation therapy (SIRT) via intrahepatic arterial administration of 90Y-microspheres, also called transarterial radioembolization, is a promising modality for the treatment of primary and metastatic liver cancer. It is based on the delivery of radioactive ^{90}Y microspheres to liver tumors.
The importance of personalized dosimetry to make TARE safer and more effective has been demonstrated in recent clinical studies, stressing the need for quantification of the dose-response relationship to ultimately optimize the administered activity before treatment and image it after treatment. ^{90}Y dosimetric studies are challenging because of the lack of accurate and precise methods but are best realized with PET combined with Monte Carlo simulations and other image modalities to calculate a segmental dose distribution.

Two microsphere products are commercially available. Thera Sphere (glass microspheres; MDS Nordion) and SIR-Spheres (resin microspheres; Sirtex Medical) were approved by the U.S. Food and Drug Administration in 1999 and 2002, respectively.

When performing TARE, radioactivity (measured in decays per second, or Becquerel [Bq]) tagged to a resin or a glass sphere is administered intra-arterially, resulting in deposition into the terminal vascular bed of the said vessel.

The efficiency of SIRT treatment is based on a vascular selectivity process responsible for a differential effect leading to a higher concentration of radioactivity within the tumor tissue than in non-tumoral tissues. The more differential this effect is, the more effective the treatment.

Selectivity of microspheres can be improved by obstructing certain vessels during a pretreatment hepatic angiogram to spare healthy tissue, but the resulting differential effect is still constrained by the arterial system as it is well known that the anatomy of the mesenteric system and the hepatic arterial bed has a high degree of variation among patients.

HCC is characterized by arteriovenous shunting bypassing the capillary bed. In the case of an arteriovenous shunt, both lungs are uniformly perfused through the vena cava, heart, and lung arteries. This shunting to the lungs will result in possible radiation pneumonitis after the administration of 90Ymicrospheres. Therefore, when treatment planning is undertaken, lung shunting should be detected and quantified.

This is performed with ^{99m}Tc-MAA scintigraphy during the angiography procedure; 75–150 MBq of 99mTc-MAA are administered in the proper hepatic artery (or in any branch of the hepatic artery when super- or hyper selective treatment is planned) through the hepatic catheter.
The lung shunt fraction (LSF) is determined by the following equation:
Lung shunt fraction = lung counts /lung + liver counts

When it comes to radioembolization's current clinical dosimetry, the ^{90}Y microspheres are calibrated, measured, and administered in activity (GBq). However, radiation therapy doses are normally planned in Gy (J/kg) to quantify absorbed dose from a radiation source in tissue. Likewise, radioembolization plans the prescribed doses to the patient in Gy, but converts it into prescribed activity before treatment.

Several methods have been proposed in the literature to assess the prescribed activity. Some of them are based on empiric models, whereas others are based on a planning treatment strategy including a dosimetry step.

The aim of treatment planning methods based on dosimetry is to optimize the tumor response and prevent complications by administering the highest possible activity to the tumor while maintaining low radiation dose to sensitive tissues such as the lungs and normal or cirrhotic liver.
This planning treatment strategy needs volume measurement of the liver and tumor tissues and the amount of implanted activity into each of these 2 compartments and lungs which is termed dosimetry & hence, dosimetry becomes a very important aspect of the efficacy of the procedure.
However, both SIR-sphere and Theraspheres threshold values are based on a maximum dose of 30Gy for a lung mass of 1.0 kg. These values were established because patients who received an estimated singular lung dose greater than 30 Gy and/or had a cumulative dose greater than 50 Gy for repeated treatments developed radiation pneumonitis.

In clinical practice, radioembolization dosimetry is calculated from different dosimetric equations to set the treatment prescribed dose as a prescribed activity.
There are currently four different clinical dosimetric methods that are dependent on the type of microsphere. Three dosimetric methods are available if resin or SIR-microspheres are used.

The **first dosimetric method** is the empiric method that bases its recommended activity on the percent tumor involvement in the whole liver. This method relies solely on CT or MRI images to determine the liver size and tumor burden percentage but is now abandoned due to its low safety margins regarding radiation-induced side effects.
The **second empirical method** formulated after the empirical method incorporates body surface area (BSA, measured in square meters)Therefore, the activity to be administered is

$$A[\text{GBq}] = (\text{BSA} - 0.2) + \left(\frac{\textit{tumour volume}}{\textit{tumour volume} + \textit{liver volume}}\right)$$

$$\text{BSA} = 0.20247 \times \text{height}[\text{m}]^{0.725} \times \text{weight}[\text{kg}]^{0.425}$$

This method assumes that the size of the patient's whole liver correlates with the patient's BSA. Thus, a prescribed activity could appropriately be adjusted to a patient's malignant liver volume without the need for liver volumetry on cross-sectional imaging but do not take into account the degree of tumor uptake. Therefore, dosimetric methods should be generally recommended.

Partition Method: The most accurate of these three SIR-sphere dosimetric equations is called the partition method or model and is the only SIR dosimetric equation formulated directly from the MIRD methodology in which the dose is calculated as

$$A_{total}[GBq] = A_{liver} + A_{lung}$$

$$A_{liver} = A_{total} \times (1-LSF)$$

$$A_{lung} = A_{total} \times LSF$$

$$A_{total}[GBq] = \text{Total Administered Activities}$$

Since, several dosimetric methods such as Monte Carlo simulations, The Medical Imaging Radiation Dose (or MIRD), and Body Surface Area (BSA) methods are used. All these methods have different protocols and their own advantages and disadvantages. This diversity of approaches does not favor standardized medical practices and leads to wide variation in the prescription of the administered activity, complicating the interpretation of clinical results and meta-analysis and the treatment efficiency.

There are a few shared limitations within all the current clinical dosimetric methods.

- Mainly, the microspheres are not uniformly distributed within the treated liver. The microsphere distribution is highly heterogeneous within both tumorous and non-tumorous hepatic tissue. Consequently, radioembolization dosimetry is best modelled as heterogeneous clusters of point-sources that emit beta irradiation. With current methods, the spatial distribution of a microsphere's absorbed dose is ignored. Rather, an absorbed dose is attributed to an entire region.

- Additionally, the long beta particle range for ^{90}Y microspheres is neglected within these methods. This limitation becomes the most apparent with the partition method when the liver is divided among the tumorous and non-tumorous regions and is in close proximity to each other. This phenomenon, when a non-targeted region obtains a dose of radiation from a neighboring targeted region is called the "crossfire" effect. The partition method was determined as inaccurate due to the exclusion of the crossfire effect within a MIRD-5 human phantom.

- Dosimetry would further be affected by the microanatomy of a patient's liver, crossfire effects at the cellular level, microsphere bifurcation effects within hepatic arteries, and the differences in therapeutic effect when different microsphere numbers and sizes are injected within a patient and also physics and hardware limitations.

Due to a myriad of inhomogeneous methodologies and dosimetric methods, patient responses based on quantified doses becomes challenging to interpret and compare.
Therefore, proper standardized dosimetry becomes a necessary first step towards a sense of congruence and comparability.

Whole body effective dose to radiation worker during manual synthesis of Re-188 labeled radiopharmaceuticals : A radiation protection based study

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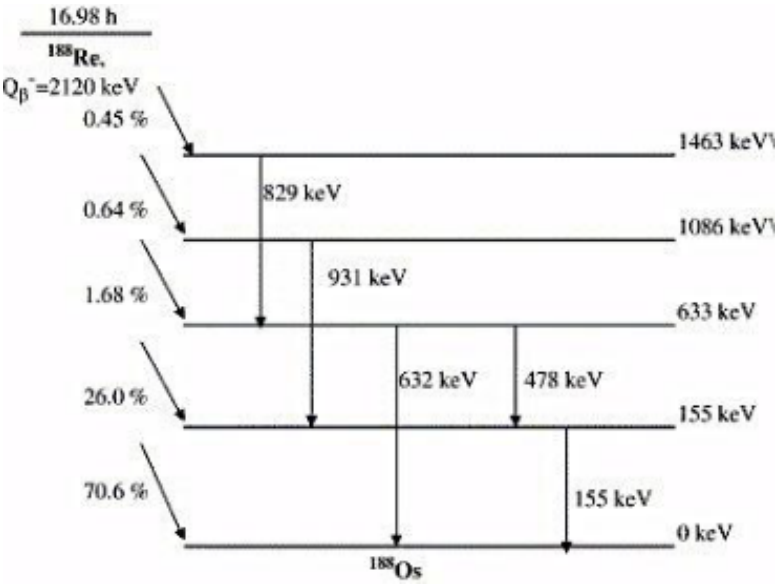
Introduction

Nuclear medicine (NM) personnel are exposed to a considerable radiation dose during activity measurements, storage, and disposal of sources, preparation and administration of radiopharmaceuticals, as well as from patients during and after the procedure **[1].**

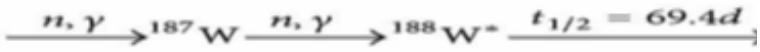
According to ICRP recommendations 103 (2007), any person handling radiation and likely to receive an occupational radiation exposure of more than 1mSv is liable to be monitored and the occupational dose limit on effective dose of 20mSv/year averaged over 5 years, not exceed 50mSv in any single year **[2],** thereafter Atomic Energy Regularity Board (AERB) reduced it to 30mSv. The recommended ICRP dose limit is monitored regularly to make sure the dose limit is not exceeded during work with unsealed radioactive sources in the department **[1].**

Due to attractive physical and chemical properties of Rhenium-188, it can be labeled to a variety of compounds for the diagnostic as well as therapeutic use. Rhenium-188 (Re-188) is a beta and gamma-emitting radioisotope of naturally occurring Rhenium, which are 37.4% Re-185 (stable) and 62.6% Re-187 (half-life ~ 1010 years). Re-188 (t1/2=16.9 hrs) decays by β- to give stable Osmium -188 (Os-188) with Eβmax. Of 2.12MeV, which is enough to penetrate and destroy abnormal cancer cells, and principle gamma rays (155keV), which can efficiently be used for imaging and radiation absorbed dose estimation. Decay scheme of Re-188 is given as follows:



Decay scheme of Re-188

Re-188 can be produced in a nuclear reactor by high-flux neutron irradiation of natural rhenium element yielding a mixture of Re-186 and Re-188. For higher radiochemical purity, highly enriched Re-187 targets can be used. However, the specific activity of the reactor produced Re-188 is insufficient for labeling purposes. Re-188 can instead be easily eluted from in-house generators through β-decay of Tungsten-188 parent (W-188) which makes its storage, transportation, elution, and usage very convenient and cost-effective. W-188 is produced in high-energy flux reactors with double neutron bombardment of W-186 **[3].**



Re-188 is an emerging agent for trans-arterial radionuclide therapy of hepatocellular carcinoma (HCC) **[4]**, and also, a promising radionuclide for use in radiosynovectomy (RSV) of joints owing to its favorable decay characteristics **[5]**.
Our department has routinely started 188Re-labelled radiopharmaceutical-based therapies such as Re-188-N-DEDC lipiodol and Sn-colloid for the treatment of HCC and inflammatory arthritis, respectively. Since Re-188 was labeled with several pharmaceuticals that involved different techniques, thus, it became important to monitor the radiation dose received by the personnel involved during the manual synthesis of these labeled radiopharmaceuticals. When radiolabeling is done manually, its importance increases significantly. The detrimental effects that ionizing radiations has on biological tissues need no mention.

Currently, the model that we followed was concerned more with radiation protection i.e., LNT or Linear No Threshold model, also stated that there is no dose below which the risk associated with the induction of cancer is zero. In other terms no dose is a risk-free dose. Therefore, it became all the way more important to keep a check on the dose that we are receiving while working in the department. Stochastic effects don't have any threshold value unlike deterministic effects. Therefore, the main necessity for doing personal dosimetry was to reduce the stochastic effects and eliminate the deterministic effects **[6]**. Thus, the present study is aimed to evaluate the personnel radiation exposure during the labeling of Re-188-labeled radiopharmaceuticals that is N-DEDC lipiodol and Sn-Colloid.

Material and Method

A radiation survey meter (Inspector, Radimage healthcare India Pvt Ltd, Noida India) was used to measure background radiation exposure before start of labeling procedure at around the labeling working bench.
A pocket dosimeter (Aloka mydose mini, PDM-222-SH, Southern Scientific Ltd, UK) was given to the personnel, placed in the pocket at chest level.

The reading on the pocket dosimeter was noted down at the end of activity division and at the end of pre-boiling and boiling steps of the labeling procedure. The start and end time of procedure (elution to injection) was noted down to know the total duration spent by radiation worker.

The labeling method for Re-188-N-DEDC lipiodol was adopted as described by **Madhava B Mallia et al. [7]**. While, for labeling of Re-188-Tin Colloid the methods described by **Jeong et al.** was adopted **[8].**

Result

We measured the whole body radiation exposure in regard to Re-188 manipulation. A total of 20 preparations were done for Re-188-N-DEDC lipiodol (n=10) and Re-188-Sn-colloid (n=10) and the readings of radiation exposure using pocket dosimeter were obtained during the labeling procedure.
Table 1 shows the number of readings obtained and total number of doses prepared with individual radiopharmaceuticals.

Table 1: Number of readings of exposure of various radiopharmaceuticals

Radiopharmaceuticals	Number of observations	No. of Dose
DEDC lipiodol	10	10
Tin colloid	10	14
Total	20	24

Our study was able to provide effective radiation exposure to the personnel involved encompassing the time from preparation till injection. The mean activity eluted from the generator was 202.7±121mCi, mean radiation exposure during elution of all 20 labelling procedures was 0.6±0.59µSv. Mean amount of Re-188O4- used for labeling with N-DEDC lipiodol and Sn-Colloid was 121.7±13.70mCi and 35.3±11.87mCi, respectively. Mean time required to complete the procedure was 95 and 171 min, respectively.

Mean radiation exposure during pre-boiling and boiling/post-boiling for N-DEDC lipiodol was 6.1±1.2 µSv and 13.2±4.58µSv, respectively. Mean radiation exposure during pre-boiling and post boiling for Sn-Colloid was 1.6± 0.51µSv and 2.6±0.69µSv, respectively.
Total mean radiation exposure for Re-188-N-DEDC and Sn-Colloid was 20.4±5.58µSv and 4.3±1.15µSv respectively. Overall mean whole body radiation exposure to the personnel during 20 radio-labeling procedures i.e. 10 for Lipiodol and 10 for Tin colloid was found to be 12.35±9.14µSv.

Table 2 shows the data of all labeling procedure of Re-188-N-DEDC lipiodol and Re-188-Sn-Colloid. The highest radiation exposure received to personnel was during labeling of Re-188-N-DEDC Lipiodol as higher activity was handled and also higher amount of activity was required for therapy.

It was observed that the amount of activity and the time for which the activity manipulation was done with the hands was highest for Re-188-N-DEDC lipiodol. Furthermore, the radiation exposure received by the personnel was higher during Re-188-N-DEDC lipiodol vial vortexed with vortex mixer.

The two parameters which were found crucial for higher exposure were the time for which the radioactivity was handled and amount of the activity handled during the radiolabelling i.e. higher the both, higher the radiation exposure.

Radiation exposure received during activity handled, and the time utilized by the personnel for above mentioned Re-188-Radiopharmaceuticals is shown in **Figure 1**.

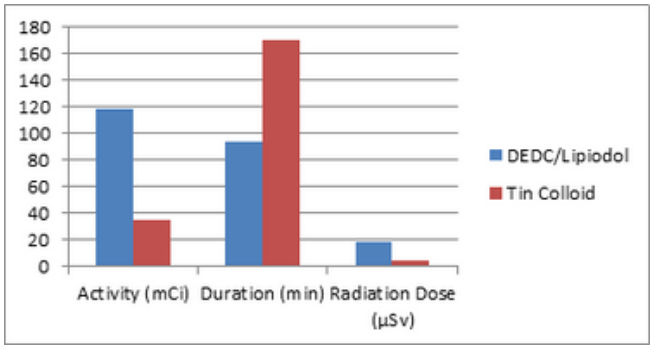


Figure 1: Comparison of activity handled, duration and the radiation exposure received by the personnel for Re-188-labeled radiopharmaceuticals.

Total effective whole body dose to the personnel involved was 247µSv in 6 months. This radiation dose received by a single nuclear medicine personnel, over a period of 6 months, it was far below the occupational limits documented by ICRP as well as AERB, India (20mSv/year).

Radiation exposure during the labeling of ^{188}Re-N-DEDC lipiodol								
S.No.	**Activity Eluted (mCi)**	**Radiation Dose During Elution (µSv)**	**Activity Used (mCi)**	**No. of Dose**	**Total Duration of RP synthesis (min)**	**Preboiling Radiation Dose (µSv)**	**Boiling, Post Boiling radiation Dose (µSv)**	**Total Radiation Dose µSv**
1	402	2	146	1	92	8	18	28
2	384	1	130	1	98	6	20	27
3	362	1	135	1	93	7	17	25
4	344	1	128	1	95	7	15	23
5	323	1	120	1	94	7	13	21
6	305	1	115	1	97	5	15	21
7	282	1	118	1	95	6	11	18
8	257	1	120	1	94	6	9	16
9	234	1	105	1	96	5	7	13
10	210	1	100	1	93	4	7	12
Mean			**121.7**		**94.7**	**6.1**	**13.2**	**20.4**
Std dev			**13.70**		**1.88**	**1.19**	**4.58**	**5.58**

Table 2 (a) : Radiation exposure during labeling of Re-188-N-DEDC lipiodol

Radiation exposure during the labeling of ^{188}Re-Tin Colloid								
S.No.	**Activity Eluted (mCi)**	**Radiation Dose During Elution (µSv)**	**Activity Used (mCi)**	**No. of Dose**	**Total Duration of RP synthesis (min)**	**Preboiling Radiation Dose (µSv)**	**Boiling/Post Boiling radiation Dose (µSv)**	**Total Radiation Dose µSv**
1	146	1	52	2	178	2	3	6
2	134	0	26	1	165	1	2	3
3	123	0	30	1	166	2	2	4
4	110	0	48	2	175	2	3	5
5	97	0	25	1	168	1	2	3
6	82	0	22	1	171	1	2	3
7	77	0	27	1	167	1	3	4
8	68	0	50	2	170	2	4	6
9	60	0	28	1	177	2	2	4
10	54	0	45	2	174	2	3	5
Mean			**35.3**		**171.1**	**1.6**	**2.6**	**4.3**
Std dev			**11.87**		**4.67**	**0.51**	**0.69**	**1.15**

Table 2 (b) : Radiation exposure during labeling of Re-188-Tin Colloid

Conclusion

Our data suggests that the manual radio-labeling of Re-188-labeled radiopharmaceuticals is safe and the whole body radiation exposure to the involved personnel is well within the prescribed limits of ICRP, i.e., 20mSv/year (averaged over 5 years). Even if in the future the synthesis rate increases to double per 6 months and the same personnel is involved in the synthesis, the mean radiation dose to the personnel involved in a year will be within AERB occupational dose limits.

The radiation exposure can be further reduced with good radio-pharmacy practices and following more radiation safety principles. Though the procedures are safe even if a single trained staff member conducts all the synthesis but it would be preferable to involve a minimum of two trained personnel to share and further reduce the radiation burden. The regular use of radiation monitoring devices such as pocket dosimeters, ring dosimeters and TLD badges should be encouraged, and radiation surveys should be routinely conducted. Further improvement is still possible, with the automation of the perrhenate transfer step. Automation of the synthesis further leads to a significant decrease in radiation exposure to the personnel.

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Fractionation of cold kits : Is it justifiable?

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Fractionation, the word itself, states that a certain quantity of a mixture, be it solid, liquid, or gas, is divided into a number of smaller quantities. The word fractionation first originated in the late 14th century from the Anglo-French, which means " breaking or dividing".

The word fractionation is used in many instances in nuclear medicine, be it in therapy where it involves the division of a total therapeutic dose of radiation into small doses to be administered over a period of days or weeks, or in radiopharmacy where fractionated elution is done to get a higher concentration of technetium-99m (99mTc) in a small volume. Besides elution, fractionation as a term can be used when dealing with cold kits.

Fractionation (Kit Splitting/Kit Fractionation) in terms of cold kits used in nuclear medicine is defined as reconstituting a freeze-dried vial used for the preparation of 99mTc-radiopharmaceuticals with inactive diluents (saline), from which samples are withdrawn for radiolabelling with 99mTc.

Fractionation of cold kits is done most commonly in 2 methods, i.e., the vial fractionate model and the patient-specific syringe fractionate unit dose model. Both methods must follow a closed procedure in order to maintain their sterility. These split kits stored in vials are then stored frozen for times varying from a few days to weeks or months, whereas unit doses in syringes are used immediately given the fact that they are kept for an incubation time stated by the manufacturer.

Fractionation of cold kits is a method that most nuclear medicine centers do around the world as it has got its advantages. One of the main advantages and the motivation for using this technique of kit splitting is the expense. It's a technique that is normally done with kits, which are very expensive, as it helps cut down the cost per study by being able to take walk-in cases instead of pooling them for another day. Patients who are in urgent or emergency cases can be attended to faster as it helps cut down the time required for preparing the radiopharmaceutical and cuts the gamma camera wait time. These factors contribute to high patient satisfaction levels as well. Other advantages are in terms of radiation dosimetry for the operator and also adjustments to the dosage for the patient.

Despite the fact that most of the pharmacopeias, especially the European pharmacopeia and Board of Radioisotope and Technology (BRIT), clearly state that fractionation is prohibited and not to be followed, most of the centers follow it, keeping the idea of cost in mind.

Fractionation has its disadvantages and challenges too. One of the main issues noted is the fractionated kit stability. A pharmaceutical review is important to note its stability, which mentions the change in the effective concentrations of the active ligand, pH buffers, stabilizers, preservatives, and antioxidants. It is a problem, especially in the syringe method, where it fails the requirements of checking the pH and the percentage of radiochemical purity. Whichever model the radio pharmacist/technologist uses, it must be checked to meet all its quality control requirements, including radiochemical purity, before injecting, hence keeping patient safety in mind. Secondly, the radio pharmacist/technologist who does the procedure must have the necessary skills and experience. Third, the change in techniques in terms of freezing and thawing can affect the particle size of the cold kit. Lastly, according to radiation regulatory boards, one must have a grade 3 level radiopharmacy laboratory in order to do in-house preparation of cold kits. This also follows the need to maintain good hospital radiopharmacy practices, thus ensuring everything is done in an aseptic and sterile environment.

Production of clinically potent radio-metals using the promising liquid target technique in medical cyclotrons

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The introduction of cyclotron facility in the medical sector has led to the intensification of artificial radioisotope production for clinical application. The first compact cyclotron was constructed in 1930-1931 by Ernest Lawrence and his student M. Stanley Livingston **[1,2].** This technology brought a revolution in the field of artificial radioisotope production for clinical applications. Since then, various radioisotopes have been artificially produced, routinely used, and experimented for different clinical conditions. The most commonly produced positron-emitting radioisotopes using medium-energy medical cyclotrons are fluorine-18 (F-18), nitrogen-13 (N-13), carbon-11 (C-11), and oxygen-15 (O-15) **[3]**. The availability of positron-emitting radioisotopes has led to an exponential increase in the research related to radio-metal based radiopharmaceuticals. The aim of this write-up is to give an insight into the advances in the production of positron-emitting radio-metals in cyclotrons using a potential liquid target-based technique.

Cyclotron Targetry

Based on the target material (solid, liquid, and gaseous), different types of target bodies are commercially available for medical cyclotrons. Routinely utilized radionuclides in clinical practice like F-18, N-13, C-11, and O-15 are generally produced via a liquid target system. The benefits of using liquid targets include easy handling, rapid heat exchange, easy target material loading and unloading, efficient water and helium cooling **[4]**. On the other hand, solid targets present numerous challenges which still needs to be tackled. Some of the major problems associated with solid targets are expensive enriched target material requirements, overheating problems, complex unloading systems (may involve high radiation exposures to the working professionals), complex chemical separation, vault dimensions, and shielding issues. Hence in the past few years researchers around the globe are working extensively for the optimization of liquid target-based production methods for radio-metals.

Liquid Targetry to produce Radio-Metals

The liquid target-based technique was initially proposed by Lindner et al., in 1973 for the production of non-conventional radioisotopes **[5]**. Cuninghame et al., produced I-123 using this technique in 1976 **[6]**. For the production of radio-metals using liquid targets usually an enriched salt of the target material, dissolved in an appropriate solvent is used **(Table-1)**. The benefit of liquid target technique is that it overcomes the shortcomings present in solid targets. It offers easy handling, easy availability, judicious utilization of target material for a single production, easy target handling, and simple chemical separation processing. The imbalance created between the demand and supply of radio-metals due to their increasing clinical applications, production of radio-metals using liquid targets has become more of a necessity than a possibility.

Radiometal	Reaction	Beam Energy (MeV)	Target Conc. (mg/ml)	Beam Current (uA)	Irrad. Time (min)	Prod. Yield (MBq/uA)
^{68}Ga	^{nat}Zn(p,n)^{68}Ga	12	307	7	60	141
	^{68}Zn(p,n)^{68}Ga	14	116	20	30	430
		16.1-12.9	33	45	50	330
		12	115	46	32	320
^{89}Zr	^{nat}Y(p,n)^{89}Zr	14	177.8-244.5	20-40	60-120	500
		12	204	7.3	60	360
^{64}Cu	^{64}Ni(p,n)^{64}Cu	16.9	25	70	300	300
		-	15	10	120	87

Table 1: Production parameters for the radio-metals obtained in a medical cyclotron

Gallium-68 Production

Clinical application of gallium-68 (Ga-68) dates back to 1960s when it was first used for imaging brain tumors [7]. 68Ga with a half-life of 68 min, decays to zinc-68 (Zn-68) by positron emission (89%, βmax 1.92 MeV). With the surge in the research and clinical usage involving Ga-68 as a choice of positron emitting radionuclide for diagnostic imaging, a sudden wave requiring uninterrupted demand of Ga-68 has been noted over the last few years. 68Ga can be produced via both germanium-68 (Ge-68)/Ga-68 generator and medical cyclotron. However, presently, Ge-68/Ga-68 generators are the main source of Ga-68 radioisotope globally. There are some limitations of using Ge-68/Ga-68 generator such as limited availability of Ga-68 radioactivity (£3.7 GBq) which decreases over the time, waiting period between subsequent elutions (£4 h), radiation dose burden, and Ge-68 breakthrough. In order to overcome these hurdles, cyclotron based alternative method of Ga-68 production using liquid target system have been explored extensively.

In 2009, Sadeghi et al., carried out the first Ga-68 production using Zn-68 solid target in a cyclotron [8,9]. Whereas the first liquid target ([Zn-68]ZnCl2)-based production of Ga-68 was demonstrated by Jensen et al., in 2011 [10]. Later in 2014, Pandey et al., produced 68Ga in a liquid target using solutions of [Zn-68]Zn(NO3)2 in dilute nitric acid [11] and following this approach many other groups have also produced Ga-68. Many challenges were encountered during the development of liquid target technique for the production of Ga-68. The major problems were the target material selection, target pressure build up during bombardment (due to the evolution of gases), and formation of salt precipitates. These effects were thoroughly studied and overcome by DeGrado et al., [12]. Pandey and co-workers successfully implicated the aqueous salt solution based Ga-68 production into the clinics [11,13].

Despite of commercial availability of liquid target technique for Ga-68 production, it is at present limited to few research institutions. The research is still underway to increase production yield of Ga-68 and make this technology more affordable for routine use.

Zirconium-89 Production

Zirconium-89 (Zr-89) with a half-life of 3.3 days (78.4 hours) decays via positron emission (23%) and electron capture 77% to stable isotope yttrium-89 (Y-89) and thus have very attractive characters for immuno-PET. Physical half-life of Zr-89 is very much compatible with the time needed to achieve optimal tumor-to-background ratios for intact mAbs (typically a few days). And also, positron Emax of 897 keV and Eavg of 396.9 keV results in good spatial resolution of PET images.

Immuno-PET, the term itself defines for an attractive non-invasive tumor detection method combining the high sensitivity of PET with high antigen specificity of monoclonal antibodies. With the advent of various PET radioisotopes, only few of them can be attributed to this approach where an utmost requirement is of in-vivo stability and decay i.e half-life of isotope should match the pharmacokinetics of the mAb.

First ever production of Zr-89 was reported by Link et al., via a (p,n) nuclear reaction by bombarding Y-89 on Y foil with 13 MeV protons. The produced Zr-89 needed several purification steps and was obtained in 80% yield with radionuclide purity ≥99 % [14]. At present, Zr-89 is mainly produced in cyclotron using Y-89 based solid targets, however, liquid targets are also under research to increase the availability of this radioisotope globally.

The production of 89Zr from liquid target system have been reported by Gemma M et al and Pandey et al. An aqueous solution of yttrium nitrate [Y(NO3)3·6H2O, in HNO3] was used as a target material and irradiated for 4 h on a TR13 cyclotron at 12 MeV (11.6 μA) for 2830 μA·min in a niobium-body siphon liquid target. The irradiation for 60 min as well for 120 min were well within error, whereas longer 220 min irradiation has a lower saturation yield compared to the 60 min irradiation of 50 %. The drop in yield was expected but the magnitude needed more work to be understood [15, 16]. Although there is a long way ahead to optimize the production of Zr-89 using liquid target in routine practice, but the initial success warrants its widespread application for an exquisite radioisotope of immuno-PET imaging.

Copper - 64 Production

Cu-64 has a half life of 12.7 h with a complex decay scheme (42.5% EC, 18% β+av 278 keV, 39% β−av 190 keV, and 0.5% γ 1346 keV). Its physical characteristics makes it an interesting radionuclide for molecular imaging and theranostics. It has an appropriate half life with a low positron energy emission comparable to 18F along with β− and γ emissions. Its diverse coordination chemistry helps in the design and development of various radiopharmaceuticals for preclinical and clinical applications [17,18].

Solid target based production of Cu-64 via Ni-64(p,n)Cu-64 reaction on a biomedical cyclotron is most common way of production, a route first proposed by Szelecsenyi et al., [19] and further developed by McCarthy and co-workers [20]. Solid target material is made of enriched 64Ni electroplated on a golden disc. Besides being well established the solid target based method has a number of disadvantages like low abundance of Ni-64 (0.95%), electroplating process and facility requirement, long irradiation time and high radiation dose in case of manual target unloading. Keeping in view all these crucial points, alternative methods were explored by the researchers. Other route investigated for the production of Cu-64 was via Zn-64(p,α)Cu-64 nuclear reaction [21-23].

Production using a liquid target was first reported by Engelbrech et al., using $64Ni(NO_3)_2$ as a target **[24]**. It was further evaluated by Alves et al., who reported a reduced yield at saturation time. They have worked on Ni-64 solution-based liquid targets and their work partially explains saturation yield variation dependency on enriched Ni-64 concentrations and the impinging proton energies **[25]**.

The promising results using the liquid target technique for the production of radionuclides have enabled us to generate a variety of new PET (I-124, Zr-89, Cu-64, Ga-68, Y-86, Sc-44) and SPECT (Tc-99m, I-123, Ga-67, In-111) radioisotopes with a decent production yield, radionuclide purity at a minimal cost along with providing us with an alternate method for production. The increase in the research involving radiometals for diagnostic and therapeutic purpose will continue to build pressure for the development of novel production processes.

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Schedule

NATIONAL

Workshop on PET-CT guided interventions
5-6 November, 2022
Postgraduate Institute of Medical Education and Research, Chandigarh, India

54th Annual Conference of Society of Nuclear Medicine, India
8-11 December, 2022
Jawaharlal Nehru Auditorium, AIIMS, New Delhi
Last date for Abstract Submission: 30th October,2022

11th Annual in-vivo Preclinical Imaging and Drug Discovery Workshop
12-14 December, 2022
ACTREC, Kharghar, Navi Mumbai

7th Annual Conference of Nuclear Medicine Physicist Association of India
4-5 February, 2023
Mahamana Pandit Madan Mohan Malaviya Cancer Centre, BHU Campus, Varanasi, Uttar Pradesh
Last date for Abstract Submission:
30th November, 2022

Schedule

INTERNATIONAL

12th International Symposium on Targeted Alpha Therapy
27 February - 2 March, 2023
Cape Town, South Africa
Last date for Abstract Submission: 7th November, 2022

18th European Molecular Imaging Meeting
14-17 March, 2023
Salzburg, Austria
Last date for Abstract Submission: 22nd November, 2022

International Symposium on Trends in Recent Radiopharmaceuticals
17-21 April, 2023
Vienna, Austria
Last date for Abstract Submission: 31st October,2022

25th International Symposium on Radiopharmaceutical Chemistry
22-26 May, 2023
Honolulu, Hawai
Last date for Abstract Submission: 23rd December, 2022

50th British Nuclear Medicine Society Annual Spring Meeting
22-24 May, 2023
Harrogate, England
Last date for Abstract Submission: 22nd January, 2023

53rd Annual Scientific Meeting of the Australian and New Zealand Society of Nuclear Medicine
26-28 May, 2023
Adelaide, South Australia
Last date for Abstract Submission: Yet to be announced

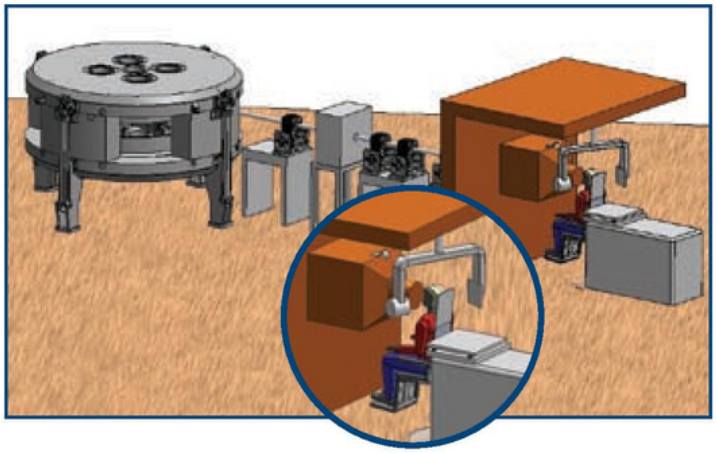
Annual meeting of Society of Nuclear Medicine and Molecular Imaging
24-27 June, 2023
Chicago, Illinois, USA
Last date for Abstract Submission: 11th January, 2023.

Upcoming Events

Best™ Cyclotron Systems

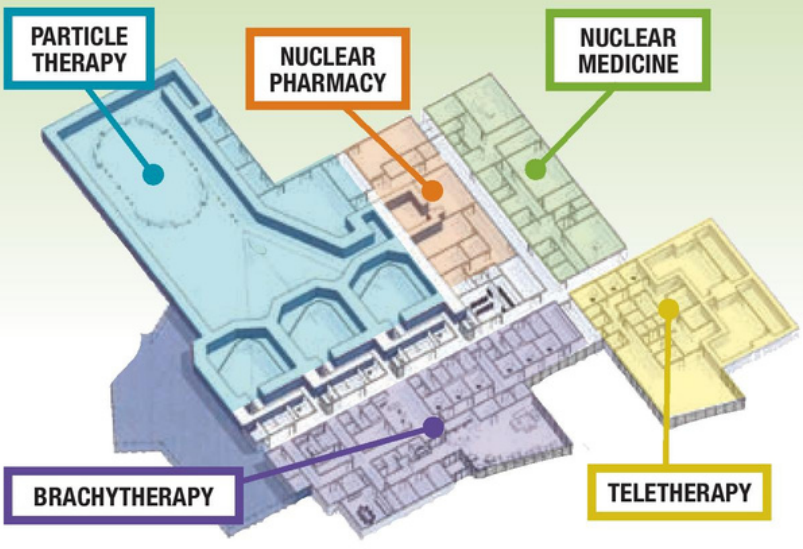
NEW! Best Model 150p Cyclotron for Proton Therapy (Patent Pending)

- From 70 MeV up to 150 MeV Non-Variable Energy
- Dedicated for Proton Therapy with two beam lines & two treatment rooms
- For all Medical Treatments including: Benign & Malignant Tumors, Neurological, Eye, Head/Neck, Pediatric, Lung Cancers, Vascular/Cardiac/Stenosis/ Ablation, etc.



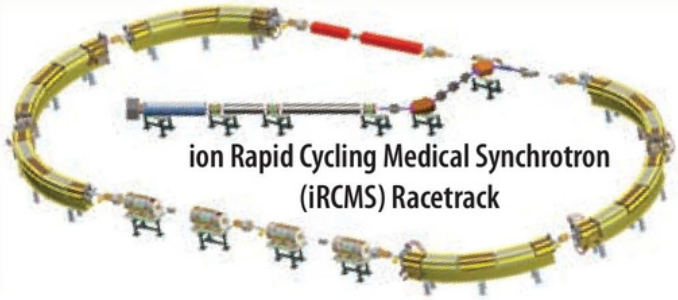
NEW Best Model 200	1–9 MeV	Low energy, self-shielded compact system capable of producing: ^{18}FDG, Na^{18}F, ^{18}F-MISO, ^{18}FLT, ^{18}F-Choline, ^{18}F-DOPA, ^{18}F-PSMA, ^{11}C, ^{13}N, ^{68}Ga and more!
NEW Best Cyclotrons	1–3 MeV	Deuterons for materials analysis (Patent Pending)
	70–150 MeV	For Proton Therapy (Patent Pending)
	3–90 MeV	High current proton beams for neutron production and delivery (Patent Pending)
Best 15p Cyclotron	1–15 MeV	Proton only, capable of high current up to 1000 Micro Amps, for medical radioisotopes
Best 20u/25p Cyclotrons	20, 15–25 MeV	Proton only, capable of high current up to 1000 Micro Amps, for medical radioisotopes
Best 35p/35adp Cyclotrons	15–35 MeV	Proton or alpha/deuteron/proton, capable of high current up to 1000 Micro Amps, for medical radioisotopes
Best 70p Cyclotron	35–70 MeV	Proton only, capable of high current up to 1000 Micro Amps, for medical radioisotopes
Best 150p Cyclotron	From 70 MeV up to 150 MeV	For all Medical Treatments including Benign and Malignant Tumors, Neurological, Eye, Head/Neck, Pediatric, Lung Cancers, Vascular/Cardiac/Stenosis /Ablation, etc. (Patent Pending)

Best Particle Therapy 400 MeV ion Rapid Cycling Medical Synchrotron (iRCMS) for Proton-to-Carbon, Variable Energy Heavy Ion Therapy—with or without Gantries—Single and Multi-Room Solutions



BEST Radiation Therapy & Diagnostic Center

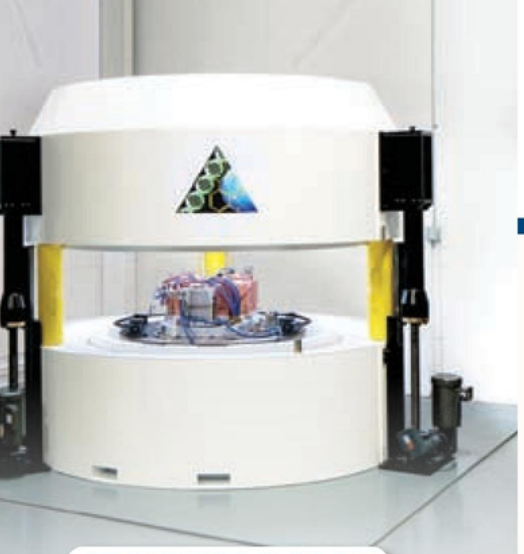
- Intrinsically small beams facilitating beam delivery with precision
- Small beam sizes—small magnets, light gantries—smaller footprint
- Highly efficient single turn extraction
- Flexibility—heavy ion beam therapy (protons and/or carbon), beam delivery modalities



ion Rapid Cycling Medical Synchrotron (iRCMS) Racetrack

Best Medical International 7643 Fullerton Road, Springfield, VA 22153 tel: 703 451 2378

AFRICA | ASIA | EUROPE | LATIN AMERICA | MIDDLE EAST | NORTH AMERICA



Best™ Cyclotron Systems

TEAMBEST GLOBAL®

One World • One Source • The Best!

healthcare for everyone

TeamBest® Your True Partner

www.teambest.com

NEW! Best Model 200 Sub-Compact Self-Shielded Cyclotron with Optional Second Chemistry Module & Novel Target

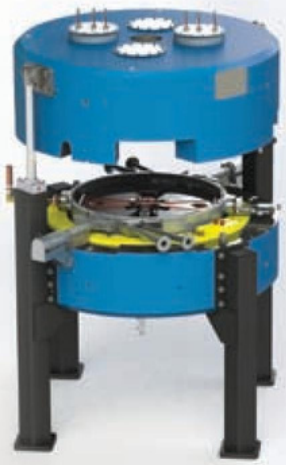
- Low energy compact system, can be placed next to PET/CT
- Easy to operate push-button graphic interface
- Automated quality control testing
- Ideal for Nuclear Cardiology/Oncology and other Applications
- Capable of producing: ^{18}FDG, Na^{18}F, ^{18}F-MISO, ^{18}FLT, ^{18}F-Choline, ^{18}F-DOPA, ^{18}F-PSMA, ^{11}C, ^{13}N, ^{68}Ga and more!

NEW! Best Model B3d Sub-Compact Low Energy Deuteron/Proton Cyclotron

- Accelerated Deuteron Particle: 1 to 3 MeV Energy
- Accelerated Proton Particle: 1 to 6 MeV Energy
- Maximum Beam Current of 2 µA
- Self-shielded system
- Small footprint (less than 5 m x 5 m)

NEW! Best 6–15 MeV Compact High Current/Variable Energy Proton Cyclotron

- 1–1000 µA extracted beam current
- Capable of producing the following isotopes: ^{18}F, ^{68}Ga, ^{89}Zr, ^{99m}Tc, ^{11}C, ^{13}N, ^{15}O, ^{64}Cu, ^{67}Ga, ^{111}In, ^{124}I, ^{225}Ac, ^{103}Pd and more!
- Up to 5 x 10^{13} neutrons per second from external target
- 21 stripping foils at each stripping port for 2 minute rapid change



NEW! Best Model B35adp Alpha/Deuteron/ Proton Cyclotron for Medical Radioisotope Production & Other Applications

- Proton Particle Beam: 1000 µA Beam Current up to 35 MeV Energy
- Deuteron Particle Beam: 500 µA Beam Current up to 15 MeV Energy
- Alpha Particle Beam: 200 µA Beam Current up to 35 MeV Energy

*Some of the products shown are under development and not available for sale currently.

www.bestcyclotron.com • www.bestproton.com • www.teambest.com

BCS USA tel: 865 982 0098 • BCS CAN tel: 604 681 3327 • BPT tel: 703 451 2378