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Assessment of whole-body radiation exposure to technologists during manual preparation of high specific activity non- carrier added 177Lu radiolabeled pharmaceuticals

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Abstract. Nuclear medicine technologists are frequently encounter radiation exposure while performing activities such as the preparation, labelling/synthesis, dispensing, and administration of radiopharmaceuticals, image acquisition on SPECT-CT, PET-CT scanners, area and personnel radiation level monitoring, and survey of radioactive waste management. Exposure levels can be notably higher while handling therapeutic radiopharmaceuticals like I-131, 177Lu , Sm-153 and Y-90. In India, carrier-added (CA) 177Lutetium (177Lu) radioisotopes are commonly used for the labelling of therapeutic purpose. Especially, a very few studies are available in the literature on personal dosimetry related to the labelling of non-carrier-added (NCA)177Lu radiopharmaceuticals.

This study is to assess the whole-body radiation exposure received by technologists during synthesis of 177Lu-PSMA-617 (prostate specific membrane antigen) and 177Lu-DOTATATE (DOTA-Tyr3-octreotate).

Furthermore, the occupational burden was compared with the occupational dose limits prescribed by various national, international regulatory authorities like Atomic Energy Regulatory Board (AERB), India and International Commission on Radiological Protection (ICRP).

Radiation exposure was measured by using a survey meter cum contamination monitor prior to initiating the labelling procedure. The instrument was positioned in the radio pharmacy lab where the technologists normally stands during the synthesis. To monitor personal radiation levels, the technologists were worn an electronic pocket dosimeter at chest level throughout labelling of 177Lu radiopharmaceuticals like DOTATATE, PSMA-617.

A total of 15 177Lu-DOTATATE and 15 177Lu-PSMA-617 synthesis were included in this study, each followed by quality control test.

Conclusion: According to our collected data, the technologist's whole-body radiation exposure during the manual radio labelling of 177Lu compounds was within the AERB recommended limits.

Keywords: Personnel dosimetry, whole body radiation dose, manual preparation, 177Lu -DOTATATE and 177Lu-PSMA-617 and Peptide receptor radio nuclide therapy.

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1 Introduction

In Nuclear medicine following radiation safety measures is utmost important, as it is dealing with unsealed sources (diagnostic and therapeutic purposes). Nuclear medicine technologists are exposed to radiation during area radiation surveys, acquisition, radiopharmaceutical dispensing administration and labelling/synthesis of radiopharmaceuticals.

While dealing with therapeutic radiopharmaceuticals like Iodine-131 (I-131), Yttrium-90 (Y- 90), Samarium-153 (Sm-153), Lutetium-177 (177Lu) and others, radiation safety measures should be followed during high administered activities and complex synthesis procedures involved due to high greater radiation exposure. An important component of radiation safety measures is personnel monitoring. Minimizing radiation exposure is the aim of personnel monitoring ALARA (As low as reasonably achievable) [1]. According to ICRP guideline 103 (2007) states that an occupational worker's effective radiation dose over a five-year period should not be more than 20 mSv, with no more than 50 mSv in any one year [2] in order to decrease the stochastic probability of radiation impacts and even to avoid non-stochastic effects.

1. The primary objective of our current study assessed the radiation exposure to the technologist during the manual preparation of 177Lu –DOTA-TATE and 177LuPSMA- 617 .

2. Secondary objective is to compare measured occupational whole body radiation doses with national (AERB) and International (ICRP) regulatory bodies. Not only we had to evaluate the influence of handled activity, synthesis duration on technologist whole body radiation dose, but also assess the feasibility and safety of manual preparation of NCA 177Lu radiopharmaceuticals in the absence of automated synthesis module methods.

177Lu is utilized extensively for peptide receptor radionuclide therapy (PRRT) applications due to its favorable physical, chemical and radiological characteristics, which include beta emissions {Max β-energy 497KeV (79%)} and concomitant gamma emissions {113KeV (8%) and 208KeV (11%)} with a half-life of 6.7 days. 177Lu is primarily produced by neutron irradiation of enriched 176Lu (or) indirectly through the decay of Yb-177 obtained from Yb-176 irradiation [3]. The non-carrier added (NCA) 177Lu produced from the latter route offers advantages, including the absence of long-lived metastable impurities (176Lu, $T_{1/2}$ = 160days) and having high specific activity, the need for lower peptide quantities for effective labelling and reducing radioactive management issues [4].

Figure 1: Indicates 177Lu production route: [5].

2 Materials and Methods

We procured 177Lu (NCA) radioisotope as Lu-Cl_3 from ITM (Isotope technologies Munich SE) company in Germany, at our facility. The precursors, peptides like PSMA-617 and DOTATATE and reagents were supplied by German company Abx, GmbH. The study was carried out for a period of 20 months (2021-2023).

2.1 Instrumentation

177Lu-DOTATATE & PSMA-617 can be prepared automatically, semi- automatically, or manually. Compared to the automatic, semi-automated methods manual method is cost-effective. In view of cost effective we were preparing 177Lu-labeled DOTATATE and PSMA-617 at our hot lab by manual method only.

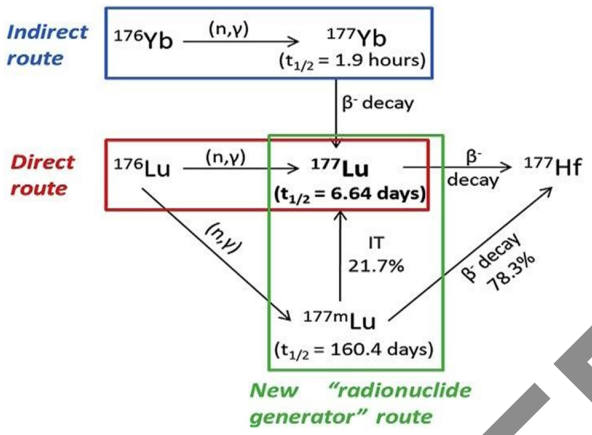

Figure 1. Indicates 177Lu production route

A survey meter cum contamination monitor was placed in technologist standing area during synthesis procedure. Periodically the accuracy of this instrument was verified with a known standard radioisotope like I-131 (Half-life = 8.04 days) by measuring the exposure rate at distance from I-131 activity. Then measure exposure rate levels at different time slots like before, during and after completion of labelling procedure. A pocket dosimeter was given to the technologist before start the labelling procedure, make sure that he/she should worn the pocket dosimeter entire during the labelling procedure by maintaining proper record. All the readings were documented after completion of the labelling of each recommended 177Lu radiopharmaceutical, like as amount of activity procured, synthesis duration time (min), productive yield and whole- body radiation dose to technologist, exposure rate.

2.2 Data analysis

Data were collected from 30 manual synthesis procedures of 177Lu-DOTATATE and 177Lu-PSMA-617 (15 each). Descriptive statistics, including mean, median, standard deviation (SD), and range (from lowest to greatest value) were ascertained. All measurements are reported as mean ± standard deviation.

3 Results and Discussion

3.1 Discussion

The objective of the present study was to estimate the radiation exposure levels of technologists during the 177Lu labelled radiopharmaceuticals like PSMA-617 and DOTA-TATE. The two compounds can be labelled with 177Lu manually or by an automated/semi- automated process [6, 7]. Currently our institute do not have semi-automatic, fully automated synthesis modules. Despite the possibility of increased radiation dose to technologists, we were preparing the labelling of both these compounds with 177Lu (NCA) by using manual method only.

The highest specific activity (>3600GBq/mg) up to 4–5 times higher was offered by 177Lu (NCA) as compared with 177Lu (CA) which can help effective radio labelling as well as effective PRRT therapy procedure. It is distinguished by having a substantially longer

Table 1. Radiation Dose readings during the labelling of 177Lu-PSMA

S. No	Procured Lu177-Cl_3 (mCi)	Product (mCi)	Waste (mCi)	Duration (Min)	%RCP	Exposure rate (mSv/Hr.)	Radiation dose (mSv)
1	354	350	3	56	99	0.046	0.013
2	348	341	6	54	98	0.042	0.011
3	191	189	1	53	99	0.035	0.010
4	180	175	4	53	97	0.032	0.009
5	176	167	7	52	95	0.030	0.009
6	175	172	2	52	98.5	0.030	0.008
7	167	161	5	53	96.5	0.027	0.008
8	162	157	4	52	97	0.026	0.007
9	159	155	3	53	98	0.026	0.007
10	156	149	5	52	95.5	0.024	0.006
11	150	147	3	52	98.3	0.025	0.007
12	145	137	6	53	94.5	0.023	0.006
13	140	136	3	52	97	0.023	0.007
14	135	132	2	52	98	0.021	0.006
15	133	131	1.5	52	99	0.022	0.006
Range	354–133						
Mean	184.73	179.93	3.7	52.73	97.3	0.028	0.00813
Std	67.2	66.94	1.73	1.06	1.4	0.00708	0.0019

Table 2. Radiation Dose readings during the labelling of 177Lu-DOTATATE

S. No	Activity (mCi)	Product (mCi)	Waste (Waste vial Cartridge) mCi)	Duration (Min)	%RCP	Exposure rate (mSv/Hr)	Radiation dose (mSv)
1	520	504	14	55	97.8	0.033	0.018
2	446	439	5	54	97.5	0.048	0.016
3	370	362	6	53	98	0.046	0.014
4	320	316	7	53	99	0.041	0.013
5	295	284	7	52	96.5	0.039	0.012
6	265	257	6	52	97	0.037	0.011
7	220	215	4	53	98	0.035	0.010
8	190	186	3	53	98.3	0.033	0.009
9	183	178	4	53	97.5	0.032	0.008
10	181	173	7	53	95.5	0.032	0.007
11	165	161	4	53	98.1	0.031	0.007
12	146	144	1	53	99	0.029	0.006
13	145	140	4	52	96.8	0.029	0.006
14	135	128	5	52	94.6	0.028	0.007
15	132	127	4.5	53	96.5	0.028	0.007
Range	520-132						
Mean	247.53	240.9	81.5	52.9	97.4	0.036	0.010
STD	116.2	113.96	2.78	0.77	1.21	0.0075	0.0037

Table 3. TLD Readings (during synthesis period of 20 months from various unsealed sources)

Quarter	Chest (mSv)	Wrist (mSv)
1	0.45	4.5
2	0.5	5.0
3	0.6	6.3
4	0.7	7.5
5	1.0	8.4
6	1.2	9.4
7	0.9	7.8

shelf life and a shorter synthesis time than the CA (carrier added) 177Lu version. The required quantity of peptides for labelling of 177Lu-DOTA-TATE and 177Lu-PSMA-617 is less and also the maximum radionuclide purity was possible with 177 Lu (NCA), On the other hand, the carrier- added 177 Lu(CA) contains up to 0.1% metastable Lutetium (177m Lu, $t_{1/2}$= 160.1days) and required appropriate radioactive management which it can financially burden to low income health care providing facilities.

Previous research by Arora G et al. [8] has addressed the estimation of whole-body radiation dose to nuclear medicine professionals during the synthesis of 177 Lu labelled radiopharmaceuticals; however, their study was limited to the use of carrier added (CA)177Lu. The radiation exposure may differ significantly. Notably, there is a lack of published data specifically evaluating whole-body radiation dose during the synthesis of 177 Lu (NCA) la-

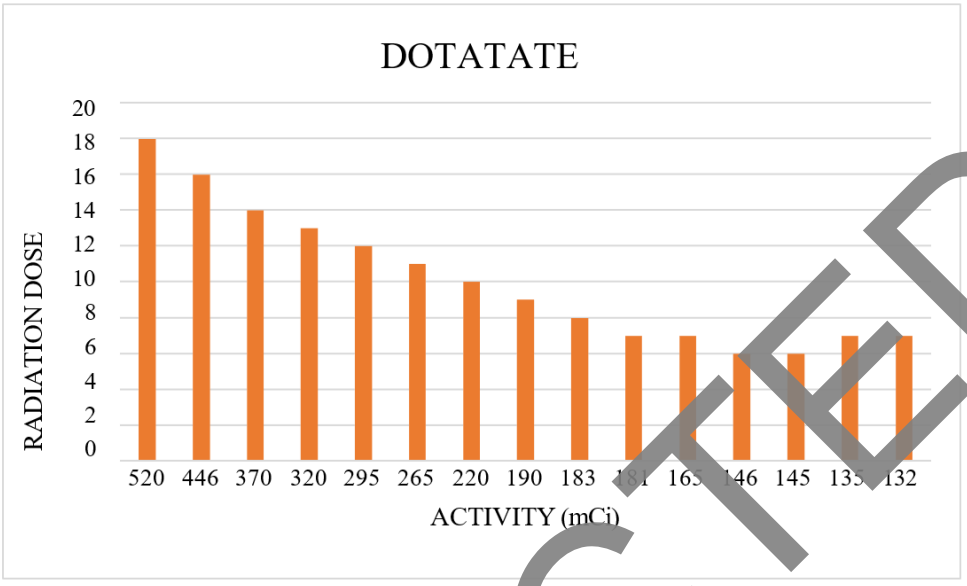

Figure 2. Represents Activity VS Radiation Dose (177Lu - DOTA-TATE)

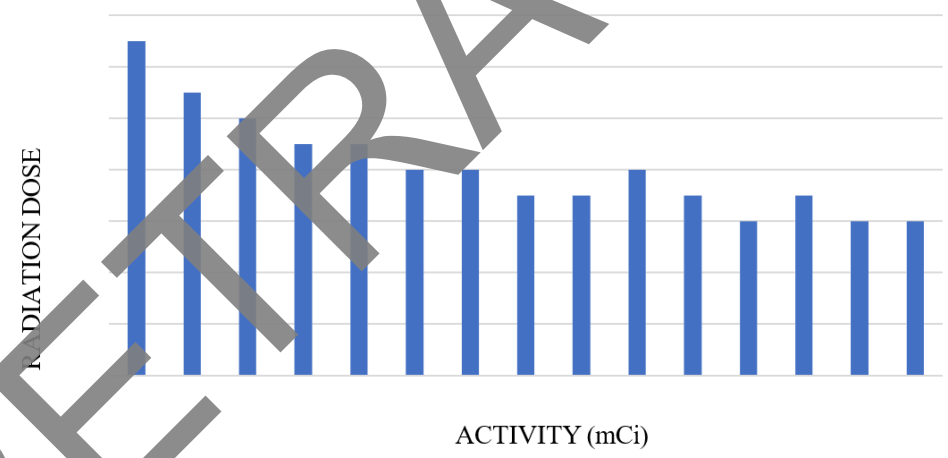

Figure 3. Represents Activity VS Radiation Dose (Represents Activity VS Radiation Dose (177Lu-PSMA-617)

belled compounds. This study was therefore undertaken to fill this critical gap in the existing body of literature.

Dash et al. [4] thoroughly studied the production methods and physical characteristics of 177Lu and highlighted the advantages of NCA 177 Lu, including its significant specific activity, absence of long-lived 177 mLu (Lu177 at metastable state) impurity, and reduced quantity of radioactive waste. Such features not only improve the therapeutic quality of ra-

diopharmaceuticals, but also additionally reduce occupational radiation exposure by lowering preparation time and waste management requirements.

According to our findings, the average radiation dose during labelling of 177Lu DOTATATE and 177Lu-PSMA-617 was 0.1 ± 0.036 mSv and 0.08 ± 0.019 mSv respectively. The amount of radioactivity handled and the time required for radio labelling are the reason for the trend seen in tables 1 and 2. 177Lu-DOTA-TATE (55min & 520 mCi) and 177Lu- PSMA-617 (56 min & 348 mCi) had the highest radiation doses i.e. 0.18 ± 0.036 mSv and 0.13 ± 0.019 mSv, respectively. The two 177Lu- based compounds had a total mean radiation dosage of 2.71mSv ± 0.05 (15x 0.1± 0.036 + 15 x 0.08 ± 0.019). If each person involved in 30 such synthesis procedure per year, the minimum radiation dose will be 2.675 mSv.

The TLD badge (Chest and Wrist) reports of the person involved was also well within the permitted range, which is 2.25 mSv for a one-year Chest TLD (whole-body effective dose) reports (comprises the radiation that technologists were exposed to from other unsealed sources like 18F, Ga68 and I131 labelled radiopharmaceuticals). These doses fall well short of the established 20mSv/year (averaged over 5 years) AERB guidelines. For a year, the TLD badge's wrist badge reading was 23.3mSv (For extremities the annual equivalent dose limit 500mSv per year). Overall, the data shows that manual radio-labelling techniques do not result in excessive occupational radiation doses when they are carried out in accordance with radiation safety regulations. When preparing 177Lu radiopharmaceuticals, Nair and Pillai [9] highlighted the importance of safe handling procedures and strict adherence to ALARA principles. According to their findings, staff training, personal dosimetry, remote handling equipment, and appropriate shielding greatly minimize occupational exposure. The low radiation doses observed in our study further validate these recommendations and confirm that manual labelling techniques, when performed under controlled conditions do not pose undue radiation risk to technologists. As shown in Tables 1 and 2, somewhat higher radiation dose seen during 177Lu-DOTA-TATE synthesis as compared to 177Lu-PSMA-617 can be attributed to the higher activity handled and longer synthesis period. Higher administered activities have been associated to increased exposure during the production of therapeutic radiopharmaceuticals, in accordance with similar findings observed by Ahmadzadehfar et al. and Delker et al. [10, 11]. This reinforces how important it is to minimize handling time and manage procedure in order to lower exposure during work.

Using NCA 177Lu has the benefit of lowering waste volume and synthesis time, which indirectly lowers occupational exposure. Automated synthesis modules can reduce exposure even more, although they might not be practical in many situations because of infrastructure and cost constraints. Furthermore, a direct comparison was not feasible since our department do not have an automated or semi-automatic synthesis module (as earlier mentioned).

This study emphasizes the significance of ALARA principles, which include personal monitoring with dosimeters:

1. Using shields and tongs
2. Staff rotation to divide workload
3. Planning the processes of synthesis in advance to reduce exposure

4 Conclusion

The findings of this study suggest that manual labelling of 177Lu radiopharmaceuticals can be performed safely, with occupational whole-body radiation doses remaining well below the limits recommended by the AERB, ICRP (20mSv/year averaged over five years). These

results affirm that, when appropriate radiation protection measures and safe work practices are implemented, manual labelling method provides a reliable and safe alternative even in the absence of automated or semi-automatic synthesizer modules.

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Nil

Conflicts of interest

There are no conflicts of interest

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