

## External dose assessment from the patients treated by $^{177}\text{Lu}$ -DOTATATE

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### ► Short report

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### INTRODUCTION

One of the most important radionuclides in the field of therapy with nuclear medicine is Lu-177, which is a new and promising tool for control of non-operable metastatic neuroendocrine tumor when it is combined with somatostatin analogues (1-3). Currently most centers offering  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate treatment perform it only in hospitals; because isolation and hospital admission are among controversial subjects. Conversely, in some countries, patients are discharged within a few hours after treatment when a determined outpatient's release criterion is achieved according to local regulations (for example 30  $\mu\text{sv/h}$  in Turkey and 25  $\mu\text{sv/h}$  in Australia) (4-5). Since, treatment with  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate is costly, additional costs of hospitalization are incurred by many patients. Long-term isolation in the hospital may also cause emotional disturbances to the patient. The use of different types of shield is questionable due to production of specific X-rays of lead following collision of high-energy gamma rays (6). However, various reports on methods of reducing the dose received by staff have been published by some

### ABSTRACT

**Background:** The present study was done to establish release criterion in the treated patients and to determine external radiation doses received by personnel and caregivers of patients with metastatic neuroendocrine tumors (NETs) during peptide receptor radionuclide therapy (PRRT) by means of Lutetium-177 ( $^{177}\text{Lu}$ ) DOTATATE.

**Materials and Methods:** For this purpose, 30 patients were enrolled in the study who received  $5.5 \pm 1.1$  (in a range of: 3.7-7.4) GBq of  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate. Dose rate was analyzed at distances 0, 0.25, 0.5, 1.0, and 2.0 m in different times after termination of infusion using an ionization chamber. **Results:** Mean dose rate at distance of 1 m from the patient, approximately 5 h after injection was considered as discharge limit. The maximum dose to caregivers in the first 48 h was equal to  $340 \pm 29$   $\mu\text{Sv}$ . Mean dose to the nurse was estimated as  $6.3 \pm 0.4$ , and  $7 \pm 0.5$   $\mu\text{Sv}$  per patient with and without lead shield, respectively. **Discussion:** According to our findings, approximately a time delay of 5 h after injection is recommended as release criterion for patients treated by Lutetium-177 ( $^{177}\text{Lu}$ ) DOTATATE. For a total of 30 patients, external radiation dose to staff was found to be within permissible levels. **Conclusion:** The use of protective equipment is recommended at all stages of procedure for staff.

national and international organizations (7). Therefore, the present study is designed to firstly focus on quantification of the caregiver's mean dose, and secondly establishment of release criterion for patients treated with  $^{177}\text{Lu}$ -DOTATATE.

### MATERIALS AND METHODS

The current study was approved by the Ethics Committee of the University (IR.SBMU.MSP.REC.1400.292), and an informed written consent was obtained from all the patients then, it was carried out according to provisions of the Declaration of Helsinki. Inclusion criteria were having over 35 years of age, being diagnosed with metastatic neuroendocrine tumor, and being candidate to be treated with  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate. Mean age of patients was equal to 52.6 years (in a range of: 38-60 years) old. A total of 30 patients undergoing treatment with  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate, were enrolled in the current study from March to August 2019. Patients were admitted in Department of Nuclear Medicine, Shohada-e Tajrish Hospital, Tehran Province, Iran. Infusion of 1,500-2,000 mL of normal

saline and amino acids, mixture of 5% lysine HCl (50 mg) and 10% L-arginine HCl (50 mg) was carried out for 4 h to reduce radiation exposure of kidneys and subsequent adverse effects. The procedure was started 30 min after administration of  $5.5 \pm 1.1$  GBq (in a range of: 3.7-7.4 GBq) of  $^{177}\text{Lu}$ -DOTATATE. All the administered patients were positioned in an isolated room with an area about 30 m<sup>2</sup>. The room included 4 beds located in 4 corners of the room, with about 2 m of distance from each other.

### Dose rate measurement

The dose limit recommended by European guidelines for discharge of patients after iodine-131 therapy was set as the basis for discharge (20  $\mu\text{Sv/h}$  at 1 meter) (8-9). Using equation (1), cumulative dose can be estimated,  $E$ , to a caregiver standing from the patient for an unlimited time, assuming that only physical decay occurs. It was assumed that rate of initial dose is  $D_0 = 20 \mu\text{Sv/h}$  at 1 m of distance, with half-life of  $^{177}\text{Lu}$ , 6.7 days, which is represented by  $t_{1/2}$ . Following calculation it was found that  $E = 4.6 \text{ mSv}$  (10).

$$E = \int_0^{\infty} D_0 \times e^{-\ln(2) \times \frac{t}{t_{1/2}}} dt \quad (1)$$

This study was carried out using an ionization chamber (Thermo, FH 40G-L10, made in Germany) calibrated by the secondary standard dosimetry laboratory (SSDL). Energy response of the dosimeter is equal to 30 keV-4.4 MeV and it has the capability to measure dose rate in the range of 10 nSv/h\_100 mSv/h. Dose rate was measured on chest position at distances of 0, 0.25, 0.5, 1, and 2 m from the patient who received  $5.5 \pm 1.1$  (in a range of : 3.7-7.4) GBq of  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate with and without 2-mm lead shield after the mentioned time (0, 1 h, 2 h, 3 h, 4 h, 5 h, 18 h and 24 h). Mean dose to staff was estimated by recording the time interval and dose rate at the mentioned distances from the patient (11). Finally, mean dose to staff and related SDs were calculated based on  $\mu\text{Sv/GBq.h}$ . The demographic information of staffs included in the current study is presented in table 1.

**Table 1.** The demographic information of staffs who are included in current study.

Staff	No.		Distance
	Female	Male	
Technologist responsible for injection	4	0	0 m (injecting radiopharmaceutical)
Technologist responsible for imaging	2	2	0.25 m (positioning the patient) 1 m (presentation information for the patient)
Nurse	2	0	2 m (check out the treatment process)
Physicist	1	1	2 m (providing protection guidelines)
Physician	2	0	0.25 m (check patient vital signs)

### Determining behavioral pattern for caregivers

Authors defined a pattern of behavior for the patient's caregivers (a member of the family). Due to different conditions of patients, caregivers were categorized into three groups. The details are given in table 2. Caregivers' mean dose was determined according to their behavioral pattern, duration of time spent with the patient, and measured dose rate.

**Table 2.** Caregivers' Behavior Pattern in different groups.

Number of group	Pattern of behavior
First group	The patient was able to perform individual activities The patient was kept in a separate room and used a separate toilet The patient slept alone The patient was traveling by a separate vehicle. The caregiver visited his patient on average 5-10 minutes for the first 5 hours
Second group	The patient was able to perform individual activities The caregiver visited his patient on average 10-15 minutes for the first 5 hours The caregiver was slept 2 meters of the patient The patient and caregiver used a shared vehicle to drive
Third group	The patient was not able to perform any personal tasks after treatment The caregiver was present during the first 5 hours of treatment at the closest distance to the patient The caregiver was slept 1 meters of the patient The patient and caregiver used a shared vehicle to drive

### Statistical analysis

Data processing and fitting were performed using Microsoft Excel (Microsoft office professional plus, 2013) and SPSS (ver. 16.0, IBM Corp.) softwares were used for statistical analysis. For this purpose, the K-S (Kolmogorov-Smirnov) test was used to investigate normal distribution of data. A value of p-value of  $\leq 0.05$  was assumed as statistically significance. Data were presented as mean and standard deviation unless stated otherwise.

## RESULTS

Mean dose rate at a distance of 1 m from the patients treated with  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate in different times after administration was measured and results are presented in figure 1. As shown in figure 1, dose rate was gradually decreased due to excretion of activity from the body. According to figure 1 for  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate therapy, equation (2) was obtained from the curve, which was fitted to the data.

$$y = 28.442 e^{-0.067x} \quad (2)$$

The  $x$  and  $y$  indicates the time (h) and dose rate ( $\mu\text{Sv/h}$ ), respectively. Mean dose rate at a distance of 1m from the patient, approximately 5 h after the injection was measured as the discharge criterion.

According to the results of current study, mean

dose rate (μSv/GBq.h) at a close distance to a patient was obtained equal to 13.6 (SD=1.2) at 0 m, 8.9 (SD=1.2) at 0.25 m, 4.1(SD=0.6) at 0.5 m, 1.3 (SD=0.2) at 1 m, and 0.6 (SD=0.2) at 2 m.

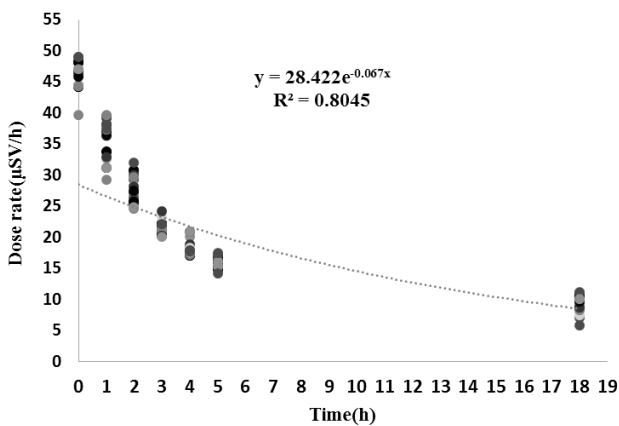


Figure 1. External dose rate (μSv/h) for patients treated with <sup>177</sup>Lu-DOTATAE therapy at 1 m distance.

**Dose to staff with and without lead shield**

The mean, minimum, and maximum doses to staff in charge of caring the patients under treatment by <sup>177</sup>Lu-DOTA-tyr<sup>3</sup>-octreotate, were measured according to the time and distance from the patient

with and without lead shield. The results are summarized in table 3. The annual mean dose of the staff, the distance and duration of time, in which they were in direct contact with the patient during each treatment period are listed in table 4. About 240 treatment sessions are performed annually at the Nuclear Medicine Center in shohada-e Tajrish Hospital (Tehran, Iran). The annual mean dose for staff in all treatment cycles was evaluated (patients selected for study as well as excluded patients). The annual mean dose received by the nurse was higher than all staff, which was approximately by 1.80 mSv. When lead shield is used, this value is estimated as 1.4 mSv. This value is estimated to be 1.7 and 0.8 mSv, for staff in charge of radiopharmaceutical injection and imaging staff, respectively. The annual mean dose was 1.3 and 0.6 mSv in case of not using and using lead-shield, respectively. Physician and physicist have the lowest annual dose received with and without using lead shield, by 0.5 and 0.6 mSv, respectively. The calculations were done based on the number of treatment sessions performed over a year assuming that nuclear medicine personnel participate in all treatment sessions.

Table 3. Mean, minimum and maximum dose (μSv per patient) of the staff during PRRT with <sup>177</sup>Lu-DOTATAE, without and with the use of lead shield.

Staff	Without lead shield			With lead shield		
	Min dose per Patient (μSv)	Max dose per patient (μsv)	Mean± SD	Min dose per patient (μSv)	Max dose per patient (μsv)	Mean ± SD
Staff in charge of radiopharmaceutical injection	6.1	8.0	6.5±0.5	5.0	6.5	5.7±0.8
Staff in charge of imaging	3.0	4.0	3.3±0.5	2.0	3.1	2.5±0.4
Physician	2.0	3.2	2.5±0.4	1.8	2.5	2.1±0.2
Physicist	2.2	3.0	2.7±0.2	2.0	2.5	2.2±0.2
Nurse	6.5	8.5	7.5±0.5	6.8	5.0	6.3±0.4

Table 4. Estimated annual mean dose to staff in treatment by <sup>177</sup>Lu-DOTATATE.

Staff	Mean annual dose using lead shield (mSv)	Mean annual dose without lead shield (mSv)
Staff in charge of radiopharmaceutical injection	1.3	1.7
Staff in charge of imaging	0.6	0.8
Physician	0.5	0.6
Physicist	0.5	0.6
Nurse	1.4	1.8

**Dose to caregivers**

Mean dose to 30 caregivers was found to be within a range of 36-390 μSv in <sup>177</sup>Lu-DOTA-tyr<sup>3</sup>-octreotate therapy after infusion of 5.5±1.1 (in a range of: 3.7-7.4) GBq. Mean dose of the first caregiver group was estimated to be 47.3 ± 8.4 μSv (in a range of: 36-60 μSv). Mean dose of the second group was equal to 184 ± 29 μSv (in a range of: 150-220 μSv). The third group had the highest mean dose, by 340.5±29 μSv (in a range of: 300–390 μSv).

**DISCUSSION**

Two important features of clinical treatment are

cost-effectiveness and availability of treatment. Many nuclear medicine centers are not able to offer this treatment because of lack of facilities for hospitalization, increasing waiting time for patients to receive <sup>177</sup>Lu-DOTA-tyr<sup>3</sup>-octreotate treatment. Based on results of the current study presented in figure 1, mean dose rate at a distance of 1m from the patient, approximately 5 h after the injection was considered to be lower than the discharge limit. According to figure 1, equation (2) would also be used to achieve release criterion which was defined less than 20 μSv/h at a distance of 1m, and can be considered as a dose limit for discharge from the patients treated with <sup>177</sup>Lu-DOTA-tyr<sup>3</sup>-octreotate. In a similar study on iodine therapy, Ahmadi

Jeshvaghane *et al.*,<sup>(9)</sup> showed that the maximum and minimum doses after release were equal to 21 (SD-18) and 11 (SD-4.0)  $\mu\text{Sv/h}$  at a distance of 1 m from the patients, respectively.

Mean dose for caregiver in three groups was measured below the level recommended by the International Commission on Radiological Protection (ICRP) for each patient [5 mSv] in each treatment period<sup>(10)</sup>. The amount of activity received by the patients and duration of the caregiver's presence at close distances to the patient are important parameters regarding the caregiver's mean dose. Abuqbeith *et al.*,<sup>(8)</sup> in a study reported the limit of 20  $\mu\text{Sv/h}$  for hospital discharge. They estimated a dose rate of 100-200  $\mu\text{Sv}$  for caregiver of the patients receiving  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate treatment<sup>(8)</sup>. Calais *et al.*,<sup>(5)</sup> estimated the mean total dose to 25 caring sessions during day of therapy and they reported a dose rate of 10-470  $\mu\text{Sv}$  for surrounding people while taking the patient to home within a period up to 5 days after treatment. However, some nuclear medicine clinics prefer to admit patients in hospital to monitor the probable side effects. In a study by Kurt *et al.*,<sup>(12)</sup> patients were admitted in two centers to be hospitalized for 48 and 72h. The maximum dose to individual members in the public per treatment cycle was  $\sim 250 \pm 55$  and  $\sim 190 \pm 36$   $\mu\text{Sv}$  when the patients were discharged after 48 and 72 h, respectively. But our findings, showed no need for intensive radiation monitoring of caregivers who had a distance more than 1 m from the treated patients. Abuqbeith *et al.*,<sup>(8)</sup> showed that the maximum mean dose received by radiopharmaceutical injection was equal to  $4 \pm 1.9$   $\mu\text{Sv}$  per patient. Calais *et al.*,<sup>(5)</sup> reported the maximum mean staff dose (of 33  $\mu\text{Sv}$ ) for the nurse. Results of the current study showed the maximum mean dose of 7.5  $\mu\text{Sv}$  per patient for nurse. Table 5 presents comparison of the results for staff. The nurse's high mean dose is due to the fact that the nurse has the most contact with the patient during treatment. The difference between results of studies may be due to experience, skills, and promptness of the staff. No measured dose to hospital staff or family members exceeded the limits.

**Table 5.** Comparison of the results of current study with international results.

	Abuqbeith <i>et al.</i> <sup>(8)</sup> $\mu\text{Sv}$ Per therapy treatment day with one patient	Calais <i>et al.</i> <sup>(5)</sup> $\mu\text{Sv}$ Per therapy treatment day with four patients	Current study $\mu\text{Sv}$ Per therapy treatment day with one patient
Staff in charge of patient imaging	$3.0 \pm 0.5$	7.0	$3.3 \pm 0.5$
radiopharmaceutical	$4.0 \pm 1.9$	17.0	$6.5 \pm 0.5$
physicist	$2.0 \pm 0.8$	9.0	$2.7 \pm 0.2$
Physician	$2.0 \pm 0.5$	8.0	$2.5 \pm 0.4$
Nurse	$5.0 \pm 1.1$	33.0	$7.5 \pm 0.5$

### LIMITATION

The limitation of this study was low number of patients included in the study. Also there were no

lead and syringe shields of varying thicknesses for general assessing the effect of protective equipment on the received dose.

### CONCLUSION

Results of the present study showed that the dose rate from the injected patients was decreased to lower than the specified threshold of 20  $\mu\text{Sv/h}$  at a distance of 1 m after approximately 5 h. which was considered as release criterion for patients treated with  $^{177}\text{Lu}$ -DOTA-tyr<sup>3</sup>-octreotate. Due to the effect of lead shield on reducing staffs mean dose, it is recommended that protective device should be used in all treatment stages. In summary, no measured mean dose to hospital personnel, caregivers, family or member of the public exceeded the annual related dose limits.

**Ethical consideration:** Provide The current study was approved by the Ethics Committee of the University (IR.SBMU.MSP.REC.1400.292).

**Declaration of Interests:** Declared none.

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