Dose Rate Levels in Patients Undergoing [^{177}Lu]Lu-PSMA-617 Therapy

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The authors declare that they have no competing interests.

Abstract

Introduction The frequency of [^{177}Lu]Lu-PSMA therapy is increasing. At present most therapies are given in Germany during a 48-hour hospital admission. Shortened hospital stays are desirable. Dutch guidelines rely on dose rate levels <20 µSv/h at 1 m for discharge. Our aim was to define the optimal length of hospital admission within national safety guidelines.

Materials and Methods Dose rate levels of patients receiving [^{177}Lu]Lu-PSMA-617 therapy were measured at 1 m at baseline and 3, 5, 8 and 19 hours post-injection. Exponential fits for each administration were created to allow for interpolation. Dose rate levels after treatment with 7.4 GBq [^{177}Lu]Lu-DOTATATE therapy and a group of 7.4 GBq [^{177}Lu]Lu-PSMA-617 therapy were compared.

Results Twenty-four patients were treated with thirty-three administrations of a median of 6 GBq [^{177}Lu]Lu-PSMA-617. Median dose rate levels after 0, 3, 5, 8 and 19 hours were 27.3, 23.3, 19.8, 18.0 and 11.0 µSv/h. At twelve hours post-injection, median interpolated dose rate levels of 91% of the patients were <20 µSv/h. When extrapolating data to 7.4 GBq, dose rate levels decrease below this limit after ten hours, which is faster than after 7.4 GBq of [^{177}Lu]Lu- DOTATATE therapy (fourteen hours).

Conclusions Intravenous [^{177}Lu]Lu-PSMA-617 treatment with 7.4 GBq per administration during a twelve hour hospital admission in The Netherlands seems safe and feasible.

Introduction

Lutetium-177 ([^{177}Lu]Lu)-PSMA-617 is a promising therapy for metastatic castration resistant prostate cancer (mCRPC) patients. Currently most [^{177}Lu]Lu-PSMA therapies are given in Germany, where mCRPC patients are admitted to the hospital for 48 hours to reduce dose rate levels to 3.5 µSv/h measured at a distance of 2 m (1) - which is 14 µSv/h at 1 m - to account for the radiation exposure of the environment. In The Netherlands patients are often admitted overnight for up to 24 hours after [^{177}Lu]Lu-PSMA therapy administration. Patients are discharged when dose rate levels decrease below 20 µSv/h at 1 m according to national guidelines (2) originally designed for iodine-131 ([^{131}I]NaI) therapy. These guidelines have recently been revised (3), taking into account the expanding amount and variety of radionuclide therapies. Guidelines are based on dose constraints that apply to persons in direct relation to the patient ('relatives' or 'care givers,') and to the general population. Based on differences in radiation sensitivity, dose constraints are set on: 1 mSv per treatment for children, 3 mSv per treatment for adults, and 15 mSv per treatment for adults >60 years. For the general population, a dose constraint of 0.3 mSv per treatment is advised. Adherence to strict radiation safety precautions for a maximum of two weeks for adult relatives is taken into account to allow for discharge of patients after therapy. We hypothesise that hospital admission after radionuclide therapy can be shortened, being both beneficial to the patients' comfort and admission-related costs. To date, post-injection dose rate levels on different time points in patients undergoing [^{177}Lu]Lu-PSMA-617 therapy have not been extensively studied, and existing literature shows conflicting results and protocols (4,5).

Methods

Patient population

Dose rate data of patients who had 6 GBq [^{177}Lu]Lu-PSMA-617 therapy at UMC Utrecht between February and May 2018 were collected at several time points (cohort #1). Criteria for treatment included (a) confirmed histological diagnosis of mCRPC without any alternative cytotoxic treatment options, (b) ≥1 previous episode of chemotherapy, hormonal therapy and either enzalutamide or abiraterone in past medical history and/or inadequacy to undergo chemo-/hormonal therapy, (c) World Health Organisation (WHO) performance status ≤2, (d) sufficient bone marrow capacity, defined as haemoglobin level >5.0 mmol/l, leukocytes >2.0 x 10^9/l, neutrophils >1.5, platelets >75 x 10^9/l, (e) sufficient renal function, defined as glomerular filtration rate (eGFR) >45 ml/min,

(f) baseline gallium-68 ([^{68}Ga]Ga)-PSMA-11 PET/CT ≤2 months prior to administration of the first therapy administration and (g) metastatic disease with dominant tumour sites showing relatively high PSMA-ligand-expression (visual assessment; tumour uptake >> normal liver parenchyma) on baseline [^{68}Ga]Ga-PSMA-11 PET/CT. Patients received up to six administrations of intravenous [^{177}Lu]Lu-PSMA-617, at six weekly intervals. Patients were informed about possible side effects and risks of this new therapeutic agent. The institutional review board of UMC Utrecht approved this retrospective study (protocol number 19-079/C).

Comparison cohorts
As a comparison, two additional patient cohorts were analysed.
First comparison cohort (cohort #2) consisted partially of patients treated with 7.4 GBq [^{177}Lu]Lu-PSMA-617 per administration instead of 6 GBq. This was implemented at the end of 2018, as a standard dose of 7.4 GBq per administration would become the expected recommendation (in line with the VISION study protocol (6)). For these patients, dose rate data at discharge (after nineteen hours; one night hospital admission) were collected. A second portion of this cohort consisted of an additional group of mCRPC patients treated with 7.4 GBq [^{177}Lu]Lu-PSMA-617 in 2019 during a twelve hour hospital admission. Dose rate levels were measured at discharge (after twelve hours).
The second comparison cohort (cohort #3) consisted of patients treated with another [^{177}Lu]Lu-bound radionuclide treatment, [^{177}Lu]Lu-DOTATATE, 7.4 GBq per administration. Between February and May 2018 multiple dose rate levels were collected in patients who had at least one [^{177}Lu]Lu-DOTATATE therapy administration during hospital admission. Criteria for treatment of these patients was in line with international recommendations (7,8).

Administration of radionuclides
[^{177}Lu]Lu-PSMA-617 therapies were intravenously injected within a five minute protocol including flushing of the syringe, using a shielded automatic administration pump (RAD-INJECT, Tema Sinergie, Faenza, Italy) and co-infused with a regular saline solution (NaCl 0.9%) during four hours. [^{177}Lu]Lu-DOTATATE therapies were administered using the same system and speed of infusion (9), co-infused with an amino-acid solution (1 liter arginine/lysine 2.5%/2.5%) during four hours.

Dose rate measurements and calculations
Patients were admitted to the nuclear medicine ward between 9-11 AM and treatment was administered at 1.30 PM. Dose rate levels were measured by the nursing staff with a radiation survey meter (Radiagem2000, CanberraTM) at a distance of 1 m, at the level of the abdomen while the patient was standing upright in the room sluice. Measurements were done at baseline and 3, 5 and 8 hours after administration of the radioligand (referred to as T0, T1, T2 and T3, respectively), and at hospital discharge (T5). T4 was used for interpolated data. Decay of activity was approximated by an exponential trend line for each therapy administration. Dose rate levels of all therapy administrations were eventually compared to the cut-off value of 20 µSv/h, as defined by National radiation guidelines. The proportion of patients with dose rate levels below this cut-off value was counted.
In the comparison cohort #3, patients treated with 7.4 GBq of [^{177}Lu]Lu-DOTATATE therapy were measured at the same time points (T0, T1, T2 and T3), and at hospital discharge (T5).
For the comparison cohort of patients treated with 7.4 GBq of [^{177}Lu]Lu-PSMA-617 (cohort #2), dose rate levels were measured only at discharge (T5), after twelve or nineteen hours.
Median dose rate levels of cohort #3 at T0 were used as a reference for cohort #1 to correct for the difference in administered activity and shift the curve upwards (in absence of T0 measures for cohort #2), under the assumption that directly after rapid administration of 7.4 GBq [^{177}Lu]Lu (independent of the ligand), activity is within bloodpool only.

Tumour load calculations
Tumour load of all included patients was semi-automatically delineated on their most recent [^{68}Ga]Ga-PSMA-11 or [^{68}Ga]Ga-DOTATOC PET/CT scans in SYNGO.VIA (Siemens Healthineers, Erlangen, Germany). Using the blood pool peak standardized uptake value (SUV_{peak}) as a threshold for tissue delineation according to the PERCIST classification (10), PSMA-derived active tumour volume: total lesions PSMA-uptake (TL-PSMA) was calculated, as a resemblance of total patient tumour load and tumour tracer accumulation. All healthy tissues were manually excluded from the semi-automatic delineation.

Statistics
Data (when skewed) and ordinal values are expressed as median and inter-quartile range. To designate a possible correlation between tumour load, PSA level, eGFR or administered dose and radiation retention intervals, the Pearson's correlation coefficient was used. Statistics were performed with Microsoft Excel 2010. Level of significance was set at a p-value <0.05.

Results

Baseline characteristics of all analysed patients are shown in table 1. Twenty-four patients (33 administrations) were included in cohort #1, fifteen patients (48 administrations) in cohort #2 and thirteen patients (25

administrations) in cohort #3. Nineteen patients were measured during one administration (fifteen in cohort #1, four in cohort #3), 24 patients during two administrations (nine, nine and six in cohort #1, #2 and #3 respectively), and nine patients during three or more administrations (six in cohort #2 and three in cohort #3).
A large variation in dose rate levels and decline was observed. In cohort #1, three out of 33 administrations (9%) dose rate levels were <20 µSv/h at 1 m directly after administration. In 22 (67%), dose rate levels decreased below this limit after eight hours and all patients were discharged with dose levels below 20 µSv/h at 1 m after nineteen hours. After exponential interpolation of all separate curves, in 91% of all administrations, dose rate levels decreased < 20 µSv/h after twelve hours. Of note, only three patients had a dose rate ≥20 µSv/h measured at twelve hours post injection (20.0, 20.8 and 20.9 µSv/h). Dose rate decline after administration of 6 GBq [177Lu]Lu-PSMA-617 (cohort #1) is shown in figure 1A (median and IQR, exponential fit added); in figure 1B, dose rates of all these separate 6 GBq [^{177}Lu]Lu-PSMA-617 therapy administrations are shown. Interpolated data for all separate administrations (T4; twelve hours post injection) are added in red.

Mathematically converting the measured 6 GBq [^{177}Lu]Lu-PSMA-617 curve to a 7.4 GBq [^{177}Lu]Lu-PSMA-617 curve, the exponential trend line of 6 GBq [^{177}Lu]Lu-PSMA-617 curve is moved upwards, to start at a dose rate similar to the 7.4 GBq [^{177}Lu]Lu-DOTATATE therapies (*dose rate level* $= 3.253 + 26.591e^{-0.047t}$, where t = time in hours). This conversion shows that after ten hours, dose rate levels decrease <20 µSv/h (i.e. 19.9 µSv/h; figure 2). Median measured dose rate levels of cohort #2 confirm this finding, as dose rate levels were 12.6 (IQR 11.0-15.5) after twelve hours (all <20 µSv/h) and dose rate levels were 14.5 (IQR 12-17.5) after nineteen hours (all <20 µSv/h).

Figure 2 also shows that dose rate levels decrease more slowly after 7.4 GBq [^{177}Lu]Lu-DOTATATE than [^{177}Lu]Lu-PSMA-617, which is in line with the known longer biological half-life of DOTATATE over PSMA-617 (11,12).
The curve for [^{177}Lu]Lu-DOTATATE however is higher, even though the

Tabel 1. Patient characteristics of the three analysed cohorts. 19 patients (20 cycles); 26 patients (28 cycles)

	Cohort #1	**Cohort #2**	**Cohort #3**
Number of patients	24	15	13
Ligand	[^{177}Lu]Lu-PSMA-617	[^{177}Lu]Lu-PSMA-617	[^{177}Lu]Lu-DOTATATE
Age in years (IQR)	70 (65-76)	72 (66-75)	62 (55-74)
Total number of cycles	33	48	25
Patients who had 1 cycle during the study (%)	15 (63)	0 (0)	4 (31)
Patients who had 2 cycles during the study (%)	9 (38)	9 (60)	6 (46)
Patients who had 3 or more cycles during the study (%)	0 (0)	6 (40)	3 (23)
Administered activity in MBq (IQR)	6081 (5981-6170)	7391(7291-7447)	7400 (7340-7400)
PSA-level in ng/ml at therapy (IQR)	100 (31-250)	91 (65-260)	N/A
eGFR in ml/min/1.73 m² at therapy (IQR)	84 (63-90)	90 (89-90)	82 (72-90)
Median tumour load on PET/CT in SUV-lbm×cm³ (IQR)	4763 (880-7417)	4715 (1411-9259)	98 (56-139)
Time in hours from therapy to discharge (IQR)	19 (18-19.5)	19 (18.8-19)[1] 12 (11.8-12)[2]	18.8 (18-19)

median tumour load is much lower (table 1). No correlations were found between dose rate measurements and tumour load, eGFR and PSA (r <0.5).

Discussion

In this observational study, dose rate levels in the majority of the analysed patients (91%) treated with 6 GBq [^{177}Lu]Lu-PSMA-617 decreased below the cut-off value of 20 µSv/h after twelve hours. Based on measured data and a mathematical curve, ten hours after 7.4 GBq of [^{177}Lu]Lu-PSMA-617 dose rate levels will be <20 µSv/h at 1 m. The cut-off value of 20 µSv/h at 1 m was introduced in The Netherlands more than twenty years ago, based on dose rate levels after ([^{131}I]NaI) therapy (2). This guideline has recently been revised (3). The dose rate level of 20 µSv/h is generally used to mark discharge in The Netherlands. It would be favourable and easy to adhere to this threshold in the setting of [^{177}Lu]Lu-PSMA-617 therapy and it is currently performed in this way.

Previous research (4) investigated dose rates of 23 patients treated with 7.4 GBq [^{177}Lu]Lu-PSMA-617. It was found that dose rates drop <20 µSv/h at 1 m within six hours after injection (15 µSv/h) with an elimination half-life of 5 ± 1 h. A faster elimination of the radioactivity was found compared to our results. This difference is interesting, and its cause is not entirely clear.
Kurth et al. (5) investigated dose rate levels and excretion of activity after 6.3 ± 0.5 GBq of [^{177}Lu]Lu-PSMA-617 therapies in fifty mCRPC patients. They show that after 3.9 ± 0.7 h, dose rate levels are 2.8 µSv/h at 2 m (11.2 µSv/h at 1 m), which is already below the German limit of 3.5 µSv/h at 2 m at discharge (14 µSv/h at 1 m). These dose rate levels are lower than those measured in our study.
A dosimetry study with 185-210 MBq [^{177}Lu]Lu-PSMA-617 by Kabasakal et al. (14) showed an elimination half-life

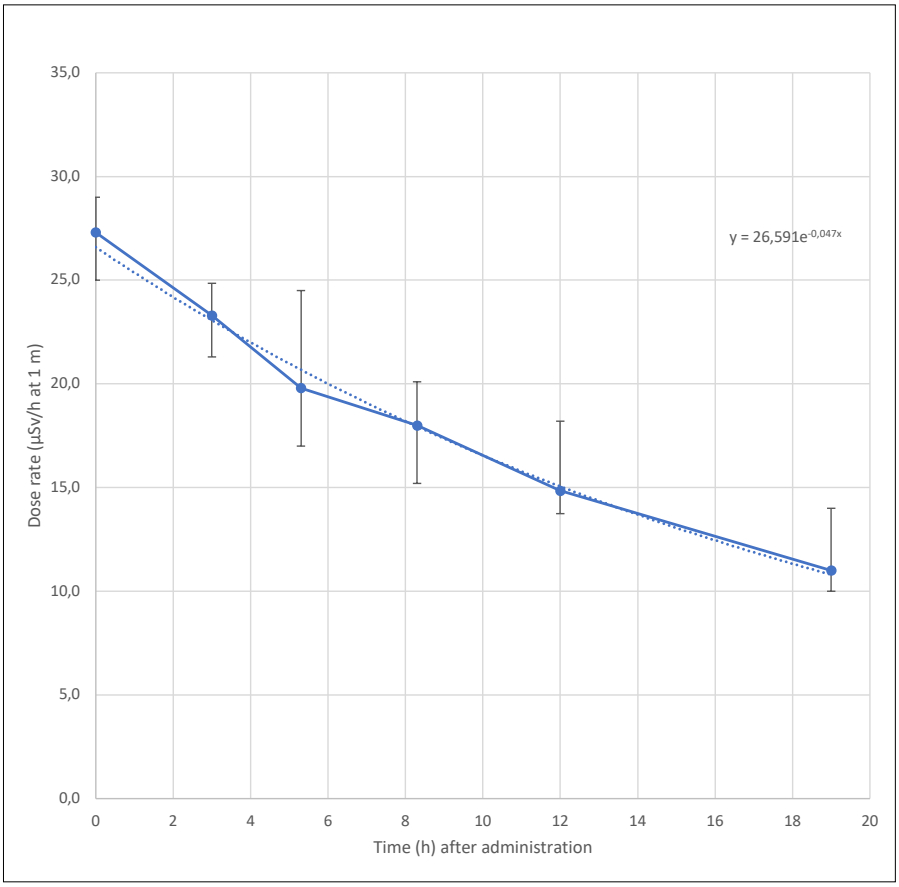

Figure 1A. Median dose rate data at 1 meter (IQR) of 6 GBq [^{177}Lu]Lu-PSMA-617 therapies (cohort #1). An exponential fit is added. Interpolated data at T4 (after twelve hours) added.

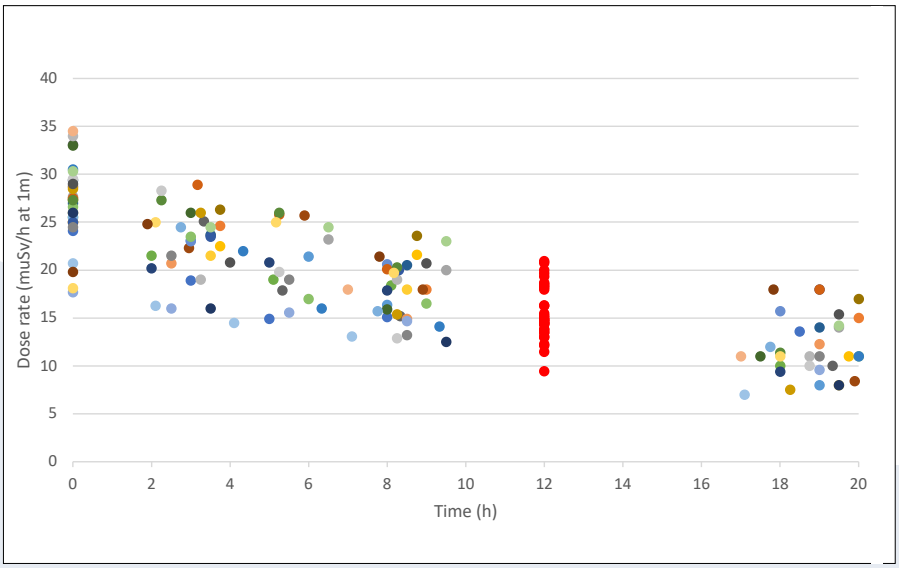

Figure 1B. Dose rate at 1 meter of all separate cycles of 6 GBq [^{177}Lu]Lu-PSMA-617 therapies (cohort #1). Interpolated dose rate data (exponential fit) of all separate therapies at T4 (twelve hours after administration) are added in red. Dose rate levels of three patients were not below 20 µSv/h at 1 meter at twelve hours.

Tabel 2. Median interval, median dose rate and number of patients treated with 6 GBq [^{177}Lu]Lu-PSMA-617 therapy (cohort #1)

Time point	Interval in hours (IQR)	Dose rate in µSv/h (IQR)	N <20 µSv/h (%)
T0 (n=33)	Directly after administration	27.3 (25.5-29.0)	3 (9%)
T1 (n=32)	3 (2.5-3.5)	23.3 (21.5-24.9)	5 (16%)
T2 (n=17)	5.3 (5.2-6.0)	19.8 (17.9-24.5)	9 (53%)
T3 (n=33)	8.3 (8.0-8.8)	18 (15.4-20.1)	22 (67%)
T4 (n=33)	12	14.8 (13.8-18.2)	29 (91%)
T5 (n=33)	19 (18.0-19.5)	11.0 (10.0-14.0)	33 (100%)

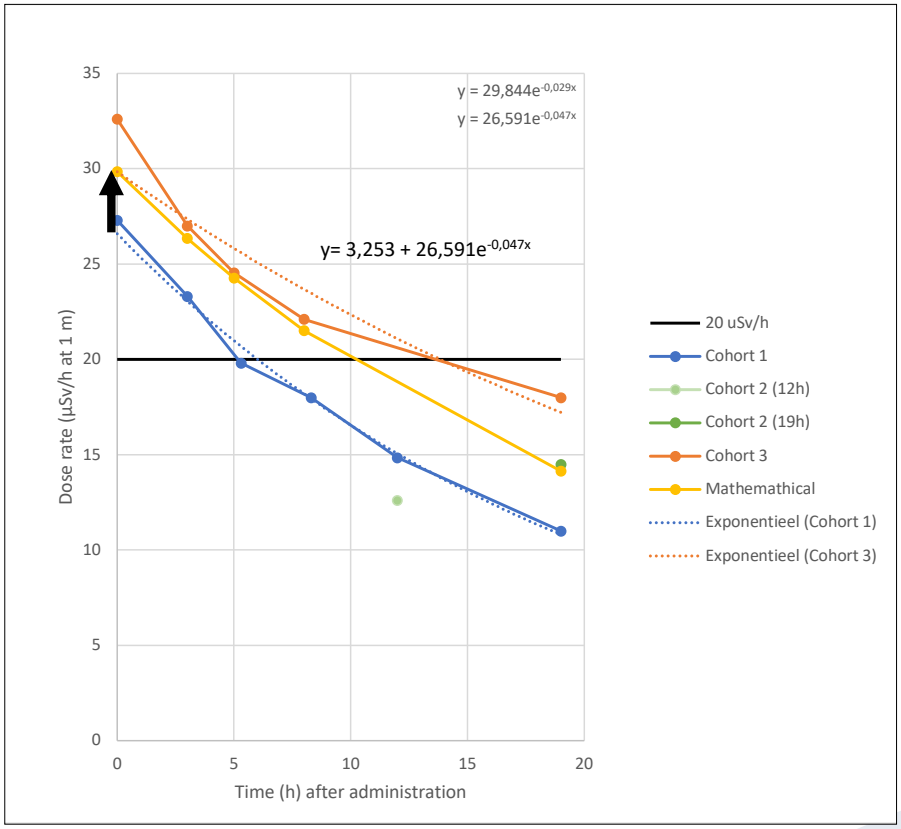

Figure 2. Dose rate curves for different cohorts. Cohort #1 (blue curve) and cohort #3 (orange curve). To account for the different therapy doses, the trend line of [^{177}Lu]Lu-PSMA-617 therapies is converted upwards (yellow curve). Median measured dose rate levels of cohort #2 are added, (green dots); twelve (n=6) and nineteen (n=9) hours after administration.

with a median of 10.2 ± 5.3 h in seven patients. This value for elimination half-life is congruent with our findings, but clearance of radioactivity is much slower than data from Demir et al. (4), and Kurth et al. (5). These differences may indicate a high degree of variability in the clearance rates between the studied patient cohorts. The small number of patients included in these studies (4,14) must be noted.

In Dutch guidelines and reports, which have recently been revised (2,3,13), examples of radiation exposure levels to caregivers are estimated, and the effect of taking radiation precautions after discharge. Estimations (3) show that when a mCRPC patient is discharged *two hours* after one administration of 7.4 GBq [^{177}Lu]Lu-PSMA-617, a caregiver will receive 0.8 mSv per administration - *without taking* radiation precautions at home, and when discharged *six hours* after one administration of 7.4 GBq [^{177}Lu]Lu-PSMA-617, a caregiver will receive 0.3 mSv per administration - *with* strict radiation precautions for a three day period. Based on these estimations ((3) and *including* strict radiation precautions for three days after discharge - six hours after administration): when patients receive four to six consecutive [^{177}Lu]Lu-PSMA-617 administrations, caregivers would receive 4 x 0.3 = 1.2 mSv to 6 x 0.3= 1.8 mSv in total, which would not exceed dose constraints of 3 mSv per treatment (for adults < 60 y). Dose constraints of 15 mSv per treatment for adults > 60 y are not exceeded with or even without radiation precautions after discharge. Of note, our data show that six hours after 6 GBq [^{177}Lu]Lu-PSMA-617 therapy, dose rate levels are 20.2 uSv/h (IQR 19.0-22.1) and 49% of patients have a dose

rate <20 µSv/h at 1 m; extrapolating to 7.4 GBq [^{177}Lu]Lu-PSMA-617, our data show that six hours after therapy, dose rate levels are 23.3 µSv/h at 1 m.

Calculations of dose rate to the public after [^{177}Lu]Lu-PSMA-617 therapy were also made (5) and measured (4). Demir et al. (4) used a TLD badge for caregivers, and measured from the moment of administration. Measurements were done up to five days after therapy and a mean total radiation dose of 202.3 ± 42.7 µSv (0.2 mSv) was found per administration. No difference could be made between time of discharge on exposure rate to caregivers, but exposure doses could be applied to treatment on an outpatient clinic base. Kurth et al. (5) calculated radiation dose to the public using different types of half-lives and different durations of hospital admission. When discharge was after 24 h, the mean dose was 99 µSv (0.01 mSv) per administration (maximum 318 µSv; 0.3 mSv), which will be within the dose constraints proposed in Dutch guidelines.

Another important issue when considering the time of discharge and the effect on the environment, is the presence of metastable [^{177}mLu]Lu. As its half-life is 160 days, its presence will affect the radioactive waste before (and the capacity for collection of radioactive waste) and after discharge from the hospital (waste water). Kurth et al. (5) show that after four hours, 50% of radioactivity was excreted, and after twelve hours, 70% of administered activity was excreted. This could support a twelve hour admission protocol as most activity is excreted in the hospital and would not be added to public waste water, limiting environmental burden.

In the present study, three patients showed dose rate levels below acceptable discharge levels at T0, directly after administration. Interestingly, in two of these three patients, dose rate levels increased at T1. It was assumed to be within normal measurement variation or measurement error. Tumour load is expected to decrease throughout treatment, since the radioligand will bind to tumour tissue, prohibiting the radioligand from being excreted. Theoretically, a higher tumour load will have increased tumour binding, thus reduced excretion and increased retention. Hence, if a correlation between tumour load and radiation retention exists, it would be expected that dose rate levels decrease faster after the second administration than after the first and so on. However, no such correlation was found in this study.

This study has several limitations, notably its retrospective design, small sample size and the variation in amount of activity administered. In current practice, a [^{177}Lu]Lu-PSMA-617 dose of 7.4 GBq is used instead of 6 GBq that was used in this observational study. A small group of patients treated with 7.4 GBq [^{177}Lu]Lu-PSMA-617 was added as a comparison. Unfortunately, no dose rate levels were measured at administration (T0) for these patients. Dose rate levels were therefore assumed to be 29.8 µSv/h at 1 m (in line with T0 of [^{177}Lu]Lu-DOTATATE), which is slightly lower than those reported before (48 ± 13 µSv/h at 1 m) (4). As TLD badges were used (4) instead of exposure rate measurement equipment, this difference might have been due to the difference in hardware used. However, all patients were discharged after twelve and nineteen hours with a dose rate level <20 µSv/h.
Exposure levels of relatives were not measured in our study. In Dutch guidelines and reports (2,3,13), it is assumed that, when taking into account strict radiation precautions after discharge, dose rate levels to relatives can be reduced by a factor 1.1-2.7 (also depending on admission duration and age of relatives (3,13)). Considering that most mCRPC patients will be sixty years of age or older, the higher dose constraints for caregivers (15 mSv per treatment) will apply and will not be reached even when more administrations are given. Of note, all existing literature and the current study on dose rate levels are based on [177Lu]Lu-PSMA-617 therapy, but other formulations exist, possibly with other clearance rates (e.g. PSMA-I&T and PSMA-J591).

Current national and institutional guidelines should take wastewater contamination into account, as an increase in radionuclide therapies will almost certainly take place in the nearby future. In line with the VISION trial (6), each mCRPC patient will be offered four to six administrations of 7.4 GBq [^{177}Lu]Lu-PSMA-617 after reimbursement, of which a substantial part (>70%) will be unbound in vivo and excreted (5). Data and guidelines concerning environmental burden are currently lacking. Further research will be needed to fully assess factors influencing radiation retention in patients treated with different activities, exposure to caregivers and relatives, environmental burden and its effect on the minimal required hospital admission time.

Conclusions

Based on this retrospective observational study, intravenous [^{177}Lu]Lu-PSMA-617 treatment with 7.4 GBq per administration during a twelve hour hospital admission in The Netherlands seems safe and feasible. Environmental considerations must also be taken into account when considering the duration of hospital admission.

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