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SHORT COMMUNICATION

Radiation exposure after ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 therapy

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Abstract

Purpose As radionuclide therapy is gaining importance in palliative treatment of patients suffering from neuroendocrine tumour (NET) as well as castration resistant prostate cancer (CRPC), the radiation protection of patients, staff, family members and the general public is of increasing interest. Here, we determine patient discharge dates according to European guidelines.

Methods In 40 patients with NET and 25 patients with CRPC organ and tumour doses based on the MIRD concept were calculated from data obtained during the first therapy cycle. Planar whole body images were recorded at 0.5, 4, 20, 68 und 92 h postinjection. Residence times were calculated from the respective time-activity-curves based on the conjugated view method. Residence times for critical organs were fitted into the commercially available OLINDA software to calculate the organ doses. The doses of tumours and salivary glands were calculated via their self-irradiation by approximation with spheres of equivalent volume. Kidney volumes were gained by organ segmentation, volumes of all other organs were estimated by means of OLINDA and hence were lean body mass corrected. Out of the whole body curves reference points for patient discharge were estimated.

Results In patients with NET discharge dates could be properly estimated from dosimetric data, which is not only crucial for radiation protection, but also makes therapy planning easier. For ^{177}Lu-PSMA-617 ligand therapy it is difficult to seriously estimate a generalized discharge date due to large interpatient variation resulting from different tumor loads and heavy pre-treatment.

Conclusion Patient release is predictable for ^{177}Lu-DOTATATE therapy but not for ^{177}Lu-PSMA ligand therapy.

Keywords Patient discharge · Radiation protection · Dosimetry · ^{177}Lu-DOTATATE · ^{177}Lu-PSMA

Introduction

The European directive 2013/59/Euratom sets the exposure limit for the public to an effective dose of 1 mSv per year [1]. Since 1 mSv is the sum of possible exposure scenarios, the dose limit for radiation exposure from outpatients or discharged in-patients is usually set to 0.3 mSv per year [2]. Furthermore, according to directive 2013/59/Euratom, Member States shall ensure that dose constraints are established for the exposure of caretakers and comforters (those who are knowingly and willingly incurring an exposure), where appropriate. Dose limitations for family members and knowingly and willingly care taking persons will differ among the Member States. ICRP guidelines as well as recommendations are generally taken as the basis for national standards [2, 3]. Hosono et al. outline in detail the radiation safety aspects according to Japanese law when treating patients with Lu-177 DOTATATE in a recent publication [4]. In the following, we take the Austrian law as a reference, in which in addition to the dose limit of 0.3 mSv for the general public, 1 mSv is set for family members as well as 3 mSv for knowingly and willingly care taking persons upon contact with patients having incorporated radioactive substances [5].

Simplified patient release criteria have long been incorporated into the Austrian Standards in Radiation Protection,

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ON S 5275-1, where it is assumed, that a patient is losing activity only via radioactive decay, while not taking into account metabolic processes [6]. The dose is calculated for a virtual person residing permanently in 2 m distance of a radioactive patient, who is treated as a point source, until radioactivity has completely decayed, i.e. the dose a further person receives is calculated by the inverse square law. In a more realistic scenario, the effective half-life has to be taken into account as well as the situation that the patient usually receives more than just one therapeutic injection per year, i.e. 4 cycles of ^{177}Lu-DOTATATE [7] and up to 6 cycles of ^{177}PSMA-617 ligand [8]. As a consequence, the general public (e.g. co-workers) as well as family members may be irradiated several times a year and any simplified patient discharge criteria lose their validity. For this case part 2 of the Austrian standard provides a guideline on how to determine decay curves by dose rate measurements at different time points and fitting these data points with a two-exponential curve [9]. In our approach, we carried out dosimetric calculations based on whole body scans in a representative number of patients suffering either from neuroendocrine tumour (NET, $n=40$) who received ^{177}Lu- DOTATATE or castration resistant prostate cancer ($n=25$) who were given ^{177}Lu-PSMA-617 ligand.

Materials and methods

Patient dosimetry

All patient dosimetry data were based on the MIRD principle [10]. Planar whole body scans were carried out at approximately 0.5, 4, 20, 68 and 92 h p.i. Patients were not allowed to visit the toilet before the 0.5-h scan in order not to lose any activity incorporated. In addition to the 24-h planar whole body scan a SPECT/CT scan of the abdomen was performed to evaluate organ and tumour volumes and distinguish between overlapping areas. Regions of interest (ROI) of tumours and relevant organs were drawn by a nuclear medicine physician based on the 24-h image and were then copied to all other scans. The geometric mean of the anterior and posterior projection was determined for all organs and lesions. The fractions of the injected activity present in organs and lesions at each time-point were determined by dividing the respective background-corrected counts with the whole body counts at time zero that were extrapolated from the 0.5-h image by means of the radioactive decay law. Time activity curves were fitted with two-exponential functions for whole body and remainder body as well as three-exponential functions for all relevant organs and lesions to deliver residence times by integrating from time zero to infinity. Residence times were fed into commercial OLINDA software to obtain organ doses [11]. Tumours were calculated with the sphere model of OLINDA. For this purpose the volumes of tumours were determined by means of SPECT/CT or PET/CT imaging and subsequently approximated with spheres of the same volume. To receive more accurate values for critical organs such as kidneys, the respective volumes were determined by organ segmentation in radiation therapy planning software PINNACLE based on a pre-therapeutic CT scan [12]. Volumes of all other organs were estimated by means of OLINDA and subsequently BMI-corrected.

Patient selection

Data of patients who received either ^{177}Lu-DOTATATE (n = 40) or ^{177}Lu-PSMA-617 ligand ($n=25$) were evaluated. Patients receiving ^{177}Lu-DOTATATE (usually 7.4 GBq per treatment) had metastatic midgut ($n=23$), lung ($n=2$), stomach ($n=2$) or pancreatic ($n=13$) carcinoid tumours. All patients with metastatic CRPC receiving ^{177}Lu-PSMA-617 ligand (usually 6 GBq per treatment) had heavy pre-treatments including chemotherapy, ^{223}Ra-dichloride and androgen deprivation therapy. All images used for dosimetry were recorded during the first therapeutic cycle.

Results and discussion

Since the aim of the study was to deliver more useful patient discharge criteria, the whole body curves out of the dosimetric calculations were evaluated. Acquired imaging data were combined to classes of 0.5, 4, 20, 68 and 92 h. The mean values as well as standard deviations were calculated at each time point. Mean values were fitted with a two-exponential curve

$$\frac{A(t)}{A_0} = k_1 e^{-\lambda_1 t} + k_2 e^{-\lambda_2 t}, \tag{1}$$

as demonstrated in Fig. 1 in the case of ^{177}Lu-DOTATATE as well as in Fig. 2, which displays the graphs for both ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 ligand. Thereby λ_i are the respective elimination constants, k_i the fractions of component i.

The discharge dates can be calculated, using the respective formula of the Austrian Standard ON S 5275-2 [9] as well as parameters k_i and λ_i derived from formula (1):

$$H^*(10) = \int_{T_E}^{T} \dot{H}^*(10)\mathrm{d}t = A_0 \frac{\Gamma_{H^*}}{r^2}\left[\frac{k_1}{\lambda_1}\left(e^{-\lambda_1 T_E} - e^{-\lambda_1 T}\right) + \frac{k_2}{\lambda_2}\left(e^{-\lambda_2 T_E} - e^{-\lambda_2 T}\right)\right]. \tag{2}$$

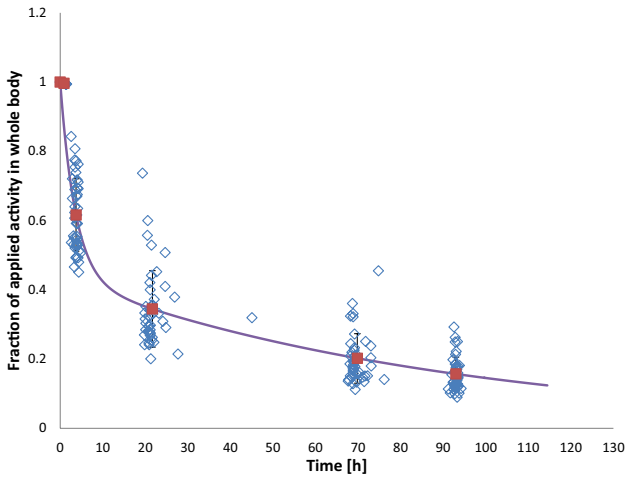

Fig. 1 Whole body retention curve for Fig. 1. Whole body retention function for ^{177}Lu-DOTATATE showing the fraction of applied activity versus time. The solid squares represent the mean values of the measured fractions of 40 NET-patients at each time point, the solid line represents a two-exponential fit curve

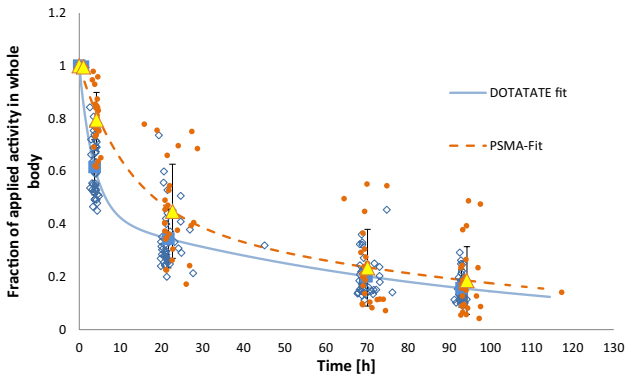

Fig. 2 Comparison of ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 whole body curves. Comparison of ^{177}Lu-DOTATATE ($n=40$) and ^{177}Lu-PSMA-617 ligand ($n=25$) whole body retention functions. The open diamonds represent the measurements for ^{177}Lu-DOTATATE, the solid circles represent the measurements for ^{177}Lu-PSMA-617 ligand

The different terms stand for: A_0 … injected activity, Γ_{H^*} … *dose* rate constant, T_E … time between application and discharge, r … distance from source.

In formula (2), T is the time after which patients return to the nuclear medicine therapy ward for their next treatment. Taking into account that patients receive more than one therapy cycle per year, there will be consequences for patient discharge to fulfill any national criteria.

According to the Austrian law, members of the general public may not receive more than 0.3 mSv per year, family members including children not more than 1 mSv per year and knowingly and willingly care taking people not more than 3 mSv per year from patients having incorporated radioactive substances [5]. Patients return for the following therapy cycles approximately every 8 weeks, so members of the general public and family members would receive a higher effective dose per year than allowed by law, when using simplified discharge criteria. In practice, it has seldomly been taken into account, that patients get more than one therapy application per year. From formula (2), the time point a patient is able to be discharged can be calculated. Such a calculated discharge date seems to be valid for patients treated with ^{177}Lu-DOTATATE but looks not as straightforward for ^{177}Lu-PSMA-617 therapy. Comparing the curves in Fig. 2, the radioactivity incorporated in patients treated with ^{177}Lu-PSMA-617 ligand seems to be eliminated slower from the body than in patients receiving ^{177}Lu-DOTATATE. As a consequence, the legal discharge date might be slightly delayed, or in other words, the inward visit of ^{177}Lu-PSMA-617 ligand treated patients may be legally longer. However, using a two-exponential fit-function for the estimation of patient discharge data makes strictly sense only for ^{177}Lu-DOTATATE-treated patients, since the interpatient variation for ^{177}Lu-PSMA-617 is too large to provide a standardized and clinically reasonable discharge procedure. The tumour load of patients suffering from prostate cancer varies very much depending on the stage of the disease as well as the time nuclear medicine therapy is initialized. Furthermore, some patients included into the current evaluation received quite high kidney doses, which may be due to pre-treatment by external beam radiation or prior chemotherapy.

Table 1 Patient discharge for ^{177}Lu-DOTATATE depending on the group of people, the patient has contact with under the assumption, that the patient receives four therapies within a year

Injected activity [MBq]	T [d]	$H^*(10)$	λ_1	λ_2	T_E [d] family	T_E [d] gen. publ.
7400	56	250	0.28	0.011	2,2	
7400	56	75	0.28	0.011		6.8
4000	56	250	0.28	0.011	0	
4000	56	75	0.28	0.011		4.5

Calculated discharge dates for patients receiving four ^{177}Lu-DOTATAE therapy cycles within year

Table 1 shows discharge dates of ^{177}Lu-DOTATATE calculated by formula (2) for patients receiving 4 therapy cycles within a year. In contrast to using simplified calculations, dosimetric data not only take into account the physical decay of the radioactive pharmaceutical, but additionally include metabolic processes. This results in an effective decay constant, which is the sum of physical and biological decay constants. The elimination of radioactivity from the body happens more rapidly due to metabolic processes, whereby the effect is largest in the first few days until excretion from the body is finished. Once metabolized and stored within the tumor, the activity will further decrease mainly by physical decay.

According to Table 1, there would be a possibility to treat patients given a dose of 4000 MBq as outpatients (in the case of further contact with family members only). Radiation safety of outpatient therapy upon treatment with Lu-177 DOTATATE [13] as well as other radiopharmaceuticals [14] has been discussed in literature as well. On the one hand, outpatient treatment may be feasible when patient release criteria are fulfilled. On the other hand, to our experience physicians would have to ensure, that NET-patients treated with Lu-177 DOTATATE, who often suffer from symptoms such as nausea as well as diarrhea, stay at least a few hours at the therapy ward, so that they do not represent a possible source of contamination upon patient discharge. In many cases it definitely makes sense to keep patients stationary to properly treat any symptoms connected with their illness.

The discharge activities, respectively, discharge dates relying on dosimetric calculations are more realistic than simplified calculations. This is the first time that such calculations were carried out for ^{177}Lu-DOTATATE, which in turn may lead to redefined patient discharge criteria. These calculations not only make therapy planning easier and more predictable, but also have benefits for radiation protection. In the case of ^{177}Lu-PSMA-617 ligand, one possible solution would be the individual measurement of patients with a dose rate meter to fulfill any national discharge criteria.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest relevant to this article.

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Informed consent Informed consent was obtained from all individual participants included in the study.

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