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ANALYSIS OF THE RADIOMETRY PERFORMED IN PATIENTS UNDERGOING RADIOACTIVE IODINE THERAPY

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ABSTRACT

The treatment for differentiated thyroid cancer (DTC) consists of a thyroidectomy followed by radioactive iodine therapy (RIT), in which the patient remains in isolation until the exposure rate of the radioactive iodine reaches a certain limit. The present research intends to estimate the length of stay of patients subjected to RIT with radiometry analysis performed throughout the patient's admission.

Methods: Information such as age, gender, weight, height, prescribed activity, liquid intake, and the use of recombinant human thyrotropin (rhTSH) was gathered from a total of 204 patients with DTC, subjected to RIT. During the admission, the exposure rates were periodically measured. The data served as variables for a multiple regression, in which the coefficients and significance of each were verified as a function of the exposure rate.

Results: The results showed that the length of stay, the administered activity, the intake volume of liquids, the use of rhTSH, and the patient's weight impacted significantly on the dose rate. The average effective half-life of the ^{131}I, considering all patients, was 12.61 ± 3.28 h, and the average time for their radiological release was 15.23 ± 5.50 h. Based on the results it was possible to develop a tool to estimate a patient's length of stay and effective half-life times.

Conclusion: The results can contribute to an optimization of the radiological protection of patients submitted to RIT, as well as allow better logistics of their admission, which can lead to more appropriate accommodation for the patient with a better use of resources.

KEYWORDS

Nuclear Medicine; radiation protection; iodine radioisotopes; half-life; therapy

INTRODUCTION

Differentiated thyroid cancer (DTC) represents about 90% amongst thyroid cancers (*1*,*2*) and, depending on the clinical case, the initial treatment for it consists of partial or complete thyroidectomy (*1*). The most common postoperative treatment is radioactive iodine therapy (RIT) with ^{131}I (*3*,*4*). RIT can also be useful to suppress normal thyroid tissue and effectively eradicate the serum levels of thyroglobulin, increasing its specificity as a tumour marker and still improving the sensibility of ^{131}I in case of a resurgence of the disease (*5*).

According to International Atomic Energy Agency (IAEA), based on the International Commission on Radiological Protection (ICRP) (*6*), the therapeutic use of radioisotopes can become a potential risk of radiation exposure for family and close individuals to the patient, as well as the environment and staff at the Nuclear Medicine (NM) facility. Therefore, this practice should follow all established safety guidelines to ensure safe release of the patient (*7*).

The ICRP and IAEA do not determine the requirement for hospitalization in RIT, emphasizing the importance of criteria that include administered activity values, treatment-related dose potentials, the interests and socioeconomic status of the patient and family members, and even the conditions of the local health system (*8*,*9*,*10*,*11*). In Brazil, the hospitalization of patients receiving activities of 1,850 MBq (50 mCi) or higher is mandatory (*12*). This requirement may vary by country, but meets the need to protect family members, members of the public, and even the environment from possible exposure or radioactive contamination (*13*). This condition demands an adequate physical structure to accommodate the patient and ensure radiation protection standards are going to be followed until the patient's discharge is safe.

The time it takes for radioactive material to be excreted from one’s organism is directly related to physical, biological, and effective radioisotope half-lives (*6*). The length of stay for a patient in RIT may vary according to prescribed and administered activity and the patient himself, due to his own metabolism. For better control and a more appropriate length of stay, it is necessary to take regular readings of the dose rate, or even exposure rate, from the patient, verifying exactly when it hits the threshold of the legislation in force (*14*).

The exposure rate measurements can make huge contributions to radiological protection; firstly, regarding the patient, but also the staff that deal directly with him. Thus, considering that the in-patient becomes a radioactive source, and with the basic precepts of radiological protection in NM – especially those about radioiodine therapy – as well as the necessity of suitable and optimized therapeutic planning, this study aims to check the length of stay of the patients submitted to RIT by analysis of the radiometry.

Thus, considering that the in-patient becomes a radioactive source, the basic precepts of radiological protection in NM – especially those about radioiodine therapy – as well as the necessity of suitable and optimized therapeutic planning, this study aims to check the length of stay of patients submitted to RIT by analysis of the radiometry.

MATERIALS AND METHODS

Data from 204 patients with DTC submitted to RIT was collected. The choice of using patients' data with DTC is related to its prevalence amongst thyroid cancers – about 90% (*1*,*2*). The considered administered activities were 3,700 MBq (100 mCi), 5,550 MBq (150 mCi), 7,400 MBq (200 mCi), and 9,250 MBq (250 mCi), according to the routines practiced in the participating NM facility. Each patient was given a unique ID number and no changes to the service routine where the study was led were made. All procedures regarding the admission process of patients in the facility, as well as ^{131}I administration, were executed by the facility's professionals. No orientations other than what the NM service provided to the patients were given. Additionally, all ethical aspects regarding information obtained through research development were respected. The research was submitted to a Brazilian ethics committee for evaluation, receiving approval according to report number 2.650.168. Written informed consent was obtained from each patient prior to participation in the study. Patient could withdraw at any time, and no incentives were offered.

The data used in this research was collected from two different sources. From the patient's medical records, gender, date of birth, height and weight (for body mass index – BMI), the activity values (prescribed and administered to the patient), and whether or not recombinant human thyrotropin (rhTSH) was used were collected. Radiometric information (day, time, and exposure rate in μSv/h) and hydric volume ingested over the admission period were collected periodically during the patient's stay. All data was recorded in a digital spreadsheet.

The first measurement was performed at patient's admission, immediately after radioiodine administration (zero hour). Thenceforth, the measurements began every two hours and the difference was registered in minutes, in relation to the initial time. The measurements themselves were performed in the therapeutic room, whilst a professional asked the patient to remain in orthostasis in front of the researcher two meters away, as defined by regulation NN 3.05, from the Brazilian National Commission of Nuclear Energy (CNEN). The patient's and the researcher's positions in both therapeutic rooms are illustrated in Figure 1. In case two patients were sharing the same room, a movable lead screen to isolate the subjects was used, reducing possible influence of measurements, and it was requested that the other patient remain seated on his bed.

To ensure distance was being maintained, a laser measuring device was used (Bosch, model GLM 20) with an accuracy of ± 3 mm, in which it was pointed to the patient's xiphoid process. From then on, the researcher would approach or move away from the patient until there was exactly two meters of distance between them. Afterwards, a digital Geiger-Müller counter (Thermo Fisher Scientific, model RadEye G20-10), with a reading sensibility between 0.01 μSv/h and 2.00 mSv/h and an energy range between 17 keV and 3 MeV, properly calibrated, was positioned at the very limit of the measuring distance.

The liquid ingested by patients was managed through the record of hydric intake at each measurement. That was possible as there was a large range of beverages in the facility which patients had access to, such as bottled water, orange juice, coconut water, coffee, and tea. The total liquid intake that was made by each patient was based on the amount of each drink they consumed multiplied by their known volumes.

The subjects were also classified according to age groups: patients under 20 years old were classified as teenagers, patients between 20 and 39 years old as young adults, middle-aged patients were between 40 and 64 years old, and elderly are the ones that are 65 years old or above.

Striving to verify if there were any influences in exposure rate measurements made in patients that were sharing a therapeutic room, the average measurements were compared between patients that were admitted alone in the facility with patients that shared a therapeutic room.

A multiple regression model was created to analyze the statistical data of all gathered factors. Thus, all factors that mathematically had some sort of influence over the length of stay of the subject were identified and defined by their statistical importance, and the extent of that influence, by means of the coefficients of the patients.

Two different methods were used to evaluate the statistical importance of each coefficient. First, the p-value coefficient was determined: the ones considered statistically important were those in which $P \leq 0.05$. Later, to check the analysis, a T-test was made to test the importance of the coefficient's regression. As a supplement of the importance analysis, Cohen's f^2 was used to quantify the potential importance of interference in a factor.

RESULTS

In total, 204 patients that were admitted to RIT were accounted for. Table 1 presents the values of effective half-life times and the total length of stay periods, up until the exposure rate reached the limit of 30 μSv/h, organized according to the categories used in research. The performed regression resulted in the coefficient of each variable used in the present study in function of the exposure rate value and its standard deviation, as well as the results of the T-tests (T) and their significances (*P*), as presented in Figure 2.

Generally speaking, all patients considered, time, activity, intake of liquids, weight and usage of rhTSH were all statistically relevant variables to the exposure rate value. In the same way, the coefficient of determination (R^2) found was to be 0.815, highlighting that the independent variables explain 81.5% of the exposure rate. Cohen's f2 demonstrated that the weight ($f^2 = 0.061$), liquid intake ($f^2 = 0.059$), and use of rhTSH ($f^2 = 0.091$) variables present a small effect size; as the time ($f^2 = 0.720$) and prescribed activity ($f^2 = 0.564$) variables were the ones that presented a big effect.

After calculating the coefficients of each variable (mean value of all patients), it was possible to write Equation 1, which demonstrates the mathematical connection between the variables and the exposure rate.

$$D = 15.879h + 0.071a - 0.149m - 1.965L - 4.990r + 0.321A + 3.037s - 1.694t + 7.050 \qquad (1)$$

where *D* is the dose rate, in μSv/h; *h* is the patient's height, in m; *a* is the patient's age, in years; *m* is the patient's weight, in kg; *L* is the liquid intake, in L; *r* is the indication of usage of rhTSH; *A* is the value of the prescribed activity, in MBq; *s* is the patient's gender; and *t* is the time, in h. Rewriting Equation 1 it was possible to isolate time and to have D(t), as shown by Equation 2.

$$D_{(t)} = -1.694t + Q \qquad (2)$$

where Q represents all variables and coefficients, except *t*.

Thus, using Equation 2 one can estimate the time necessary for the dose rate to reach 50% of the initial (0.5 $D_{(0)}$), representing the effective half-life (T_{eff}) of the radioactive iodine, as shown by Equation 3.

$$T_{eff} = \frac{0.5D_{(0)} - Q}{-1.694} \qquad (3)$$

In addition, it is possible to estimate the total hospitalization time (T_{total}) until the dose rate reaches the value of 30 μSv/h, as shown in Equation 4:

$$T_{total} = \frac{30 - Q}{-1.694} \quad (4)$$

Regarding the patient's categories in subgroups according to their characteristics, the results of the coefficients and their respective significances were altered, as shown in Table 2.

Based on the equations previously described, it was possible to develop a widget that allows to calculate patient's length of stay and effective half-life of the radioactive iodine. The result depends on the initial dose rate value measured in the very beginning of the admission. In case of wanting to estimate the total length of stay before the admission (without any measured dose rate), the calculator estimates the initial dose rate value using the prescribed activity value, as shown in Equation 5.

$$D = \frac{(7.647 \times 10^{-5} A) \times 3.7 \times 104}{d} \quad (5)$$

where *D* represents the calculated dose rate, in μSv/h; *A* is the prescribed activity, in MBq; and *d* is the distance between the gauge and the patient, in m. The widget calculator is available online at <http://android.florianopolis.ifsc.edu.br/rit.php> for anybody to have access to and use.

DISCUSSION

The results showed that the administered activity, the intake volume of liquids, the use of rhTSH and the patient's weight impacted significantly on dose rate reduction. However, age and gender do not contribute significantly to the dose rate value. The average effective half-life of the ^{131}I, considering all patients, was 12.61 ± 3.28 h, and the average time for their radiological release was 15.23 ± 5.50 h. Based on the results and data collected it was possible to develop a tool to estimate each patient's length of stay and effective half-life times.

All patients participating in the research had a total thyroidectomy performed due to a DTC. The present study observed a female predominance in the occurrence of DTC, with a ratio of 3:1 compared with the males, which is in agreement with other studies (*14*,*15*,*16*,*17*,*18*). The DTC occurrence was higher amongst middle-aged patients, which corroborates with other studies (*18*), followed by young-adult patients.

Several studies also seek to relate the BMI values of patients with various topics related to NM, from the assessment of the risk of developing thyroid cancer according to the BMI (*19*,*20*), to the influence of this parameter in the image processing (*21*). The connection between thyroid cancer incidence and the patient's BMI comes from the fact that obesity is a widely known risk factor for thyroid cancer development; thus, theoretically, the higher the BMI, the higher the disease's incidence. However, nearly half of this study's patients were overweight, followed by patients with a normal rating, and obese patients. The group of underweight patients wasn't representative in this research.

The setting of the prescribed activity for the treatment depended exclusively on medical criteria and ranged from 3,700 MBq (100 mCi) to 9,250 MBq (250 mCi), with the activities of 3,700 MBq (100 mCi) being the most common amongst them all, corroborating with other studies (*1*,*22*).

Regarding the differences amongst the prescribed activity and the administered activity, there was little variation, with a standard deviation of at most ± 60.68 MBq (1.64 mCi). The same deviation was found in other studies (*14*) complying with the possible differences in activities prepared in clinical practice.

When calculating activity values from the dose rate, a difference was observed. Conversion of dose rates to activity can introduce errors in the resulting values, since the calculation is based on a point source (*14*). Other remaining factors may also influence dose rate measurement, such as background radiation. If the radiation in the environment (*6*,*23*), is higher than usual, the results of the measurement can be affected. In this research, room contamination can be discarded because the room was completely cleaned and decontaminated before a new patient's admission.

By comparing the average values of dose rate measurements in patients that were given therapeutic activities of 3,700 MBq (100 mCi) and shared the same room with another patient, it's possible to perceive a slight increase in the average dose rate as the value of the administered activity of the other patient increases. For the patients that received 3,700 MBq (100 mCi) and shared a room with another patient with the same administered activity, the average dose rate was 59.27 μSv/h. For those who shared a room with patients that received 5,550 MBq (150 mCi), the average dose rate was 60.51 μSv/h. For those patients who were with another that received 7,400 MBq (200 mCi), the average dose rate was 64.80 μSv/h. Considering these scenarios, the presence of another patient emitting radiation in the same environment may have some influence over the dose rate measurement, although there are other factors to be considered, such as BMI values, the distinct activity values, etc. In this case, if a higher background radiation increases the dose rate measured for one patient, it will only contribute to delayed release of the patient.

The use of shields and the better use of the geometry of the environment may help to lower this influence. When comparing the average dose rate measurements of patients that were admitted individually or who shared a room, no significant difference was found, as the average dose rate value of individually admitted patients was 61.10 μSv/h.

The effective half-life found in this research matches ones found in other pieces of research (*14*,*24*). When considering the gender of the patient, the effective half-life of female patients was slightly shorter than that of males, going against the findings of other researchers (*24*). Such results may be related to a more aggressive course of the disease in these patients, which would lead to higher uptake of radioactive iodine in the body (*25*). In addition, the time taken by males to reach the limit dose rate was about three hours longer than women.

Considering the patients' age range, the elderly patients presented almost one hour higher effective half-life values compared to the other age groups. This may have to do with metabolic slowdown and kidney changes as a person ages. Younger patients tend to present a better kidney function (*25*), which may have an influence on the decrease of the effective half-life. However, a patient's age doesn't have a direct correlation to its length of stay, since that depends a lot on the clinical condition of the patient (*25*). Thus, it is important to assess the patients' characteristics, clinical conditions, and entire health history.

When considering weight, obese patients generally presented greater effective half-life times than the other groups, which can be related to metabolic aspects. However, these patients also presented the lowest average length of stay if compared to normal and overweight BMI groups. By receiving the ^{131}I, the patient as a whole becomes the source, given the biodistribution of the element; the radiation is emitted throughout the body. An obese patient has larger body dimensions compared to a normal patient, influencing the amount of radiation detected. Still, the higher the body mass of the patient, the greater the radiation scatter will be due to the interaction of it with the body tissues (*26*).

The effective half-life found in this research varied in direct accordance with the prescribed activity, going from 12.11 ± 2.66 hours for patients that received 3,700 MBq (100 mCi), to 13.77 ± 4.96 hours for patients that received 7,400 MBq (200 mCi). Such results differ from other studies (*14*) that noticed a decrease of the effective half-life as the administered activity grew. Such difference can be related to the patients' conditions, or to the radioactive iodine uptake, since the patients which are given higher activities usually have a different tumour than that of DTC, which have a low radioiodine uptake.

Although the effective half-life depends, to a great extent, on biological factors related to the metabolism of radioactive iodine in the body, the physical characteristic of the nuclear disintegration indicates that the greater the administered activity value, the greater the time required for a certain dose rate to be reached (*6*). The results showed that as activity values became higher, hospitalization times increased up to 200%.

The use of rhTSH is also another variable that presented differences in length of stay and effective half-life. Patients who used the medication had effective half-lives about two hours shorter than those who underwent hormone suspension. The same result was found when considering the length of stay. The rhTSH group took on average four hours less to reach the borderline dose-release rate compared to the non-drug group, in line with other studies (*24*,*27*).

Likewise, the patients' hydric intake seemed to influence the effective half-life and consequently, the length of stay. Patients who consumed a smaller volume of fluids had a longer effective half-life than patients who ingested larger volumes. Hydric intake varied widely amongst patients, since it depends a lot on their characteristics regarding drinking. An adequate hydration may lead to dilution of the radioiodine in the urine, which leads to reduced retention of the radioisotope in the urinary tract and contributes to decreased dose absorption in the bladder and other adjacent tissues (*28*).

Ionizing radiation exposure does not depend only on length of stay, as there are biological and physiological aspects that cannot be manipulated. However, optimizing the hospitalization process as well as encouraging patients and NM services to employ good hygiene and safety practices can influence exposure time. Having a prior notion of how long the patient will be hospitalized can lead to an optimization of hospitalization schedules, allowing more patients to be attended to (*25*), whilst reducing the costs associated with the hospitalization process be it materials and supplies or even personnel. Lower activities such as 3,700 MBq (100 mCi) contributed to an average length of stay of 12 hours until the dose rate reached 30 μSv/h, against the 35 hours for the higher activities, like 9,250 MBq. Therefore logistics for carrying out the hospitalization can also be improved, allowing the administrator to schedule alternatively patients to complete 24 or 48 h periods of room occupancy. Although discharge from RIT takes into consideration the patient's clinical condition, and not just radiometric criteria, it can assist in decision-making regarding patient release and overall therapy planning.

In addition to the advantages that planning before treatment brings, the use of tools to optimize the hospitalization process can also be important during the hospitalization itself, serving as a patient feedback system. Thus, for example, the patient may be encouraged to ingest fluids in adequate volume, aiming to accelerate the process of excretion of the radioiodine when there is no kidney problem associated with the patient (*29*).

Also, optimizing the hospitalization process brings direct benefits to the patient's well-being. The demystification of the hospitalization process and all issues related to ionizing radiation and NM itself are important for the patient to have his treatment carried out in the most pleasant way possible, as he reaches an NM service already weakened by a number of negative factors such as the discovery of a cancer and a surgical intervention. Moreover, since the nuclear attacks during World War II, and the nuclear accidents that occurred around the world, the term "nuclear" is not well regarded by the overall population. Thus, NM suffers, to some extent, from the stigma left by such events (*30*,*31*), even though it represents only 12% of the total individual dose (*23*) when considered in the overall context, along with other forms of human exposure to ionizing radiation, natural or not.

A longer length of stay can generate important psychological effects in patients, since hospitalization itself is already the result of a health problem (*32*,*33*). Thus, a reduced hospitalization time and special attention from the team that assists the patient are fundamental for their comfort and physical and mental well-being. Therefore, estimating the approximate length of stay can be important information for the patient, bringing comfort and allowing him to organize himself, knowing how the whole process works.

Establishing a standard effective half-life or determining how long a patient will actually be hospitalized is complex, especially when considering that the recommendations and guidelines on procedures generally take into account the radioisotope's physical half-life rather than considering its pharmacological and biokinetic characteristics. However, closer control of the hospitalization process can result in higher quality of the service provided, even impacting the quality of the treatment itself, overall. As pointed out by the IAEA (*34*), the future of all therapy is the treatment of the patient with an individualized approach in which the differences and interests of the patient, as well as of society, are respected as a whole.

CONCLUSIONS

This study can contribute to the decision-making related to efficient accommodation of DTC patients during the RIT. Although the length of stay may vary between patients and all variables involved, the developed calculator allows estimation of the effective half-life and total length of stay, contributing to the patients' well-being. Also, it is a very useful tool for the management of booking and patient load, optimizing the scheduling of the treatment for those who need it whilst allowing cost savings related with long stays.

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DISCLOSURE

No potential conflicts of interest relevant to this article exist.

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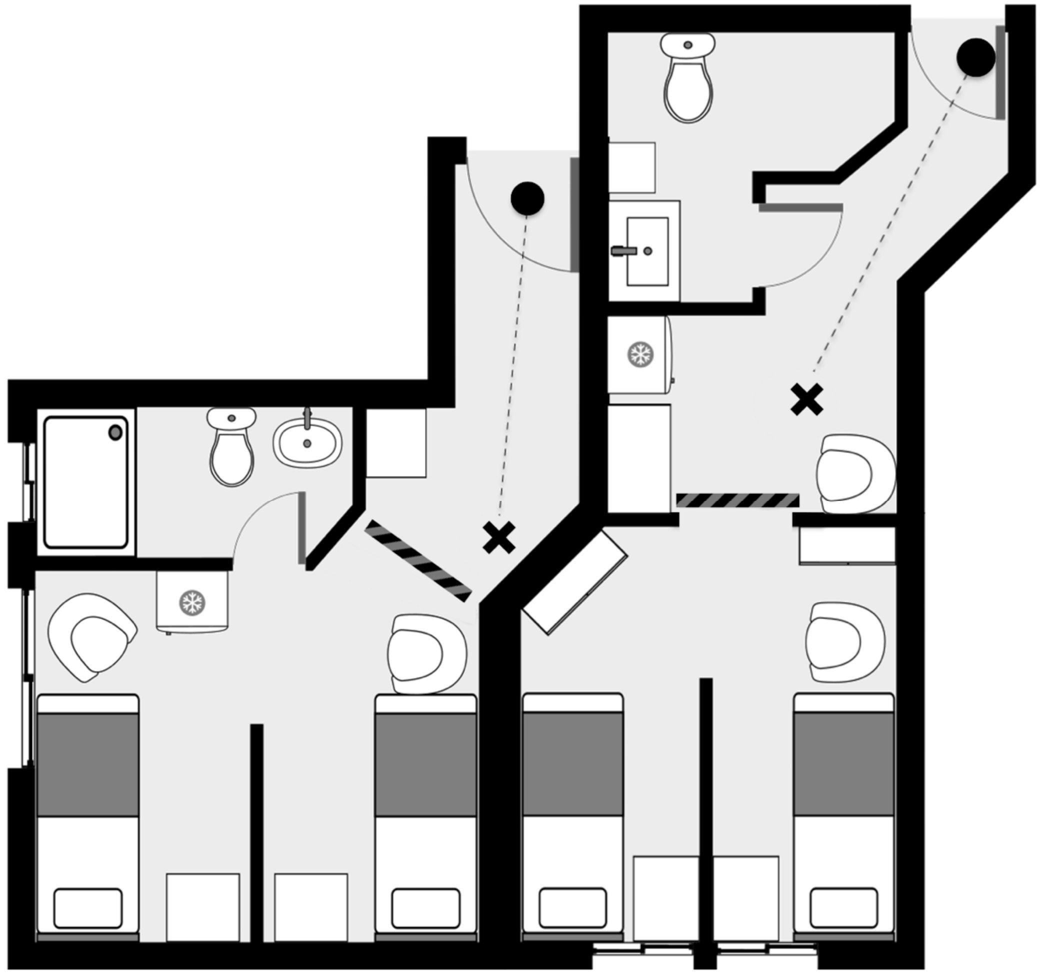

Figure 1. Patient's and the researcher's positions (cross and dot, respectively) in both therapeutic rooms. The lead screen used to shield radiation is represented as a striped line and it was positioned before measuring dose rate, reducing the influence of other patients.

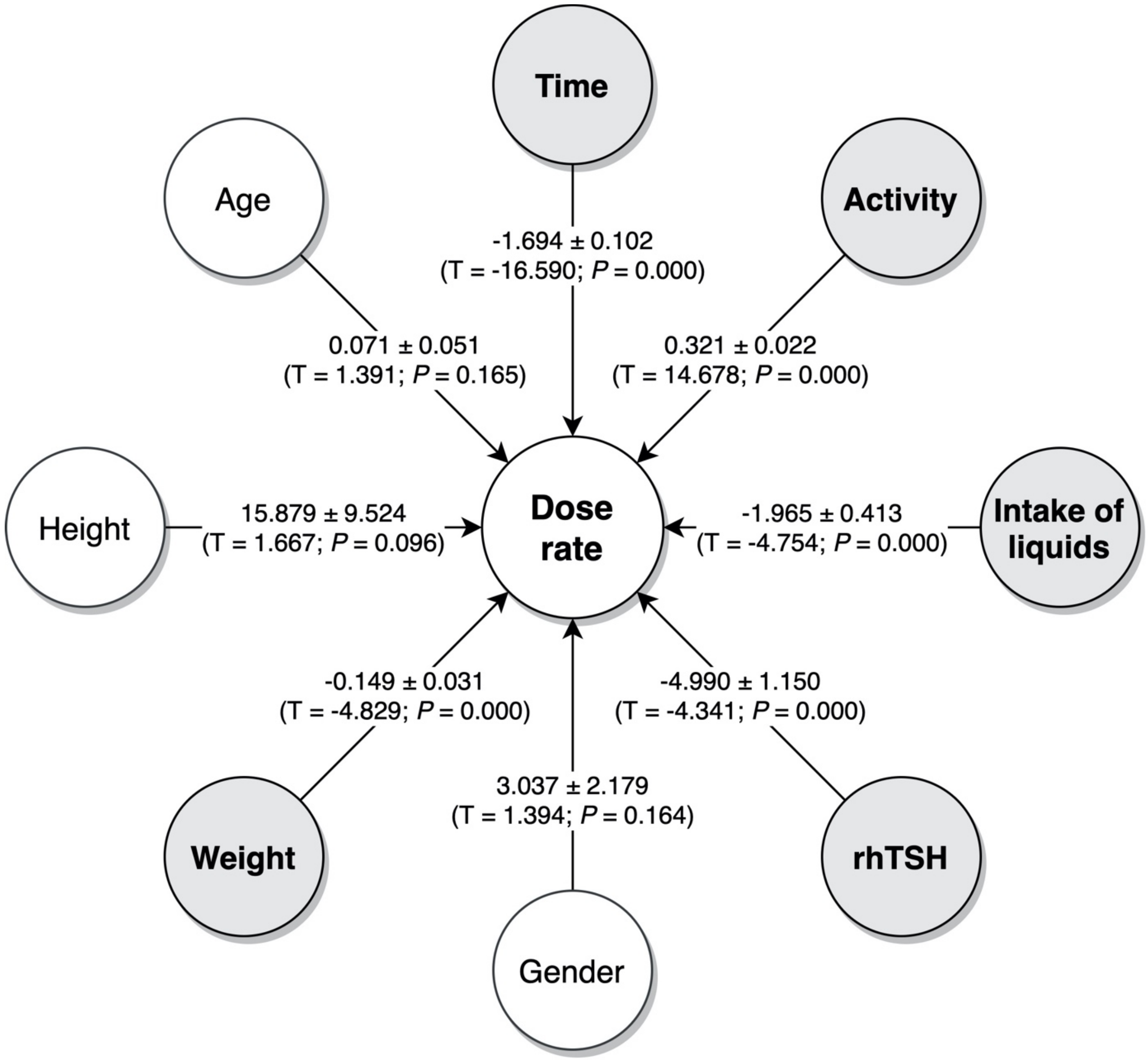

Figure 2. Variables considered and their influence on the dose rate. The coefficients and standard deviations are presented, as well as the results of the T-test (T) and significance (*P*).

Table 1. Mean effective half-life and length of stay according to the different variable's classifications.

Variables	n	%	Effective Half-Life		Length of Stay	
			T_{eff} (h)	SD (h)	T_{total} (h)	SD (h)
Gender						
Female	149	73.04 %	12.49	3.24	14.28	4.92
Male	55	26.96 %	12.94	3.41	17.80	6.17
Age Group						
< 20 yo.	1	0.49 %	13.45	0.00	15.11	0.00
20-39 yo.	77	37.75 %	12.86	3.31	15.05	5.26
40-64 yo.	114	55.88 %	12.34	3.27	15.46	5.84
≥ 65 yo.	12	5.88 %	13.52	3.35	14.22	3.82
BMI Classification						
Underweight	2	0.98 %	11.74	1.43	13.43	1.58
Normal	63	30.88 %	12.12	3.18	15.11	15.11
Overweight	98	48.04 %	12.71	3.55	15.56	15.56
Obese	41	20.10 %	13.19	2.75	14.72	14.72
Activity						
3,700 MBq	138	67.65 %	12.11	2.66	11.99	1.63
5,550 MBq	51	25.00 %	13.66	4.03	19.91	1.82
7,400 MBq	13	6.37 %	13.77	4.96	28.19	1.34
9,250 MBq	2	0.98 %	13.49	0,36	35.60	1.89
rhTSH Usage						
No	123	60.78 %	13.57	3.58	16.73	5.30
Yes	80	39.22 %	11.13	2.03	12.92	5.00
Liquid Intake Volume						
0 ⊢ 2 L	11	5.39 %	14.42	2.01	14.11	2.89
2 ⊢ 4 L	67	32.84 %	13.15	3.32	16.21	6.43
4 ⊢ 6 L	77	37,75 %	12,01	3,43	14,79	5,11
6 ⊢ 8 L	37	18,14 %	11,86	2,83	14,46	5,21
8 ⊢ 10 L	8	3,92 %	13,53	2,44	16,03	5,04
> 10 L	3	1,47 %	13,45	2,40	14,32	3,72
Total/Mean Times	204	100,00 %	12,61	3,28	15,23	5,50

Table 2. Variable coefficients according to the dose rate value, classified according to the patient's characteristics.

Variables	Coefficient	SD	T-test	*P**	Conclusion
Gender					
Female					
Age	0.039	0.051	0.760	0.448	Not significant
Weight	-0.146	0.038	-3.802	0.000	Significant
Height	12.441	10.941	1.137	0.256	Not significant
Activity	0.326	0.025	12.802	0.000	Significant
rhTSH	-4.041	1.142	-3.539	0.000	Significant
Liquid intake	-2.271	0.404	-5.619	0.000	Significant
Time	-1.446	0.100	-14.393	0.000	Significant
Male					
Age	0.157	0,.135	1.164	0.247	Not significant
Weight	-0.154	0.054	-2.838	0.005	Significant
Height	19.417	21.228	0.915	0.362	Not significant
Activity	0.328	0.055	6.012	0.000	Significant
rhTSH	-9.341	3.907	-2.391	0.019	Significant
Liquid intake	-0.667	1.164	-0.573	0.568	Not significant
Time	-2.428	0.278	-8.727	0.000	Significant
BMI					
Normal					
Age	-0.028	0.081	-0.349	0.728	Not significant
Gender	3.548	2.208	1.607	0.110	Not significant
Activity	0.360	0.040	9.064	0.000	Significant
rhTSH	-5.330	1.643	-3.243	0.001	Significant
Liquid Intake	-2.574	0.818	-3.148	0.002	Significant
Time	-1.597	0.177	-9.010	0.000	Significant
Overweight					
Age	0.092	0.080	1.149	0.252	Not significant
Gender	4.037	2.298	1.757	0.081	Not significant
Activity	0.311	0.030	10.460	0.000	Significant
rhTSH	-5.430	2.441	-2.224	0.028	Significant
Liquid Intake	-1.838	0.647	-2.842	0.005	Significant
Time	-1.744	0.180	-9.682	0.000	Significant
Obese					
Age	0.175	0.170	1.033	0.305	Not significant
Gender	3.697	4.244	0.871	0.387	Not significant
Activity	0.372	0.059	6.290	0.000	Significant
rhTSH	4.194	2.962	1.416	0.162	Not significant
Liquid Intake	-1.787	0.991	-1.804	0.076	Not significant
Time	-1.684	0.219	-7.702	0.000	Significant
Age Group					
20-39 yo.					
Gender	9.761	4.831	2.021	0.045	Significant
Weight	-0.173	0.121	-1.424	0.157	Not significant
Height	-14.304	23.165	-0.618	0.538	Not significant
Activity	0.268	0.040	6.718	0.000	Significant
rhTSH	-2.669	1.919	-1.390	0.167	Not significant
Liquid Intake	-2.832	0.944	-3.001	0.003	Significant
Time	-1.702	0.201	-8.480	0.000	Significant
40-64 yo.					
Gender	1.485	2.545	0.584	0.560	Not significant

Weight	-0.128	0.035	-3.698	0.000	Significant
Height	25.323	11.500	2.202	0.029	Significant
Activity	0.351	0.031	11.288	0,000	Significant
rhTSH	-5.819	1.640	-3.548	0.000	Significant
Liquid Intake	-2.256	0.539	-4.183	0.000	Significant
Time	-1.585	0.141	-11.216	0.000	Significant
≥ 65 yo.					
Gender	-17.999	4.331	-4.156	0.000	Significant
Weight	0.158	0.150	1.048	0.299	Not significant
Height	71.859	20.425	3.518	0.001	Significant
Activity	0.018	0.002	9.459	0.000	Significant
rhTSH	-0.464	2.598	-0.179	0.859	Not significant
Liquid Intake	-4.174	0.707	-5.906	0.000	Significant
Time	-0.013	0.003	-4.530	0.000	Significant

*$P \leq 0.050$