

Absorbed dose estimation to cohabitants and co-travelers of patients treated with radioiodine for differentiated thyroid carcinoma

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Abstract

Objective: Thyroid remnant ablation with radioiodine is a well-established treatment for patients with differentiated thyroid carcinoma (DTC) after thyroidectomy. After hospitalization of approximately 2-4 days, these patients return home presenting a possible radiation hazard to the people around them. This work aims to estimate the possible radiation burden to people (co-travelers and cohabitants) which came in contact with the patients after their release from the hospital, analyzing data obtained during their hospitalization. **Materials and Methods:** Data from 1065 patients were used to estimate the possible radiation burden to their age, type of contact with the patient (co-traveler, cohabitant) and patient family status, assuming different exposure scenarios for each group and based on the written precautions given to all patients before discharge. Relations between the iodine effective half-life (T_{eff}), estimated from patient dose rate measurements during hospitalization, patient age and the method used for thyroid preparation for ablation (thyroid hormone withdrawal-THW or administration of recombinant human thyroid stimulating hormone-rhTSH) were also investigated. **Results:** Median absorbed dose to adult cohabitants was estimated to be 8.3 μ Sv (0.1-117.2 μ Sv), to babies (0-5yr) 15.7 μ Sv (1.2-196.1 μ Sv), to young children (5-10yr) 13.1 μ Sv (0.8-100.7 μ Sv), to children (10-18yr) 8.4 μ Sv (0.5-116.8 μ Sv) and to co-travelers 4.8 μ Sv (0.2-114.9 μ Sv). The highest doses to cohabitants were estimated in the few cases where the patient was a single parent of one or more children (median children dose 28.9 μ Sv, range 11.2-279.4 μ Sv). A statistically significant difference in median T_{eff} between THW (15.1h) and rhTSH (13.9h) patient groups was found. **Conclusions:** Provided necessary precautions are followed, radiation burden to the family members and co-travelers of DTC patients treated with radioiodine following thyroidectomy can be kept well below the corresponding dose limits and constraints.

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Introduction

Radioiodine (RAI) administration is a well-established practice in the management of patients with differentiated thyroid carcinoma (DTC) after total thyroidectomy, in order to eliminate residual normal thyroid tissue not removed by surgery (ablative treatment) and to treat residual microscopic, macroscopic or metastatic disease (adjuvant treatment) [1-3]. Prior to RAI administration the thyroid stimulating hormone (TSH) levels must be sufficiently elevated (>30mIU/L) in order to optimize iodine uptake and therefore maximize treatment efficacy [2-4]. Thyroid stimulating hormone levels can be elevated either by following the thyroid hormone withdrawal (THW) protocol or by administering recombinant human thyroid stimulating hormone (rhTSH) 2 days and 1 day before RAI treatment [2-6].

Depending on national regulations, radioiodine administration is followed by a 2-4 days period of hospitalization, after which patients are released from the hospital and allowed to return to their homes, with written instructions to avoid prolonged close contact with family members for some period of time. The decision for patient release is based on dose rate measurements at a distance of 1m from the patient [7, 8]. Currently, in Greece, the practical criterion for patient release is the dose rate at a distance of 1m from the patient to be lower than 40 μ Sv/h, as proposed by the European Commission [9].

The International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP) and the European Union (EU) have proposed dose constraints for members of the public who come in contact with patients who have received therapeutic amounts of radiopharmaceuticals [8-10]. Different dose constraints apply to different groups, as outlined in Table 1 [10].

Table 1. Dose constraints for different groups of people as proposed by international organizations [10].

Group	Proposed dose constraint
Members of the public – non comforters, non-carers (e.g. taxi driver who drives the patient back home)	0.3mSv/episode
Adult comforters and carers up to 60 years old	3mSv/episode
Adult comforters and carers more than 60 years old	15mSv/episode
Pregnant family members	1mSv/year
Children family members up to 2 years old	1mSv/year
Children family members 3-10 years old	1mSv/episode

There have been a number of studies in the literature which showed that the absorbed doses received by family members were generally below the corresponding dose constraints [11, 12]. Nevertheless, most of them were performed on a limited number of patients and family members [7, 13-15]. Monte Carlo studies have also been made, in order to simulate the exposure geometries in different situations and estimate doses to family members and members of the public of iodine-131 (¹³¹I) patients [16, 17]. The main purpose of the present study is to estimate the absorbed dose to the people who came in close contact, either as care-givers and co-habitants or as co-travelers, with more than 1000 patients who received RAI treatment in our hospital during a period of almost 10 years.

Materials and Methods

From April 2009 to December 2018, a total of 1065 patients, 258 males (24.3%) and 807 females (75.7%) who were diagnosed with DTC underwent total thyroidectomy and were subsequently administered with ¹³¹I for thyroid ablation and/or adjuvant therapy at the Nuclear Medicine Department, Papageorgiou General Hospital, Thessaloniki Greece. The age of the patients ranged from 12 to 84 years (mean age: 48.2 years). Administered ¹³¹I activities ranged from 18 50 to 9250MBq. In order to elevate TSH levels, 669 patients (62.8%) were injected intramuscularly with two doses of 0.9mg rhTSH (thyrogen, thyrotropin alfa for injection, Genzyme Corporation, Cambridge, MA) two days and one day before RAI administration and 396 patients (37.2%) followed the thyroid hormone withdrawal (THW) protocol [4]. A

negative β -chorionic gonadotropin blood test was required for all female patients of reproductive capacity in order to exclude pregnancy. Breastfeeding patients were consulted to completely stop breastfeeding at least 3 weeks before radioiodine administration.

After RAI administration, all patients were kept in isolation for 3-4 days into two dedicated properly shielded rooms. At regular time intervals during their hospitalization (every 3-4 hours from 09:00 to 21:00), dose rate measurements were performed using a radiation survey meter (ALMO 3, MED Nuklear-Medizintechnik GmbH, Dresden) calibrated in terms of ambient dose equivalent ($H^*(10)$). The probe of the survey meter was permanently mounted on a wall in a hall just outside the shielded rooms. The dose rate readings were displayed on the survey meter screen at the nurse's stand, located outside the designated controlled area. Using special markings on the floor, all patients stood at a distance of 1m and 2m from the survey meter and the corresponding dose rate readings were recorded by the nursing staff. The whole procedure was performed remotely and was explained and rehearsed with each patient before administration. Usually, at day 3, the dose rate at a distance of 1m from the patient had dropped not only below the national discharge criterion of 40 μ Sv/h, but also below the even more strict dose rate constraint of 15 μ Sv/h that was locally adopted as release criterion in our Department. If the dose rate at 1m was measured above 15 μ Sv/h, the patient was advised to remain in isolation for one more day. Some patients decided against this suggested additional isolation and were allowed to leave the hospital after given strict written instructions to avoid contact with other people for one more day. In any case, just before patient discharge, a final measurement of the dose rate at 1m and 2m (Dout,1m, and Dout,2m) from the patient was performed by a medical physicist, using another calibrated portable radiation survey meter (451P Fluke Biomedical, Cleveland, OH).

The regularly performed dose rate measurements during each patient's hospitalization followed a bi-exponential model, with an initial rapid decay component during the first few hours, followed by a second, less rapid, component. The dose rate data recorded after the first 24 hours were used to calculate the effective half-life (T_{eff}) of ¹³¹I for each patient, by fitting them to an exponential decay equation (Figure 1). Measurements with an R^2 exponential fit value less than 0.90 were excluded from further analysis.

At discharge, all patients were given oral and written instructions with the necessary precautions concerning the minimization of exposure to family members and other members of the public, according to their family status, means of transportation and final destination. Such instructions included keeping a distance of at least 2 meters from children and pregnant women and avoiding unnecessary close contact with other adults, maintaining separate sleeping arrangements, voiding in a seated position and flushing the toilet 2-3 times afterwards.

For each patient, a detailed record was kept with information regarding the number of people that were likely to come in contact with, their age and their relation with the

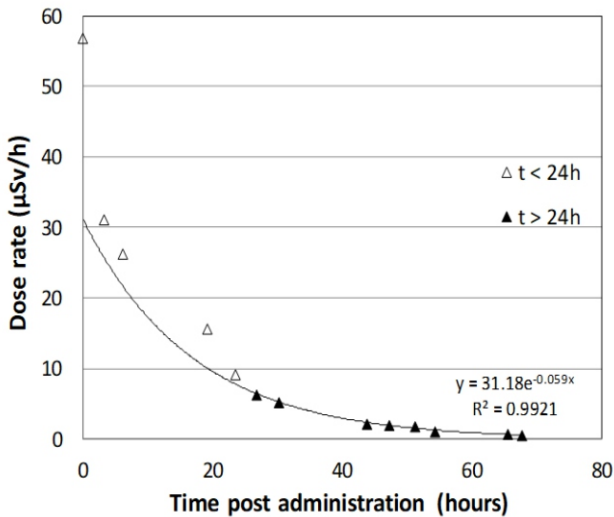


Figure 1. A representative example of consecutive dose rate measurements at a distance of 2m from a patient, showing the initial rapid dose rate decrease and the exponential fit to the data after the first 24h in order to calculate T_{eff} .

patient. These people included family members, other carers and comforters and co-travelers. All patients were interviewed about the means of transportation they would use to leave the hospital (public transport or private vehicle) and their destination. Work colleagues were not included due to the fact that all patients had been given an, at least, one week's off their work.

The following formula was used to calculate the total radiation dose D_{tot} (μSv) to people who would be in contact with a patient from the time of discharge to infinity (e.g. family members):

$$D_{tot} = 1.44 \cdot D_{out,1m} \cdot T_{eff} \cdot E \quad (1)$$

where $D_{out,1m}$ ($\mu\text{Sv/hr}$) is the dose rate at 1m at patient discharge, T_{eff} (hr) is the effective half-life calculated from patient's dose rate measurements as explained previously and E is an occupancy factor properly chosen to represent the fraction of a 24h-day that a person would spend at a distance of 1m from the patient. Different E values were chosen for different groups of exposed people, depending on their age and the general patient's family status, considering that they would follow the radiation protection instructions they were given. For example, if only adults lived in the same home with the patient, E was chosen to be equal to 1/10. For children, depending on their age, E was assigned values between 1/4 and 1/8, but in those cases where the patient himself was the only adult living together with young children, E was set to 1/2 (Table 2).

The following formula was used to calculate the total radiation dose D_t (μSv) to people who came in contact with a patient for a specific period of time, t , right after patient's discharge from the hospital (e.g. co-travelers):

$$D_t = 1.44 \cdot D_{out,1m} \cdot T_{eff} \cdot \frac{(1 - e^{-\ln 2 \cdot t / T_{eff}})}{r^2} \quad (2)$$

where r is their distance from the patient during that period of time. Different values of r were selected depending on the type of transportation (also shown in Table 2). Time, t , was estimated based on the distance travelled and the type of transportation used. All co-travelers were adults, because all patients were appropriately instructed not to be accompanied by children. For patients who travelled with public transport, only the closest co-traveler was considered for dose estimation.

Table 2. Selected values of occupancy factor, E (for cohabitants) and distance, r (for co-travelers).

Cohabitant status	Values of E	Means of transportation	Values of r (m)
Adults	1/10	Car or taxi	1
Children 0-5 yrs	1/4	Bus	0.5
Children 5-10 yrs	1/6	Airplane	0.5
Children 10-18 yrs	1/8	Train	0.5
Children of any age with no other adult cohabitant	1/2	Boat	1

Statistical analysis was performed with the SPSS ver. 24 (IBM Corp. Armonk, NY). Normal distribution of the quantitative parameters was checked with Shapiro-Wilk tests. Mean values and standard deviations (SD) were calculated for normally distributed variables. Median values and interquartile ranges (IQR) were calculated for non-normally distributed variables. t -tests and Mann-Whitney tests were appropriately used to compare mean and median T_{eff} values between rhTSH and THW patients. Pearson and Spearman correlations were appropriately used to identify significant correlations between quantitative variables. Statistical significance was accepted for $P < 0.05$.

Results

Median ^{131}I T_{eff} calculated from the successive external dose rate measurements for the rhTSH and the THW patients was 13.9 (5.4) and 15.1 (5.4) hours respectively. Since T_{eff} can be

affected by the patient's metabolic activity which varies with age, patients were grouped into 8 age groups (10-20, 20-30, ..., 70-80 and 80-90 years old). Figure 2 shows the distribution of calculated median $^{131}\text{T}_{\text{eff}}$ values with age group, separately for the rhTSH and the THW patients.

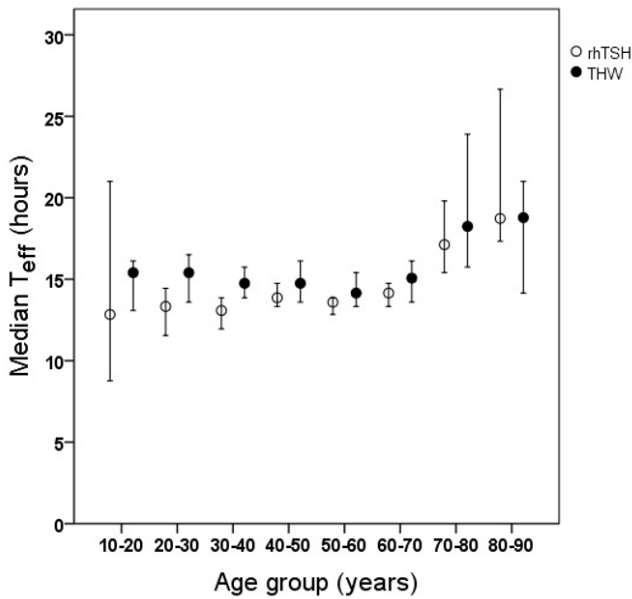


Figure 2. Distribution of median $^{131}\text{T}_{\text{eff}}$ values with age group, calculated separately for the rhTSH and the THW patients. Error bars denote the corresponding 95% confidence intervals.

Median dose rate at 1m at patient discharge ($D_{\text{out},1\text{m}}$) for the rhTSH and the THW patients was 3.4 (4.8) and 5.5 (6.0) $\mu\text{Sv/h}$, respectively. The distribution of ($D_{\text{out},1\text{m}}$) with age group, separately for the rhTSH and the THW patients is presented in Figure 3.

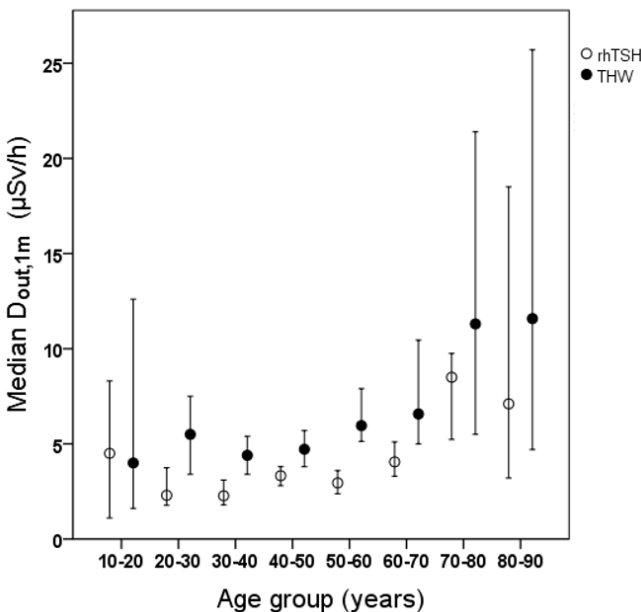


Figure 3. Distribution of median dose rate at 1m with age group, calculated separately for the rhTSH and the THW patients. Error bars denote the corresponding 95% confidence intervals.

From the total of 1065 patients 225 (21.1%) lived alone, 633 patients (59.4%) lived together with other adults only, 197 patients (18.5%) lived together with both adults and children and a small group of 10 patients (0.9%) lived together with children only (no other adult lived in the house) and as a consequence, after being discharged from the hospital, they were their children's only carers.

In total, 1231 adults and 332 children were identified as cohabitants. From the 332 children cohabitants, 57 (17.2%) were between 0-5 years old, 85 (25.6%) were between 5-10 years old and 190 (57.2%) were between 10-18 years old. A separate analysis was performed for 16 out of the 332 children who belonged to the 10 aforementioned patients. The maximum absorbed dose to these 16 children was estimated to be approximately 280 μSv and the mean absorbed dose 74.4 μSv (SD 87.8 μSv).

Figures 4 to 7 present the distribution of the estimated doses received by adult cohabitants (Figure 4) and by the remaining 316 children cohabitants of the three different age groups (Figure 5: 0-5 years old, Figure 6: 5-10 years old, Figure 7: 10-18 years old).

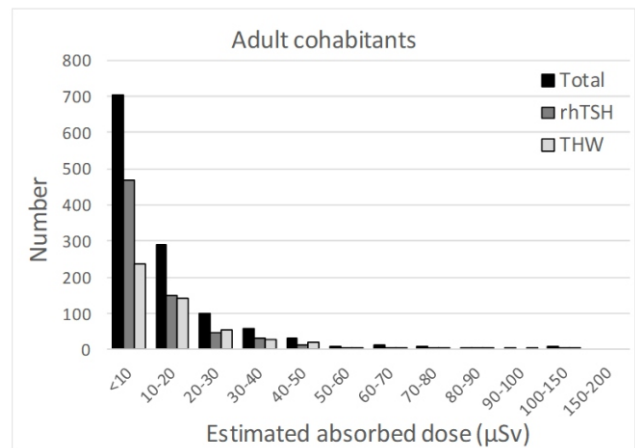


Figure 4. Estimated absorbed doses to adult cohabitants.

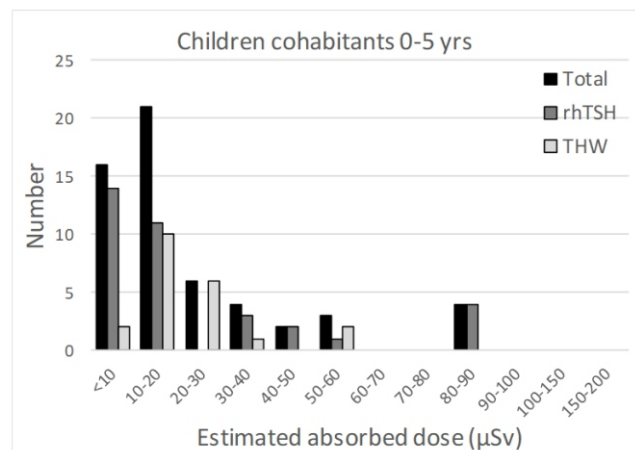


Figure 5. Estimated absorbed doses to children cohabitants of ages 0-5 yrs.

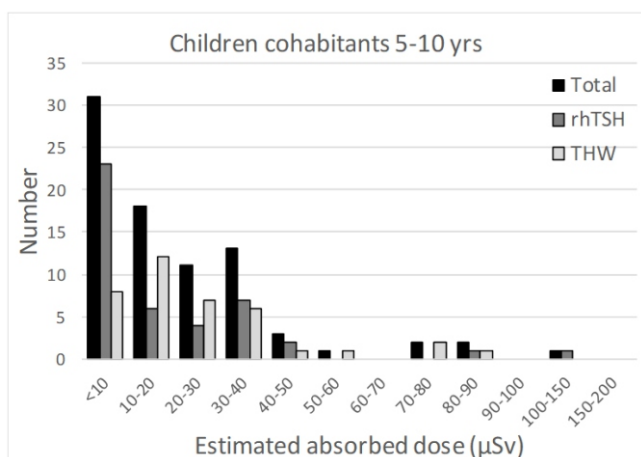


Figure 6. Estimated absorbed doses to children cohabitants of ages 5-10yrs.

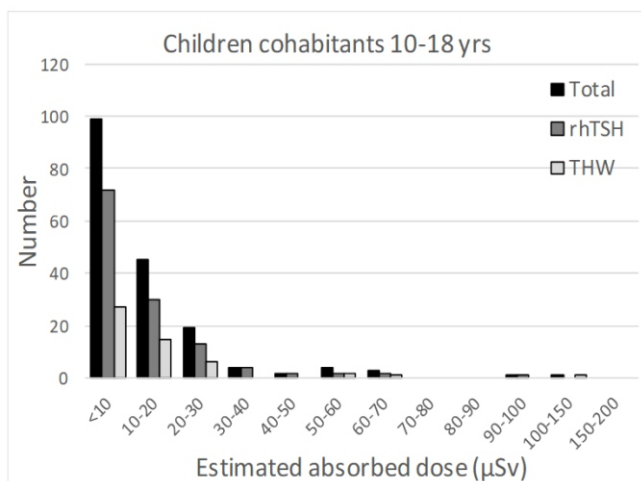


Figure 7. Estimated absorbed doses to children cohabitants of ages 10-18yrs.

A total of 343 out of the 1065 patients (32.2%) lived in a different city and had to travel home either by private (309 patients, 90.1%) or by public transportation (34 patients, 9.9%). From those using public transport, 24 travelled by taxi, 4 by train, 2 by bus, 2 by boat and 2 by airplane. The median travel duration was estimated to be 1.5 hours (range: 0.5-15.0 hours). Figure 8 shows the distribution of the estimated doses received the co-travelers, taking into account only the doses received during the travel.

A total of 244 patients (71.1%) were accompanied in their journey by a member of their family who, after reaching home, would also be exposed as a cohabitant. Figure 9 presents the distribution of the total estimated doses received by this group of 244 individuals who were both co-travelers and cohabitants.

All previous estimated doses (mean, median values and ranges) are summarized in Table 3.

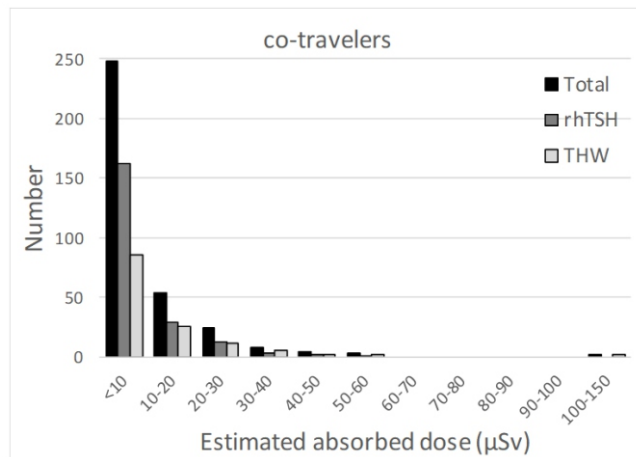


Figure 8. Estimated absorbed doses to co-travelers.

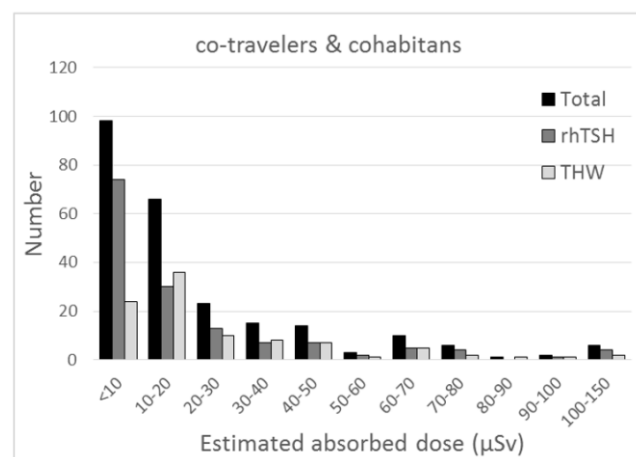


Figure 9. Total estimated absorbed doses to those co-travelers who were also cohabitants.

Table 3. Estimated absorbed doses to cohabitants and co-travelers.

Group	Mean Dose (μSv)	Median Dose (μSv)	Range (μSv)
Adults	13.7	8.3	0.1-117.2
Only children cohabitants	74.4	28.9	11.2-279.4
Children 0-5yrs	22.4	15.7	1.2-196.1
Children 5-10yrs	20.4	13.1	0.8-100.7
Children 10-18yrs	13.7	8.4	0.5-116.8
Co-travelers	8.9	4.8	0.2-114.9
Co-travelers & cohabitants	22.5	11.6	0.3-147.1

Discussion

Median ^{131}I effective half-life for all 1065 patients was 14.2 hours (0.59 d), which is similar to other published values. Median ^{131}I T_{eff} was found to be lower for those patients who were treated with rhTSH (0.58d) compared to those who followed the THW protocol (0.63d) and this difference was statistically significant ($P=0.001$, Mann-Whitney test). Similar results have also been reported by several authors [18-20]. Papadimitriou et al. (2006) [18] have reported median values of 0.44d for their rhTSH group and 0.56d for their THW group. North et al. (2001) [19] have reported a median value of 14.8h (0.62d) for THW patients, whereas Menzel et al. (2003) [20] have found a mean value of 0.43 ± 0.11 d for rhTSH patients and 0.54 ± 0.11 d for THW patients.

Examination of each age group separately revealed that the differences in T_{eff} observed in the present study between rhTSH and THW patients were statistically significant only for the groups 20-30 ($P=0.043$) and 30-40 years old ($P=0.025$). Median T_{eff} remained relatively constant with age for all age groups until the age of 70 and rose slightly after that.

At the time of discharge, the median dose rate at from all 1065 patients was found to be $4.0 \mu\text{Sv/h}$ (IQR: $5.4 \mu\text{Sv/h}$). This value is one order of magnitude lower compared to the regulatory limit of $40 \mu\text{Sv/h}$, but it is due to the more strict release criterion of $15 \mu\text{Sv/h}$ that is generally adopted in our department. Recently, Edis et al. (2019) [21] reported mean dose rate values lower than or near $10 \mu\text{Sv/h}$ at 1m from adult DTC patients after 2-4 days of hospitalization. Only 95 patients (8.9%) were released with a measured $D_{\text{out},1\text{m}}$ higher than $15 \mu\text{Sv/h}$ (maximum $38 \mu\text{Sv/h}$). There were differences in dose rate at patient discharge between thyroid stimulation methods: as a consequence of the reduced T_{eff} in rhTSH patients, $D_{\text{out},1\text{m}}$ was also lower for these patients compared to those who followed the THW protocol. In this case, the observed differences were statistically significant for the groups 20-30 ($P<0.001$), 30-40 ($P<0.001$), 40-50 ($P<0.001$), 50-60 ($P<0.001$) and 60-70 years old ($P=0.011$).

The maximum estimated absorbed dose to adult cohabitants was less than $120 \mu\text{Sv}$, much less than the relevant dose constraint of 3mSv . More than half of the adult cohabitants (702 out of 1231-57.0%) were estimated to receive absorbed doses of less than $10 \mu\text{Sv}$ (Figure 4). Estimated absorbed doses to children cohabitants were larger, due to the higher occupancy factors (E) considered for children, but they were always below $200 \mu\text{Sv}$. Larger values were estimated for children 0-5 years old ($E=1/4$), followed by 5-10 years old ($E=1/6$), whereas estimated doses for children 10-18 years old were almost the same as for adults. The largest doses, as expected, were estimated for those children living with the patient who was the only adult in the house. The highest occupancy factor was considered appropriate for these children, which lead to a maximum estimated absorbed dose around $300 \mu\text{Sv}$. Nevertheless, even in this worst case scenario, the estimated absorbed doses remained well below the relevant dose con-

straint of 1mSv . Several authors have measured cohabitant radiation doses using electronic or thermoluminescent dosimeters and have concluded that they were much lower than the regulatory limits. Remy et al. (2012) [22] measured a mean dose of $51.5 \mu\text{Sv}$ to patients relatives within the first 7 days after discharge. Jeong et al. (2014) [23] have reported a mean effective dose to caregivers of $120 \mu\text{Sv}$. The same mean value of $120 \mu\text{Sv}$ (range $30\text{-}380 \mu\text{Sv}$) was also reported by Zehtabian et al. (2017) [24]. The fact that our adult maximum estimated doses are comparable to the actual mean measured values in the literature can be attributed to the very low $D_{\text{out},1\text{m}}$ at patient discharge that was measured in the present study. Furthermore, the value of 1/10 for the occupancy factor, E, considered in this study may have been somewhat optimistic.

Total estimated doses to cohabitants, both adults and children, calculated using equation (1), were lower for the patients receiving rhTSH compared to those following the THW protocol ($P<0.001$), which is an expected result since both $D_{\text{out},1\text{m}}$ and T_{eff} were lower for this group of patients.

Statistically significant differences were also observed in co-traveler doses between rhTSH and THW patients ($P<0.001$, Mann-Whitney test). The maximum dose to a non-relevant co-traveler was $115 \mu\text{Sv}$, which is much less than the relevant dose constraint of 0.3mSv . That maximum co-traveler dose of $115 \mu\text{Sv}$ was estimated for a patient who was administered with 3.7GBq of ^{131}I , was discharged from the hospital at day 3 with a dose rate at 1m of $8.8 \mu\text{Sv/h}$ and travelled to his hometown for 3.5 hours by bus. More than 70% of all co-travelers (248 out of 343-72.3%) were estimated to receive absorbed doses of less than $10 \mu\text{Sv}$ (Figure 8). Most co-travelers were patients' relatives and received absorbed doses as cohabitants too. Their maximum dose was estimated less than $150 \mu\text{Sv}$, whereas almost 40% of them (98 out of 244-40.2%) were estimated to receive absorbed doses of less than $10 \mu\text{Sv}$ (Figure 9). These estimates are in agreement with the measured doses by Ramírez-Garzón et al. (2014) [25] for a similar exposure scenario. For those individuals, the dose received as co-travelers corresponded, on average, to 38.2% of their estimated total dose. In other words, the dose received during the few hours of travel was, on average, more than 70% of the dose received while living together with the patient until total radioactive decay and body elimination of the radioiodine. This is an important result for the nuclear medicine staff to keep in mind when they are giving instructions to patients before releasing them from the hospital, because they often forget to stress the importance of the patients keeping as large a distance as possible from their co-travelers during their trip home. For example, when a patient is driven home by a member of his family with their private car, he or she must sit in the rear seat, diagonally to the driver, in order to maintain the largest possible distance. As expected, the percentage of the total dose received by co-travelers during the travel correlated strongly to the duration of the travel (Spearman's rho: 0.855, $P<0.001$). When the travel duration exceeded 1.5 hours, there were times where the dose during the travel was higher than the estimated corresponding co-habitant dose.

For trips longer than 2.7 hours, it was consistently higher.

There are a few limitations in our study. First, the dose rate measurements at 1 and 2 meters from the patients were subject to uncertainties estimated in the order of at least 20%, due to the uncertainty of the survey meter response and the limited reproducibility in the positioning of the patients and their posture. The effective half-lives calculated from these dose rate values also suffer from analogous uncertainties, however the fact that only 25 patients were excluded from the analysis due to poor (<0.90) R^2 exponential fit value, indicates an acceptable level of consistency in dose rate measurements. Another limitation is the use of the point source assumption for the estimation of the doses (to the extent that the inverse square relationship of the dose rate with distance was accepted) which was chosen for its simplicity and ease in calculations, taking into account the large number of patients in the study.

In conclusion, dose rate measurements and detailed travel arrangements and habitus were obtained from 1065 patients receiving RAI treatment for DTC, in order to estimate the radiation burden to the members of their family and co-travelers after patient discharge from the hospital.

The whole-body radioiodine clearance was found to be faster for those patients receiving rhTSH, in order to elevate TSH levels, compared to those following the THW protocol.

Provided that necessary precautions are followed, the absorbed doses to family members and co-travelers of DTC patients receiving therapeutic amounts of ^{131}I after total thyroidectomy can be kept generally low, well below the corresponding dose limits and dose constraints, mainly due to the fast clearance of radioiodine from the patients' body. Based on these results, the strict release criterion of the dose rate at 1m being less than $15\mu\text{Sv/h}$ is being gradually relaxed and the $40\mu\text{Sv/h}$ is being adopted, when there is significant pressure from the department administration to increase patient throughput, due to long waiting lists.

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