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Estimation of Clearance Rate of Iodine-131 From Thyroid Cancer Patients Based on Individual Patient's Characteristic.

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Research Article

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Abstract

Differentiated thyroid carcinomas (DTC) are the most frequent malignancies of the endocrine system in 2015 in Japan. The purpose of this study is to estimate clearance rate of Iodine-131 from thyroid cancer patients based on individual patient's characteristics.

Materials and methods: We conducted retrospective study including 87 cases with DTC who had received RAI from June 2016 till July 2018. Patients who had complete information on primary tumor size (PTS) as mentioned in their histopathology reports, TNM staging, serum TSH (uIU/ml), free-T3 (pg/mL), free-T4 (ng/dL), thyroglobulin level (Tg) (ng/ml) (one month before, on the day of the treatment, and one month after receiving RAI), anti-Tg antibodies (IU/mL), dose of Levothyroxine (before and after RAI), as well as renal function (creatinine, BUN, eGFR), exposure rate (μSv/h) and taken dose (mCi) were included in our study.

Results: Univariate analysis showed significant associations of effective half-life with several factors (gender, body height, body weight, eGFR, size of tumor, dose of Levothyroxine, free-T3 one month after receiving RAI).

Conclusion: Effective management of these factors could help the doctors to optimize the occupancy of isolated rooms with higher output, but also reduce the operational cost of the hospital and improving the comfort to patients.

Introduction

Thyroid cancer causes 41,000 cancer deaths worldwide in 2018[1], and it the most frequent malignancies of the endocrine system in Japan. In 2015, 17,900 new cases of differentiated thyroid carcinomas were diagnosed, and 1,800 patients died from this disease in Japan[2]. The standard of treatment of patients with differentiated thyroid cancer (DTC) is total thyroidectomy followed by radioiodine therapy to destroy any remaining thyroid tissue (i.e. ablation) and/or destroy metastasis[34].

The recommended doses of radioiodine-131 (RAI) for ablation for low and high risk patients are 1110-3700 MBq (30-100 mCi) and 3700-7400 MBq (100-200 mCi) respectively[56]. Iodine-131 is isotope with physical half-life of 8.05 days and emits beta particles (maximum energy 606 keV) and high energy gamma rays (364 KeV). According publication of ICRP[7], when Iodine-131 enters the human body, approximately 30% is taken up by thyroid and another 70% is assumed to be excreted in the urine. Iodine-131 is excreted from the thyroid in the form of organic iodine. This organic iodine distributes among all organs and tissue of the body, other than thyroid. 90% of the organic iodine excreted from the thyroid is returned to transfer compartment and the rest is excreted via the feces. Another iodine is excreted by various body liquids, such as saliva, sweat, milk and blood and in exhaled breath can also been measured. Patients who are treated with high doses of RAI are the source of significant radiation exposure to medical staff, general public and patients' family members. Radiation exposure from treated patients mainly caused by gamma rays emitted from patients and also by beta particles in case of surface contamination or accidental ingestion.

Precautions are necessary to restrict the radiation exposure to public, to the patients' family and to the staff treating these patients. To address this issue, patients receiving RAI treatment are hospitalized and stay in isolation rooms until exposure rate decrease to safe limit. Number of guidelines and regulations have been established when patients shall be discharged from hospital. Usually DTC patients receiving RAI treatment in Japan are staying in isolated room until exposure rate is less than 30 μSv/h at 1-meter distance from patient. The isolation period of patients varies from 3-7 days and depends upon retained activity in patient's body. Quantity of this retained activity of RAI depends on the amount of remnant functioning thyroid tissue (thyroid bed and distant metastases) and Iodine-131 clearance rate from the body.

The purpose of this study is to estimate clearance rate of Iodine-131 from thyroid cancer patients based on individual patient's characteristics.

Materials And Methods

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol was approved by the ethics committee of Nagasaki university hospital (Protocol Number: 19102110). The ethics committee of Nagasaki university hospital waived the need of informed consent from participants because this research was a retrospective and non-invasive, and the identifying information was not included in the collected data.

Patients

We conducted a retrospective study of the cases of 74 patients with DTC who had received RAI treatment in the period between June 2016 and July 2018 at Nagasaki University Hospital. There were 23 males and 51 females, and their mean age was 58.6 years (range, 14-83 years). We included only those patients who had complete information of primary tumor size (PTS) as mentioned in their histopathology reports, TNM staging, serum TSH (uIU/ml), free-T3 (pg/mL), free-T4 (ng/dL), thyroglobulin level (Tg) (ng/ml) (one month before, on the day of the treatment, and one month after receiving RAI), anti-Tg antibodies (IU/mL), dose of Levothyroxine (before and after RAI), as well as renal function (creatinine, BUN, eGFR), exposure rate (μSv/h) and taken dose (mCi). In Japan, the equation to calculate eGFR[8] is follow:

Japanese Equation (3 variables): 194 X $(SCr)^{-1.094}$ X $(Age)^{-0.287}$ X 0.739 (if female)

SCr: serum creatinine

According to the American Thyroid Association (ATA)[3], we stratified DTC patients in three groups (low risk, intermediate risk, high risk). The group of patients planned for rTSH preparation underwent radioactive iodine ablation soon after surgery and received 0.9mg thyrotropin intramuscularly on two days before I-131 administration. The other group of patients were instructed to be on low iodine diet 2 week before RAI treatment and do not take any iodine containing drug (Levothyroxine withdrawal method)[9]. On the day of RAI administration, patients were instructed to fast 2 hours for food but take at least 1 liter of water to ensure good hydration. Administration is performed on Monday before noon or Wednesday just after noon. Dose of 3700MBq or 5550MBq (100 or 150 mCi) of I-131 capsule is orally taken. Dose is determined by clinical decision (body size, age, volume of metastasis etc). In our hospital fixed dose is used. All patients were hospitalized in an isolated room following RAI administration. In isolation room, patients were consulted by nuclear physician about the purpose of RAI, importance of good hydration and bowel clearance as well as necessary steps after getting RAI to minimize radiation exposure to others. Foods are delivered and patients drink bottled water to avoid unintentional iodine intake and to avoid unnecessary environment contamination. Dose rate was measured (immediately, 12h, 24h, 36h, 48h, 60h) at 1 meter distance from anterior mid trunk using NaI scintillation survey meter (Aloka TGS-172 Survey meter). As per Nagasaki University Hospital requirement, patients were released when their dose rate was <30 μSv/h at 1 meter distance. All dose rate measurements were performed after patients emptied their urinary bladder.

Using these dose rates, the effective half-life ($E_{1/2}$) of I-131 was calculated. The actual effective half-life is determined by two factors, long physical half-life of I-131 and short biological half-life which determined by the biological washout. Considering the small sample time point number to calculate half-life and much longer and fixed physical half-life than biological half-life, we determined to use simple mono-exponential fitting instead of complex bi-exponential fitting for the effective half-life calculation. The measured dose rates cannot be expressed in μSv/h because each patient has different exposure rate, but expressing as ratio is easier for mathematical calculation. Ratio 1 is equal to 1, because it is initial (first) dose rate at the time of I-131 administration, ratio 2 is relation of exposure rate of 2nd measurement to initial exposure rate, etc.

Statistical analysis

All statistical analyses were performed using the JMP Pro14 software. Univariate correlation analysis was used to compare factors which made influence on clearance of Iodine-131. All factors are expressed as median (1st quartile, 3rd quartile) values. P-values less than 0.05 were considered significant.

Results

Patients’ characteristics

The patients’ characteristics are listed in Table 1.

Table 1. Patients' characteristics

Parameters	Total (n=74)
Age *(mean, range) (y)*	58.6 (14-83)
Gender	
• *Male*	23
• *Female*	51
Body height *(median, range) (cm)*	158.7 (143.3 – 185.9)
Body weight *(median, range) (kg)*	59.8 (35 – 106.8)
Blood urea nitrogen (BUN) *(median, range) (mg/dL)*	11 (5 – 22)
Creatinine *(median, range) (mg/dL)*	0.82 (0.54 – 75)
Estimated glomerular filtration rate (eGFR) (*ml/min/1.73* m^2) *(median, range)*	61.63 (35.47 – 93.45)
Tumor size *(median, range) (mm)*	25.5 (1-100)
Taken dose *(median, range) (MBq)*	3700 (2590-5550)
Method of TSH elevating	
• *Levothyroxine withdrawal method*	70
• *rTSH*	4
Level of anti-Tg antibodies *(median, range) (IU/mL)*	10 (10-4000)
Level of Levothyroxine before RAI *(median, range) (μg)*	125 (50-225)
Level of Levothyroxine after RAI *(median, range) (μg)*	125 (75-225)

There were 74 patients (23 males and 51 females), and their mean age was 58.6 (range 14-83) years.

The distribution of TNM staging and risk of structural disease recurrence is presented in Table 2.

Table 2. TNM staging of patients and risk of structural disease recurrence.

Tumor staging	Total (n=74)
T_0	4
T_1	8
T_2	7
T_3	39
T_4	16
Lymph node staging	
N_0	15
N_1	6
N_{1a}	15
N_{1b}	37
N_x	1
M staging	
M_0	56
M_1	11
M (no data)	7
Risk of structural disease recurrence (N. of patients)	Low – 0 Intermediate – 11 High - 63

The serum levels of hormones at the different points of time are presented in Table 3.

Table 3. Serum level of hormones.

Serum level at the time of receiving Radioactive Iodine	**T3** **(pg/mL)**	**T4** **(ng/dL)**	**Thyroglobulin (ng/ml)**	**Thyroid Stimulating Hormone (uIU/ml)**
4 weeks before RAI *(mean ± SD)*	*3.56 ± 1.62*	*2.07 ± 2.13*	*987.42 ± 5489.2*	*1.28 ± 3.82*
1 week before RAI *(mean ± SD)*	*1.12 ± 0.73*	*0.30 ± 0.39*	*2155.07 ± 12306.5*	*25.84 ± 26.2*
The day of RAI *(mean ± SD)*	*0.73 ± 0.54*	*0.21 ± 0.3*	*2293.71 ± 12212.6*	*82.82 ± 42.6*
2 weeks after RAI *(mean ± SD)*	*1.26 ± 0.85*	*0.99 ± 0.63*	*19.4 ± 19.31*	*44.86 ± 47.4*
4 weeks after RAI *(mean ± SD)*	*2.93 ± 0.64*	*1.87 ± 0.42*	*952.03 ± 5224.5*	*4.06 ± 9.36*

The exposure rates of patients are listed in Table 4.

Table 4. Patients' dose measurements.

Measurement	**Dose rate (median, range) (μSv/h)**
Immediately after RAI	119 (74-220)
12 hours later RAI	49.5 (21-116)
24 hours later RAI	30 (9.6-75)
36 hours later RAI	13 (0-48)
48 hours later RAI *(number of patients – 3)*	33 (29.2-36)
60 hours later RAI *(number of patients – 2)*	31 (29-33)

Univariate analysis showed significant associations of effective half-life with several factors (see table 5).

Table 5. Association between effective half-life and physiological parameters.

Parameter	Effective $t_{1/2}$
Age	P value - 0.8388 R^2 - 0.0004
Gender (M ±SD)	F – 32.21±3.142 M – 49.21±3.142
Body height	P value - **0.0019** R^2 - **0.1100**
Body weight	P value - **0.0183** R^2 - **0.0652**
Blood urea nitrogen *(BUN)*	P value - 0.9465 R^2 – 5.464
Creatinine	P value - 0.1004 R^2 - 0.0321
Estimated Glomerular Filtration Rate *(eGFR)*	P value - **0.0001** R^2 - **0.1646**
Tumor size	P value – 0.4605 R^2 – 0.0070
Taken dose	P value – **0.0145** R^2 - **0.0958**
Method of TSH elevating	P value – 0.0674 R^2 – 0.0580
Level of Levothyroxine before RAI	P value - **0.0388** R^2 - **0.0492**
Level of Levothyroxine after RAI	P value - **0.0027** R^2 - **0.1007**

Among the serum levels of hormones only free-T3 taken 4 weeks after receiving radioactive iodine have showed significant association with effective half-life (see Table 6). As the T3 is the hormone of human metabolism, we tried to find association of free-T3 with body weight and height, however no significant association was found.

Table 6. Association between effective half-life and serum level of hormones.

	T3	T4	Tg	TSH
4 weeks before RAI	Pvalue - 0.2152 R^2 - 0.06	Pvalue - 0.7077 R^2 - 0.0018	Pvalue - 0.2533 R^2 - 0.0183	Pvalue - 0.2884 R^2 - 0.0150
1 week before RAI	Pvalue - 0.4381 R^2 - 0.007	Pvalue - 0.1598 R^2 - 0.0236	Pvalue - 0.2746 R^2 - 0.0143	Pvalue - 0.7386 R^2 - 0.0013
The day of RAI	Pvalue - 0.5979 R^2 - 0.003	Pvalue - 0.0720 R^2 - 0.0389	Pvalue - 0.2484 R^2 - 0.0160	Pvalue - 0.3756 R^2 - 0.0094
2 weeks after RAI	Pvalue - 0.5445 R^2 - 0.2074	Pvalue - 0.7968 R^2 - 0.0256	Pvalue - 0.6617 R^2 - 0.1144	Pvalue - 0.2753 R^2 - 0.3712
4 weeks after RAI	Pvalue - **0.0252** R^2 - **0.1782**	Pvalue - 0.3038 R^2 - 0.0142	Pvalue - 0.2875 R^2 - 0.0156	Pvalue - 0.2394 R^2 - 0.0186

Discussion

In the present study we found difference of some physiological parameters according to effective half-life of Iodine-131. We also found that serum level free-T3 4 weeks after receiving RAI therapy was correlated with clearance rate of Iodine-131 from human body. Interestingly, serum levels of thyroid hormones did not show any correlation with physiological parameters, such as body weight and body height.

Radioactive Iodine-131 has been routinely used for ablation remnant thyroid and/or therapy of metastasis after total thyroidectomy in thyroid cancer patients for many years. Major concern for medical staff, general public and patients is radiation exposure caused by high energy gamma rays and risk of contamination by beta particles of RAI [10,11]. In Japan, patients receiving RAI must be admitted in isolation and release once dose rate at 1 meter distance is less than 30 μSv/h.

In this study we have evaluated usefulness of different factors for clearance rate of iodine-131 from human body and early discharge from isolation room.

Previous study [1213] has shown a longer effective half-life in male than female patients who received RAI for thyroid cancer due to an aggressive course of disease in males. Our study supports that previous findings.

In this study we found that patients with larger body weight and body height have longer effective half-life than patients with smaller body weight and height. It can be explained simply, that bigger body needs more time to excrete iodine-131 from the body.

For preparation for RAI therapy, levothyroxine need to be withdrawn, which induce state of hypothyroidism in patients and lead to a reduction in glomerular filtration rate and retention of iodine-131[14–1617,18]. Consumption of large amounts of liquids is encouraged mainly after one day post-therapy administration to enable the excretion of free iodine-131 from blood circulation, on considering that after this period of time all free iodine-131 will produce only body irradiation without any impact on patient therapy[16]. In our study we found that eGFR is related with effective half-life. It can be explained that better kidney function related with faster clearance.

We identified the fact that serum level of free-T3 4 weeks after RAI is related with clearance rate. To find an explanation of our findings, we performed comparison between serum level of hormones and body weight/height. No statistically significant correlation was found. We do not have perceptible explanation for this finding in our study. Probably, number of patients was too small.

No significant association between serum level of TSH, Tg and free-T4 has also been reported by other studies[12]. Our findings also support their results.

We recognize that there are several limitations in our study. First - Acquisition and patient follow-up were retrospective. We did not analyze prospectively influence of each factor on clearance rate. Second - we did not measure urinary iodine concentration for precise calculation of effective half-life of RAI. Third - The sample size of patients with differentiated thyroid carcinoma who underwent for radioactive iodine therapy was small, which may limit our conclusions. Fourth – we did not consider behavioral factors, like the number of baths the patients are taking, that may have an impact on the obtained dose rates.

Conclusion

Findings of our study would be important for treating nuclear physicians to utilize their treatment facilities in an efficient way to accommodate more patients to receive RAI treatment. Occupancy of limited facilities for 3 or more days contributes to increase waiting time and significant delays in administration of RAI treatment and this has a significant negative impact on survival of these patients[19]. Furthermore, prolong internment also enhances the treatment cost and has its own psychological and logistic impacts on patients and families. We consider that effective management of these factors could help the doctors to optimize the occupancy of isolated rooms with higher output, but also reduce the operational cost of the hospital and improving the comfort to patients.

Declarations

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Additional information

Manuscript has been seen and approved by all authors. There is no overlap with other materials. The authors declare that there is no conflict of interest.

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References

1. Bray, F. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin.* **68**, 394–424 (2018).
2. Foundation for Promotion of Cancer Research. Cancer Statistics in Japan - 2015. (2015).
3. Haugen, B. R. *et al.* 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* **26**, 1–133 (2016).
4. Mittendorf, E. A. *et al.* Followup of Patients with Papillary Thyroid Cancer: In Search of the Optimal Algorithm. *J. Am. Coll. Surg.* **205**, 239–247 (2007).

5. Cooper DS, Doherty GM, Haugen BR, Kloss RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association Management Guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **19**, 1167–1214 (2009).
6. Grazia Castagna, M. *et al.* Post-surgical thyroid ablation with low or high radioiodine activities results in similar outcomes in intermediate risk differentiated thyroid cancer patients. *Eur. J. Endocrinol.* **169**, 23–29 (2013).
7. ICRP rublication 54.
8. Imai, E., Yasuda, Y. & Makino, H. Japan Association of Chronic Kidney Disease Initiatives (J-CKDI). *Japan Med. Assoc. J.* **54**, 403–405 (2011).
9. Horie, I., Ando, T., Imaizumi, M., Usa, T. & Kawakami, A. Hyperkalemia develops in some thyroidectomized patients undergoing thyroid hormone withdrawal in preparation for radioactive iodine ablation for thyroid carcinoma. *Endocr. Pract.* **21**, 488–494 (2015).
10. Barbaro D, Grosso M, Boni G, Lapi P, Pasquini C, Orsini P, Turco A, Meucci G, Marzola MC, Berti P, Miccoli P, Mariani G, R. D. Recombinant human TSH and ablation of post-surgical thyroid remnants in differentiated thyroid cancer: the effect of pre-treatment with furosemide and furosemide plus lithium. *Eur J Nucl Med Mol Imaging* **37**, 242–9 (2010).
11. Azizmohammadi, Z. *et al.* A study of the time of hospital discharge of differentiated thyroid cancer patients after receiving iodine-131 for thyroid remnant ablation treatment. *Hell. J. Nucl. Med.* **16**, 103–106 (2013).
12. Remy H, Borget I, Lebolleux S, Guilabert N, Lavielle F, Garsi J, Bournaud C, Gupta S, Schlumberger M, R. M. 131I Effective half-life and dosimetry in thyroid cancer patients. *J Nucl Med* **49**, 1445–50 (2008).
13. Fatima, N. *et al.* Factors predicting early release of thyroid cancer patients from the isolation room after radioiodine-131 treatment. *Asian Pacific J. Cancer Prev.* **17**, 125–129 (2016).
14. Duranton F, Lacoste A, Faurous P, Deshayes E, Ribstein J, Avignon A, Mourad G, A. A. Exogenous thyrotropin improves renal function in euthyroid patients. *Clin Kidney J* **6**, 478–483 (2013).
15. Bricker NS, H. C. J. Observations on the mechanism of the renal clearance of I-131. *J Clin Invest* **34**, 1057–1072 (1955).
16. Willegaignon, J. *et al.* Prediction of iodine-131 biokinetics and radiation doses from therapy on the basis of tracer studies: An important question for therapy planning in nuclear medicine. *Nucl. Med. Commun.* **37**, 473–479 (2016).
17. Martin Schlumberger, M.D., Bogdan Catargi, M.D., Ph.D., Isabelle Borget, Pharm.D., Ph.D., Désirée Deandreis, M. D., Slimane Zerdoud, M.D., Boumédiène Bridji, M.D., Ph.D., Stéphane Bardet, M.D., Laurence Leenhardt, M.D., P. D., Delphine Bastie, M.D., Claire Schvartz, M.D., Pierre Vera, M.D., Ph.D., Olivier Morel, M.D., Danielle Benisvy, M. D., Claire Bournaud, M.D., Françoise Bonichon, M.D., Catherine Dejax, M.D., Marie-Elisabeth Toubert, M. D. & Sophie Leboulleux, M.D., Marcel Ricard, Ph.D., and Ellen Benhamou, M. . Strategies of Radioiodine Ablation in Patients with Low-Risk Thyroid Cancer. *N. Engl. J. Med.* **366**, 1663–1673 (2012).

18. Anca M. Avram, Y. K. D. Thyroid cancer radiotheragnostics: the case for activity adjusted 131I therapy. *Clin Transl Imaging***6 (5)**, 335–346 (2018).
19. Higashi T, Nishi R, Yamada S, Nakamoto Y, Ishizu K, Kawase S, Togashi K, Itasaka S, HiraokaM, Misaki T, K. J. Delayed initial radioactive iodine therapy resulted ni poor survival in patients with metastatic differentiated thyroid carcinoma: a retrospective statistical analysis of 198 cases. *J Nucl Med***52**, 683–689 (2011).

Figures

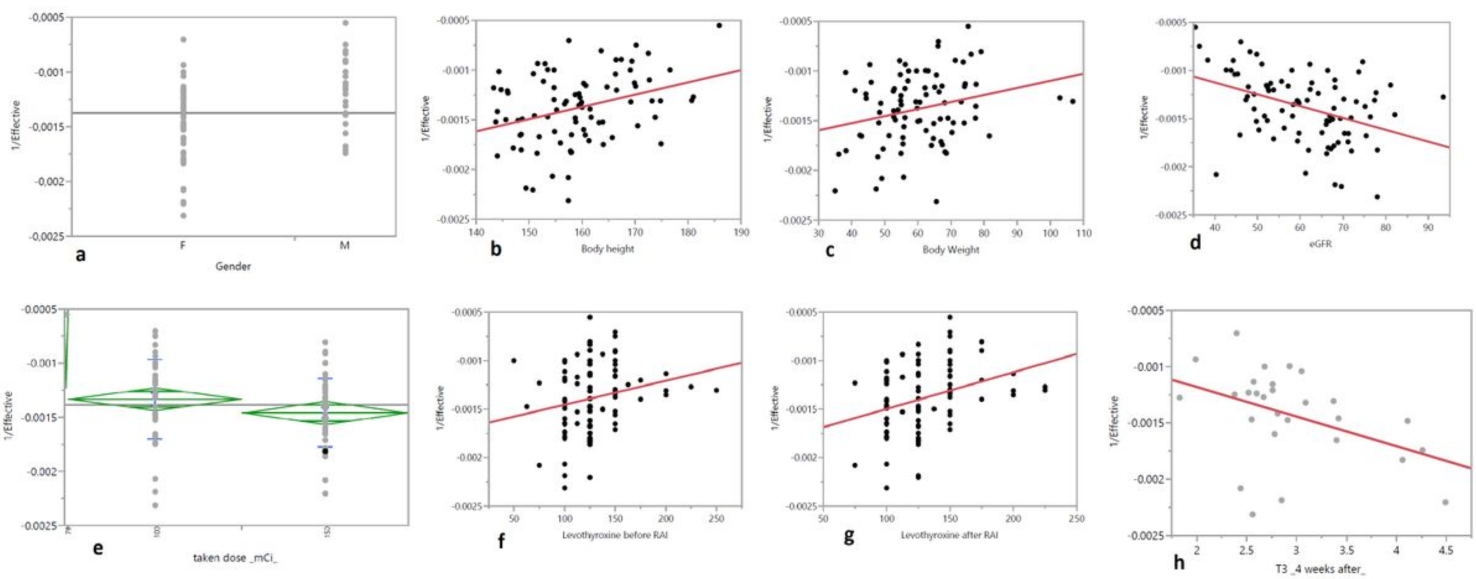

Figure 1

Univariate analysis of associations of effective half-life with several factors: (a) gender; (b) body height; (c) body weight; (d) Estimated glomerular filtration rate (eGFR); (e) taken dose; (f) Dose of levothyroxine before RAI; (g) Dose of levothyroxine after RAI; (h) Serum level of free-T3 4 weeks after RAI.