

ONE SIZE DOES NOT FIT ALL: THE MERIT OF ABSORBED DOSES TO THE BLOOD IN ^{131}I THERAPY FOR DIFFERENTIATED THYROID CARCINOMA

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Abstract—The amount of ^{131}I necessary for successful ablation in patients with differentiated thyroid cancer (DTC) is still subject to debate. This study investigates the relationship of the absorbed dose of radiation to the blood while administering ^{131}I activity with several other parameters in DTC patients. This prospective study included 90 DTC patients who were classified into three groups according to their level of dosage: 3.7 GBq (38.9%), 5.55 GBq (55.6%), and 7.4 GBq (5.5%). Blood dosimetry of treated patients was performed using external whole-body counting with a Geiger Muller dosimeter located 2 m away from the patients. Dose rate was measured at 2, 4, 5, 24, and 48 h after the administration of radioiodine. Based on the results of whole-body dose rate measurements, 48 h after administration of 3.7, 5.55, and 7.4 GBq of radioiodine, absorbed doses to patients' blood were estimated at 0.49 ± 0.12 , 0.71 ± 0.21 , and 0.76 ± 0.11 Gy, respectively. Increasing radioiodine dosage from 3.7 GBq to 5.55 GBq significantly increased blood dose, while there was no significant difference in blood dose between radioiodine dosages of 5.55 GBq and 7.4 GBq. The absorbed dose to the blood was significantly correlated to the patients' gender and the presence of lymph node metastases, but it was not significantly correlated to the type of pathology and regional or distant metastases. Ablation activities exceeding 5.55 GBq produce no further increase in the accumulated activity per volume of blood. The literature regarding this issue is scarce, and further studies are required to verify these preliminary results.

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INTRODUCTION

EACH YEAR, 26,000 patients in the United States and 1,500 in the United Kingdom are diagnosed with thyroid-related cancers (Hackshaw et al. 2007). The reports reveal that the rate of differentiated thyroid cancers (DTC) have increased 40% in the United States from 2000 to 2005 (Azizmohammadi et al. 2013; Hackshaw et al. 2007). DTC is the most common sub-category of thyroid cancer. Thirty percent of patients suffer from recurrence of the disease.

Routine treatment strategy for DTC consists of a total thyroidectomy followed by radiation therapy with radioiodine to ablate remaining thyroid tissue (Verburg et al. 2011). According to recent research, DTC therapy combining surgery with radioiodine ablation is usually associated with a 10-y survival for 90% of patients (Hackshaw et al. 2007). Radioiodine ablation for DTC patients matters for the following reasons. First, the presence of remnant thyroid tissue after surgery makes it difficult to detect and treat regional or distant metastases (Miccoli et al. 1998; Van Nostrand et al. 2002). Second, thyroid cancers typically tend to be multifocal, so residual thyroid tissue will more likely include malignant cells. Third, poorly differentiated thyroid cancers can become anaplastic carcinoma. In all cases, radioiodine ablates malignant and metastatic cells that escaped the surgery, reducing the risk of recurrence (Henkin et al. 2006). Because this therapy is well known as an effective method to treat DTC, it has become an internationally standard approach (Dietlein et al. 2007; Gharib et al. 2010; Hanscheid et al. 2006; Luster et al. 2008).

After a patient is treated with radioiodine, an important following step is the attempt to determine the dose that is absorbed in lesion. Up to now, several techniques have been established in this regard. One of the first approaches used for dosimetry of patients after radioiodine thyroid therapy was a method introduced by Benua et al. (1962) that has provided a way to calculate the limited dose to blood that can be tolerated and also the dose to the lesion per unit of administered activity. The procedure describes that the maximum amount of administered activity to a patient can be

defined as the amount of activity that leads to an absorbed dose to blood of 2 Gy. Later, this method was developed by Furhang et al. (2002), in which some parameters were fitted to patients' clearance data to provide a dosimetry algorithm. In recent years, Hanscheid et al. (2006) set up dosimetric procedures in which the need for blood sampling to determine patient absorbed dose has been eliminated. One important, if controversial, aspect of radioiodine ablation is determining the standard amount of radioiodine activity required for an optimally successful ablation. Past trials have associated values ranging from 0.99 GBq to 3.7 GBq with favorable outcomes in the ablation of remaining tissue in newly diagnosed DTC cases (Sawka et al. 2008). Higher dosages are recommended for metastatic cases, but these can cause serious complications affecting bone marrow and healthy tissues, so activity values are limited to around 7.4 GBq (Lassmann et al. 2010; Zakani et al. 2011). On the other hand, while higher doses of radioiodine increase success rates, some studies discovered no further improvement in ablation success for amounts higher than 1.85 GBq (Bal et al. 2004; Hackshaw et al. 2007). While the optimal amount of radioiodine remains subject to debate, a study by Frederik **AQ3** et al. showed that the absorbed dose to the blood is a more useful predictor of ablation success in thyroid cancer patients than the amount of administered radioiodine (Verburg et al. 2011).

Therefore, the current study investigates whether increasing the administered radioiodine, which may increase complications, would necessarily increase its absorbed dose to the blood. It also correlates absorbed dose to the blood with patients' gender, age, type of pathology (PTC or papillary thyroid carcinoma and FTC or follicular thyroid carcinoma), and whether metastases are in the lymph node, regional, or distant.

METHODS AND MATERIALS

Ninety (90) DTC patients were included in this study. The necessary histological information was obtained from patients' documents. No patients were excluded for any reasons due to their gender, age, or pathology.

All patients underwent external whole-body counting to measure the absorbed dose to the blood of the DTC patients after radioiodine ablation. This method of blood dosimetry, which does not require blood sampling, is based on the fact that 14% of the whole-body residence time is attributed to the blood (Hanscheid et al. 2006). Following treatment, patients were stratified into three groups who were administered 3.7 GBq (38.9%), 5.55 GBq (55.6%), and 7.4 GBq (5.5%); then external whole-body counting of each patient was performed by a Geiger Muller dosimeter. During whole-body counting, the dosimeter was located 1 m above ground level at a distance of 2 m behind

each patient. The first measurement was performed approximately 2 h after radioiodine administration, with further measurements following at 4, 5, 24, and 48 h. An exponential decay curve was fitted to the dose measurements to obtain a 48-h whole-body radioiodine dose-rate curve for each patient.

The following formula, recently published by Hanscheid et al. (2009), calculated absorbed dose to the blood per unit of administered radioactivity (D_{blood}/A_0) using dose-rate curve data:

$$\frac{D_{\text{blood}}}{A_0} (\text{mGy/MBq}) = - \frac{15.12}{\text{BLV}(\text{mL}) + \frac{0.0188}{[\text{wt}(\text{kg})]^{2/3}}} \left(\frac{t(\text{h})}{\ln[R(t)]} \right)$$

BLV is the individual blood volume estimated from the patient's weight (wt) and height (ht) according to the equation proposed by Retzlaff et al. (1969):

$$\text{BLV} = 31.9 \times \text{ht} + 26.3 \times \text{wt} - 2402 \text{ for male}$$

$$\text{BLV} = 56.9 \times \text{ht} + 14.1 \times \text{wt} - 6460 \text{ for female,}$$

$R(t)$ is radioiodine retention at time t , and $t(h)$ is the time after radioiodine injection. The ANOVA test and independent t -test compared the various parameters. The correlation of absorbed dose to the blood with administered activity of radioiodine, gender, age, type of pathology, and lymph node, regional, or distant metastases was considered statistically significant at $p < 0.05$.

RESULTS

All 90 adult patients enrolled in this study had been newly diagnosed with DTC and recently underwent total or near-total thyroidectomies: 26 were men (28.9%) and 64 were women (71.1%); five (5.6%) patients had follicular cancer, 85 (94.4%) patients had papillary cancer, 46 (51.1%) patients had metastases in the lymph node, 40 (44.4%) patients had regional metastases, and nine (10%) patients had distant metastases. Mean (\pm SD) of the patients' age, height, and weight were 42.88 (\pm 16.43) y, 158.49 (\pm 8.66) cm, and 69.62 (\pm 10.61) kg, respectively.

Based on their height and weight, patients' individual blood volume was estimated at $5,197.90 \pm 176.34$ mL for men and $3,165.95 \pm 121.79$ mL for women.

Results of dose rate measurements by Geiger Muller dosimeter at various times were used to draw a 48-h dose-rate curve. Fig. 1 presents such curves following administration of 3.7, 5.55, and 7.4 GBq of radioiodine. **F1**

Based on Hanscheid's equation and using data of BLV and retention measurement, which was calculated by normalization of the last measurement (48 h after

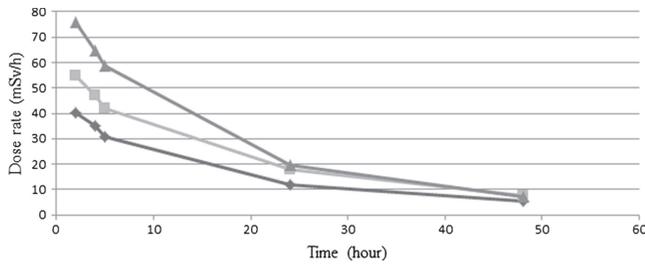


Fig. 1. 48-h dose-rate curves following administration of 3.7 GBq (diamond), 5.55 GBq (rectangle), and 7.4 GBq (triangle) of radioiodine.

administration of radioiodine) to the initial measurement (2 h after administration of radioiodine) of dose rates, absorbed dose to the blood of patients was determined as 0.49 ± 0.12 , 0.71 ± 0.21 , and 0.76 ± 0.11 Gy for administration of 3.7, 5.55, and 7.4 GBq of radioiodine, respectively. Statistical analysis of data revealed that increasing the radioiodine dose from 3.7 GBq to 5.55 GBq significantly increases the absorbed dose to the blood of patients, while no significant difference was observed between patients who received doses of 5.55 GBq and 7.4 GBq.

T1 Table 1 presents the mean (\pm SD) values of absorbed dose to the blood 48 h after radioiodine administration, broken down by gender, type of pathology, presence of residual thyroid tissue after thyroidectomy, and whether there were lymph node, regional, or distant metastases.

The mean absorbed dose to the blood in male and female subgroups was estimated to be 0.53 ± 0.14 Gy and 0.66 ± 0.21 Gy, respectively. The difference between these two groups was statistically significant ($p = 0.026$).

Regarding the type of pathology, absorbed dose to the blood was estimated 0.62 ± 0.20 and 0.66 ± 0.20 Gy, for patients with PTC and with FTC, respectively. The difference between these groups was not statistically significant ($p = 0.951$).

Analysis of absorbed dose to the blood in patients with (0.62 ± 0.22 Gy) and without (0.63 ± 0.15 Gy) residual thyroid tissue after thyroidectomy revealed no difference between these two groups ($p = 0.115$).

Also, the median absorbed dose to the blood in patients with lymph node metastases was estimated to be 0.67 ± 0.23 and 0.58 ± 0.17 Gy without. Difference between these two groups was statistically significant ($p = 0.036$).

The median absorbed dose to the blood for patients with regional metastases was 0.64 ± 0.18 and 0.61 ± 0.22 Gy with out. The observed difference was not significant ($p = 0.586$).

Finally, the absorbed dose to the blood in patients with distant metastases was estimated at 0.72 ± 0.12 Gy and at 0.62 ± 0.21 Gy without. Statistical analysis of data revealed no significant difference in absorbed dose to the blood between the two groups ($p = 0.155$).

Table 1. Values of absorbed dose to the blood 48 h after administration of radioiodine with respect to the sex, type of pathology, presence of residual thyroid tissue after thyroidectomy, metastases (to lymph node, regional and distant) and administered activity.^a

Absorbed dose to the blood (Gy)	Sex		Pathology		Metastases						Administered activity (GBq)				
	Male	Female	FTC	PTC	Residual tissue		Lymph node		Regional			Distant			
					Po	Ne	Po	Ne	Po	Ne		Po	Ne		
	0.53 ± 0.14	0.66 ± 0.21	0.66 ± 0.20	0.62 ± 0.20	0.62 ± 0.22	0.63 ± 0.15	0.67 ± 0.23	0.58 ± 0.17	0.64 ± 0.18	0.61 ± 0.22	0.72 ± 0.12	0.62 ± 0.21	0.49 ± 0.12	0.71 ± 0.21	0.76 ± 0.11

^aPTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

DISCUSSION

In recommended protocols for DTC therapy, radioiodine ablation has long been associated with a lower rate of recurrence and distant metastases, as well as a reduced risk of cancer mortality, than undergoing only surgery (DeGroot et al. 1990; Massin et al. 1984; Mazzaferri 1997; Schlumberger 1998; Simpson et al. 1988; Tsang et al. 1998).

While some physicians favor low radioiodine levels approximating 1.11 GBq, others prefer higher amounts of up to 7.4 GBq (Beierwaltes 1987; Hay et al. 2002; Ramanna et al. 1985). Furthermore, because of some technical difficulties, physicians in most centers often use a predetermined and fixed radioiodine level from 1.11 to 7.4 GBq rather than techniques based on bio-kinetic properties of patients (Bal et al. 2004).

The British Thyroid Association guidelines, specifically, recommend radioiodine ablation after a total thyroidectomy for DTC patients with tumors larger than 1 cm. While there is no agreement on the standard amount of radioiodine, an ablation dose of 3.7 GBq is usual, even though some centers prefer ablation doses as low as 1.11 GBq (Watkinson et al. 2004).

The European consensus report on ablation recommends activity of 3.7 GBq for those DTC patients with a high risk of recurrence, distant metastases, or incomplete tumor resection (Pacini et al. 2005).

From a historical point of view, it has long been accepted that a single administration of a higher radioiodine level results in a more successful ablation. This was based on the hypothesis that the larger the amount of radioiodine, the more likely it is than lower levels to ablate remnants and destroy residual micro-metastases (Beierwaltes et al. 1984).

AQ4 A study by Mazzaferri and Kloosto of 30-y recurrence rates of DTC patients treated with radioiodine ablation after their thyroidectomies found no significant difference between low-dose (1 to 1.85 GBq) and high-dose (1.89 to 7.4 GBq) groups (Mazzaferri 1997).

One benefit of lower radioiodine dosage is smoother outpatient treatment, because it reduces the radiation exposure to the patient's environment and household members. As well, lower dosage also lowers financial cost, lessens the amount of time a patient spends in isolation, shortens hospital stays, and lowers whole-body irradiation (DeGroot et al. 1990; Grigsby et al. 2000). Furthermore, because the risk of a second primary malignancy is correlated with radioiodine ablation, a lower dose reduces this risk (Rubino et al. 2003).

While this study kept the amount of administered radioiodine relatively low, the authors evaluated whether higher doses would necessarily increase the absorbed dose to the blood. This study revealed that absorbed dose to the blood of patients with DTC administered with 5.55 GBq

of radioiodine is significantly higher than that of patients administered with 3.7 GBq of radioiodine. However, there is no significant difference in the absorbed dose to patients' blood when treated with 7.4 GBq of radioiodine compared to 5.55 GBq. Given that the absorbed dose to the blood is a better predictor of ablation success than overall radioiodine administered (Verburg et al. 2011), these findings suggest that 5.55 GBq would be the most favorable dose compared to 3.7 GBq and 7.4 GBq of radioiodine in thyroid ablation. Dosage of 5.55 GBq is not only more advantageous therapeutically, but it also causes fewer therapeutic problems than a dose of 7.4 GBq.

These findings contrast the results of Mazzaferri on 1004 DTC patients undergoing radioiodine ablation of thyroid remnant. That study categorized patients into two groups: those treated with 1–1.85 GBq (mean 1.74 GBq) of radioiodine and those treated with 1.89–7.4 GBq (mean 4.1 GBq). That study observed no significant difference in recurrence rates between the two groups of patients (Mazzaferri 1997). One possible reason for this is that the current study used different values of radioiodine activity in the ablations. The Mazzaferri study patients were administered various amounts of radioiodine ranging from 1 GBq to 7.4 GBq, which made it impossible to assess the effect of each dose on the ablation's overall success. As well, because this analysis used only two dose groups of less than and greater than 1.85 GBq, the current study was more nuanced, dividing patients into three dose groups of 3.7, 5.55, and 7.4 GBq.

The authors observed that the absorbed dose to the blood in female patients is significantly higher than in male patients. As well, absorbed dose to the blood is significantly higher in patients with lymph node metastases than without. This study also indicates that there is no correlation between absorbed dose to the blood and whether a patient has PTC or FTC pathology or regional or distant metastases.

One of the main problems in this study was related to measuring whole-body dosage using a Geiger Muller dosimeter in which the operator was exposed to radioiodine radiation. In most advanced nuclear medicine centers, dosimeter systems are launched 2 m above the patient's coach **AQ5** to record external whole-body radiation.

This study suffered from a shortage of patients undergoing a 7.4 GBq radioiodine dosage and a small overall sample of participating patients compared to other studies. Therefore, further research requires a larger number of patients split into more categories of radioiodine dosages to find the optimum activity for the best therapeutic ablation outcomes.

CONCLUSION

There is no further increase in the overall activity per volume of blood when radioiodine ablation dosages exceed

5.55 GBq. The literature on this issue remains scarce, and further studies are needed to verify these preliminary results.

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