

Planning of ^{131}I Therapy for Graves Disease Based on the Radiation Dose to Thyroid Follicular Cells

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We evaluated the effects on the absorbed dose to thyroid follicular cells of self-absorption of ^{131}I radiation (specifically, β -rays) in the follicular colloid. **Methods:** Thyroid follicles were modeled as colloid-filled spheres, containing a uniform concentration of ^{131}I and surrounded by a concentric monolayer of cells. Assuming close packing of identical follicles, we used Monte Carlo simulation to assess the absorbed dose to follicular cells. **Results:** Because of β -ray self-absorption in colloidal spheres with radii larger than 50 μm , the absorbed dose to follicular cells is less than the average thyroid absorbed dose. **Conclusion:** For the same thyroid mass, radioiodine thyroid uptake, and effective half-life, patients with follicles with colloidal sphere radii of 100, 200, 300, and 400 μm should be administered 9%, 15%, 21%, and 30% more ^{131}I , respectively, than patients with colloidal sphere radii of less than 50 μm , to yield the same absorbed dose to follicular cells.

Key Words: Monte Carlo; diffuse toxic goiter; absorbed dose; echogenicity; thyroid follicle

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Radioiodine (^{131}I -iodide) therapy is generally the treatment of choice for uncomplicated Graves disease in adults. The ideal goal is to destroy or otherwise affect enough thyroid tissue to produce euthyroidism. Despite efforts to assess clinically the target absorbed dose by accounting for the gland size and radioiodine kinetics, the success of radioiodine therapy remains largely unpredictable (1,2).

The current methods define the whole thyroid as the target organ, although the biologic effects are primarily due to irradiation of thyroid follicular cells. The current article presents evidence that a ^{131}I absorbed dose to thyroid follicular cells differs from the mean thyroid absorbed dose

and that such differences increase with increasing sizes of thyroid follicles.

MATERIALS AND METHODS

Systemically administered iodide is captured by the thyroid and organified and appears in the follicular colloid within minutes of administration, as demonstrated by autoradiographic studies in rats (3). In contrast, the biologic half-life of thyroidal iodine is quite long, varying from 15 to 60 d and yielding an effective half-life of 5–7 d for ^{131}I . This means that most ^{131}I decays occur within the colloid, that is, extracellularly.

In the current analysis, we considered only the β -radiation of ^{131}I . The contribution of γ -radiation to total average gland absorbed dose (average thyroid absorbed dose from both γ -radiation and β -particles of ^{131}I) increases with the gland size and depends on the gland shape; for a 20-g gland, it is 6% (Appendix). This component is not negligible and should be taken into account. However, because of the relatively long mean free path of γ -rays, compared with particle ranges, the absorbed energy distribution of γ -rays is expected to be uniform across the thyroid volume (i.e., insensitive to thyroid microarchitecture).

The β -radiation-absorbed dose to thyroid follicular cells, D_{cell} , is due to β -particles emanating from their own colloid (the self-dose [D_{self}]) and from β -particles coming from the colloid of neighboring follicles (the cross-dose [D_{cross}]):

$$D_{\text{cell}} = D_{\text{self}} + D_{\text{cross}} \quad \text{Eq. 1}$$

We assumed that a thyroid is composed of identical follicles. E_0 denotes the total energy of all β -particles emerging from the ^{131}I distributed uniformly in the colloid of the thyroid follicles. Then D_{self} equals the energy absorbed in follicular cells originating from their own colloid E_{self} divided by the mass of follicular cells m_{cells} :

$$D_{\text{self}} = \frac{E_{\text{self}}}{m_{\text{cells}}} \quad \text{Eq. 2}$$

Because of somewhat irregular arrangements of follicles, one cannot assume a regular geometric model of follicular packing. Such an irregular arrangement of follicles leads to the assumption that all radiation energy emanating from the follicles, $E_0 - E_{\text{coll}} - E_{\text{self}}$, is uniformly absorbed over the thyroid mass, m_{thy} , where E_{coll} is the radiation energy self-absorbed within the colloid. This

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yields the following equation for the nonself, or cross-, absorbed dose, D_{cross} :

$$D_{\text{cross}} = \frac{E_0 - E_{\text{coll}} - E_{\text{self}}}{m_{\text{thy}}}. \quad \text{Eq. 3}$$

Combining Equations 1–3 yields the total follicular cell–absorbed dose:

$$D_{\text{cell}} = \frac{E_0}{m_{\text{thy}}} \left[\frac{E_{\text{self}}}{E_0} \frac{m_{\text{thy}}}{m_{\text{cells}}} + 1 - \frac{E_{\text{coll}}}{E_0} - \frac{E_{\text{self}}}{E_0} \right]. \quad \text{Eq. 4}$$

Assuming that all energy of β -particles and secondary radiation are totally absorbed in the thyroid (Appendix), E_0/m_{thy} is the average dose to thyroid tissue, assessed on the basis of the administered activity and measured thyroid uptake, mass, and effective half-life.

For clarity, we defined the dimensionless quantity, the relative absorbed dose to follicular cells, \hat{D}_{cell} , as the ratio of D_{cell} to the average thyroid dose, E_0/m_{thy} :

$$\hat{D}_{\text{cell}} = \frac{E_{\text{self}}}{E_0} \frac{m_{\text{thy}}}{m_{\text{cells}}} + 1 - \frac{E_{\text{coll}}}{E_0} - \frac{E_{\text{self}}}{E_0}. \quad \text{Eq. 5}$$

Multiplying the administered activity determined to deliver a prescribed mean absorbed dose to the thyroid by the quantity $1/\hat{D}_{\text{cell}}$, termed the activity correction factor, yields the administered activity that would deliver the same prescribed dose specifically to follicular cells.

\hat{D}_{self} , the first term on the right side of Equation 5, is the relative self-absorbed dose to follicular cells:

$$\hat{D}_{\text{self}} = \frac{E_{\text{self}}}{E_0} \frac{m_{\text{thy}}}{m_{\text{cells}}}, \quad \text{Eq. 6}$$

which equals the self-absorbed fraction of the follicular cells weighed by thyroid–to–follicular cell mass ratio. The relative cross-absorbed dose to follicular cells is simply the fraction of total energy of β -particles that leaves the original follicles:

$$\hat{D}_{\text{cross}} = 1 - \frac{E_{\text{coll}}}{E_0} - \frac{E_{\text{self}}}{E_0}. \quad \text{Eq. 7}$$

Finally, the ratio of the relative self-absorbed and cross-absorbed doses to follicular cells equals the ratio of the respective absolute absorbed doses:

$$D_{\text{cross}}/D_{\text{self}} = \hat{D}_{\text{cross}}/\hat{D}_{\text{self}}. \quad \text{Eq. 8}$$

To calculate the relative absorbed dose to follicular cells and its self- and cross-components, one should assess the fractions of total energy self-absorbed in the colloid and in the follicular cells and the thyroid-to-follicular cell mass ratio.

We used the Monte Carlo code EGS5 (4) to calculate the self-absorbed fractions E_{coll}/E_0 and E_{self}/E_0 . The input model of the thyroid follicle was a unit-density water sphere, comprising a spheric shell of cells and a concentric inner sphere filled with uniform concentration of ^{131}I . The initial electron energies were sampled from the ^{131}I β -spectrum as calculated by Simpkin and Mackie (5). The emissions of discrete electrons were simulated as

well. The numbers of simulated electron histories were always sufficiently large that the statistical uncertainties (errors) were less than 1%. Electrons and photons were followed until their energy reached the transport cutoff values, which were both set equal to 1 keV. Below this cutoff, the energy was deposited locally. Secondary particles were followed if their initial energy was greater than 1 keV. The calculations were performed for radii of colloid spheres ranging from 10 to 400 μm and follicular cell thicknesses of 5, 10, and 15 μm .

The thyroid–to–follicular cell mass ratio was calculated assuming that 90% of thyroid tissue is composed of follicles (6). Denoting by r the radius of colloid sphere and by h the thickness of epithelial cell layer, this ratio is:

$$\frac{m_{\text{thy}}}{m_{\text{cells}}} = 1.1 \frac{(r+h)^3}{(r+h)^3 - r^3}. \quad \text{Eq. 9}$$

RESULTS

The self-absorbed fraction in colloid spheres ranges from several percentage points for small radii (i.e., up to 50 μm) to 45% for large radii (i.e., 400 μm). The relative absorbed dose to follicular cells ranges from about 1, in the case of colloid radii below 50 μm , to about 0.77 for a 400- μm radius. The follicular cell thickness had minor effects (Table 1).

In terms of the practical useful activity correction factor, $1/\hat{D}_{\text{cell}}$, patients having colloid spheres with radii of 100, 200, 300, and 400 μm should be given 9%, 15%, 21%, and 30% more ^{131}I activity than that administered to patients with colloidal spheres of radii of less than 50 μm .

DISCUSSION

The motivation for this work was our clinical results on the cohort of patients with Graves disease treated with radioiodine. The patients with a normoechoic gland with a planned average thyroid dose of 200 Gy (ablative dose) had comparable outcomes to patients with a hypoechoic gland with planned average thyroid doses of only 100–120 Gy (nonablative doses).

Within the thyroid, the majority of ultrasound reflections occur at interfaces between follicular cells and colloid. Thyroid glands, which are hypercellular (i.e., have relatively little colloid), have fewer reflective surfaces and thus are hypoechoic, whereas normoechoic (or hyper-echoic) patterns are seen in glands with normal (or high) colloidal content (i.e., with normal-size [or large] follicles and relatively small cellular volume) (7,8). Although at presentation the hyperactive glands are almost always hypoechoic (7), antithyroid medication occasionally normalizes follicular structure. Consequently, patients who had prior antithyroid therapy present with a wide spectrum of echogenicities (9,10). In normal thyroids, follicular radii range from 100 to 500 μm , and untreated hyperactive glands are characterized by cell hypertrophy and hyperplasia and small, almost-emptied colloidal spaces due to accelerated hormone turnover (11). In practice, because

TABLE 1

Relative Doses of Thyroid Epithelial Cells* from β -Radiation of ^{131}I Uniformly Distributed in Colloid Spheres of Varying Sizes

Radius of colloid droplet (μm)/epithelial cell thickness (μm)	Percentage of radiation self-absorbed in...		Mass ratio of thyroid and epithelial cells	\dot{D}_{self}	\dot{D}_{cross}	\dot{D}_{cell}	$\dot{D}_{\text{cross}}/\dot{D}_{\text{self}}$	$1/\dot{D}_{\text{cell}}^\dagger$
	Colloid sphere	Epithelial cell						
10/5	2.17	1.54	1.56	0.024	0.963	0.987	40.0	1.013
10/10	2.17	2.95	1.26	0.037	0.949	0.986	25.6	1.014
10/15	2.17	4.20	1.18	0.049	0.936	0.986	19.0	1.015
50/5	9.14	1.36	4.42	0.060	0.900	0.955	14.9	1.047
50/10	9.14	2.65	2.61	0.069	0.882	0.951	12.8	1.051
50/15	9.14	3.87	2.02	0.078	0.870	0.948	11.1	1.055
100/5	16.2	1.22	8.08	0.099	0.826	0.924	8.38	1.082
100/10	16.2	2.38	4.42	0.105	0.814	0.920	7.74	1.087
100/15	16.2	3.55	3.21	0.114	0.803	0.917	7.04	1.091
150/5	22.3	1.14	11.7	0.133	0.765	0.899	5.72	1.112
150/10	22.3	2.30	6.25	0.144	0.754	0.897	5.24	1.114
150/15	22.3	3.32	4.42	0.147	0.743	0.890	5.06	1.123
200/5	27.7	1.07	15.4	0.165	0.712	0.877	4.32	1.140
200/10	27.7	2.08	8.08	0.168	0.702	0.870	4.18	1.149
200/15	27.7	3.01	5.64	0.170	0.693	0.863	4.08	1.160
250/5	32.8	0.97	19.1	0.185	0.663	0.848	3.58	1.180
250/10	32.8	1.94	9.91	0.192	0.653	0.845	3.40	1.183
250/15	32.8	2.78	6.86	0.190	0.644	0.835	3.38	1.197
300/5	37.1	0.94	22.7	0.214	0.620	0.834	2.90	1.200
300/10	37.1	1.82	11.7	0.214	0.611	0.825	2.86	1.213
300/15	37.1	2.68	8.08	0.217	0.602	0.820	2.78	1.221
350/5	41.7	0.83	26.4	0.219	0.575	0.794	2.62	1.260
350/10	41.7	1.72	13.6	0.233	0.566	0.800	2.43	1.250
350/15	41.7	2.55	9.30	0.237	0.558	0.795	2.35	1.258
400/5	45.7	0.78	30.1	0.235	0.535	0.769	2.281	1.300
400/10	45.7	1.62	15.4	0.250	0.527	0.776	2.110	1.289
400/15	45.7	2.35	10.5	0.247	0.519	0.766	2.100	1.305

*Ratio of thyroid epithelial cell absorbed dose and average absorbed dose to thyroid, calculated by Monte Carlo method (Eqs. 4 and 7).

$^\dagger 1/\dot{D}_{\text{cell}}$ is activity correction factor, which, when multiplied with activity calculated on basis of average absorbed dose to thyroid, would result in same absorbed dose to thyroid epithelial cells. \dot{D}_{self} and \dot{D}_{cross} are components of \dot{D}_{cell} due to self-irradiation and irradiation from neighboring follicles, respectively.

of variable antithyroid drug-induced involution of thyroid tissue, a wide range of follicle sizes is expected. Thus, our clinical results (10) seem reasonable in terms of more radiation being “wasted” in the larger follicles of normoechoic glands than in the smaller follicles of hypoechoic glands.

However, the results of this simulation only partly explain our clinical results (10). Although the effect of the substantial fraction of radiation energy absorbed within large colloid spheres on diminishing the ^{131}I radiation dose to thyroid follicular cells is significant, it is not as large as might be anticipated. To explain these results, one should consider the components of the relative absorbed dose to follicular cells. The colloid self-absorption diminishes the relative cross-absorbed dose to follicular cells, which depends solely on the fraction of radiation energy emerging from each follicle (Eq. 7). However, this effect is balanced to some extent by the opposing effect on the relative self-absorbed dose to follicular cells: the larger the colloid

sphere, the lesser the fraction of follicular cells in thyroid mass and the greater the self-absorbed dose (Eq. 7). For small follicles, the cross-absorbed dose is several times larger than is the self-absorbed dose. However, as the follicle size and colloidal self-absorption increase, the relative contribution of cross-absorbed dose rapidly diminishes to about only 2 times the self-absorbed dose in the case of a 400- μm radius of follicular colloid.

The generalization of the current model, allowing for the distribution of follicle sizes in a thyroid, is also possible. The assumption of identical follicles was used only in Monte Carlo estimations of the self-absorbed fractions E_{coll}/E_0 and E_{self}/E_0 ; Equations 1–9, however, also hold in cases of nonuniform follicular sizes. Given the distribution of follicle sizes, the fractions of radiation energy self-absorbed in colloid and follicular cells can be estimated from the current results, assuming uniform concentration of radioiodine in all colloidal spheres.

The histologic data on the thyroid follicular sizes describe the distribution of the sizes of cross-sections of irregularly packed follicles in random cut planes. These data underestimate the actual follicular sizes, which can be assessed only in the follicular equatorial planes. In addition, the use of punch biopsies instead of surgical specimens (7,8) has never been evaluated, and one cannot exclude the possibility that pooling the punched tissue through a narrow metal cylinder selectively draws the subpopulation of smaller follicles. Data on the actual sizes of thyroid follicles are currently incomplete. In any case, the current study demonstrates that the thyroid microstructure may be at least partially responsible for more favorable clinical responses of hypoechogenic thyroids, with smaller colloidal spaces and therefore lower intracoloidal self-absorption of ^{131}I β -radiation. However, the possible effects on follicular cell response of patient-to-patient differences in intrinsic radiosensitivity certainly cannot be ignored.

We used 2 assumptions in assessing the relative absorbed dose to follicular cells: the spatially uniform absorption of radiation emanating from the follicles (the fraction not self-absorbed in colloid and follicular cells) and close packing of the follicles, regardless of their size. The latter is suggested by micrographs of normal and hyperactive thyroid tissue showing that, although varying in size, follicles are always closely packed (11), with the assumption that follicles comprise 90% of the mass of the thyroid likewise based on animal data (6). The assumption of uniform distribution of cross-absorbed dose means that radiation emanating from a given follicle is not preferentially absorbed in any of the 3 thyroid compartments, colloid or follicular cells, or interfollicular spaces. Although the assumption may not be perfectly realistic in all patients, it agrees with partly irregular, close packing of follicles and avoids the need for a geometric model of follicular packing in assessing cross-dose.

Insight into follicular structure could also prove useful in ablative radioiodine therapies (toxic nodular goiter, metastases of differentiated thyroid carcinoma), at least as a prognostic factor. The predominance of the follicular cell cross-dose over the self-dose is specific for β -radiation of ^{131}I . In the case of Auger emitters, such as ^{125}I , the opposite would be true, because the dose is largely confined to the follicle in which the electrons are emitted.

CONCLUSION

The characteristic histologic structure of thyroid tissue, organized in follicles, and the hormone kinetics, effectively segregating radioiodine in follicular lumen, affect the distribution of radiation-absorbed dose between the follicular cells and other gland structures, even in the case of the relatively long-range β -emitter ^{131}I . This may require a patient-specific approach to radioimmunotherapy of Graves disease. Methods to assess the variable thyroid histology in clinical settings should be addressed.

APPENDIX

Relative Contributions and Absorbed Fractions of γ - and β -Radiations of ^{131}I Uniformly Distributed in a Typical Thyroid Lobe

A typical thyroid lobe was modeled as a rotational ellipsoid with semiaxes $a = b = 1.0$ cm and $c = 2.5$ cm (volume, 10.5 cm³), filled with a uniform activity concentration of ^{131}I . For calculation of photon self-absorbed fractions ϕ_γ (E_i), we used the Monte Carlo code EGS5 (4). All relevant photon emissions of ^{131}I , as listed at the National Nuclear Data Center Web site (12), were considered. According to the MIRD schema (13), the photon component of the lobular S value (mean absorbed dose per unit cumulated activity, that is, per 1 decay) due to ^{131}I self-irradiation is:

$$S_\gamma = \frac{1}{m} \sum \Delta_i \phi_\gamma(E_i),$$

where $\Delta_i = n_i E_i$ is the product of emission probability (n_i) and energy (E_i) of photon emissions, and $m = 10.5 \times 10^{-3}$ kg. Summing across the relevant γ -emissions:

$$S_\gamma = 1.72 \times 10^{-13} \text{Gy}/(\text{Bq} \times \text{s}).$$

The γ -radiation self-absorbed fraction is the average photon energy absorbed per decay of ^{131}I , $m \times S_\gamma$, divided by the intensity weighted mean photon energy, which gives:

$$\gamma\text{-self-absorbed fraction} = 0.030.$$

A similar approach was used to calculate the β -component of the self-irradiation lobular (i.e., lobe to lobe) S factor due to ^{131}I :

$$S_\beta = \frac{1}{m} \int d(E) \phi_\beta(E),$$

where $\phi_\beta(E)$ is the self-absorbed fraction of the β -particle of energy E , and the integration was performed over the continuous ^{131}I β -spectrum and included summation over the discrete emissions of electrons. The initial values for the ^{131}I β -energy spectrum were sampled according to the method of Simpkin and Mackie (5). For β -radiation, the EGS5 code yields directly the self-absorbed fraction (average electron energy absorbed per decay of ^{131}I , $m \times S_\beta$, divided by the mean electron energy), as previously described by Grosev et al. (14), yielding:

$$\beta\text{-self-absorbed fraction} = 0.974.$$

Because the mean electron energy calculated from the β -spectrum is 190 keV, one obtains:

$$S_\beta = 2.82 \times 10^{-12} \text{Gy}/(\text{Bq} \times \text{s}).$$

Thus, for a typical thyroid lobe with uniformly distributed ^{131}I , the self-irradiation S value is:

$$S = S_{\beta} + S_{\gamma} = 2.99 \times 10^{-12} \text{ Gy}/(\text{Bq} \times \text{s}).$$

The percentage contribution of γ -radiation to total lobe dose is:

$$100 \times S_{\gamma}/S = 5.75\%.$$

Considering the whole organ, one could take into account the cross- γ -radiation of the contralateral lobe, which we omit here for simplicity.

Thus, the underestimation error of ignoring the γ -component to the average thyroid dose from ^{131}I self-irradiation and the overestimation error of ignoring the partial penetration of β -radiation to some extent cancel out. For a typical thyroid lobe, the total error is an underestimation of about 3.4%.

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