# Radiation Dose to the Testes after $^{131}I$ Therapy for Ablation of Postsurgical Thyroid Remnants in Patients with Differentiated Thyroid Cancer

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Radioiodine-131 is used in differentiated thyroid cancer (DTC) for ablation of postsurgical thyroid remnants and destruction of metastases. The question may be raised of whether $^{131}I$ treatment of DTC in male patients may give an irradiation dose to the testes that could impair fertility. Few data in the literature concern the dose absorbed by the testes after $^{131}I$ therapy for DTC. Because $^{131}I$ kinetics may be altered by the hypothyroid condition commonly present at the time of treatment and by the radioiodinated iodoproteins released by the damaged thyroid tissue, the dose values reported in the International Commission on Radiological Protection (ICRP) tables for euthyroid men may not be appropriate. To clarify this problem, three male subjects undergoing $^{131}I$ therapy for ablation of thyroid remnants shortly after thyroidectomy for DTC were studied. **Methods:** The mean administered activity was 1256 MBq, and the duration of the study was 2 wk. The gamma dose was measured by thermoluminescent dosimeters (TLDs) applied to the lower poles of the testes. Correction factors were calculated for the distance of the TLD from the center of the testes and for attenuation by the testes of the $\gamma$ rays reaching the TLD. After correction, the gamma dose to the testes ranged from 21 to 29 mGy. The gamma dose calculated by the Medical Internal Radiation Dose (MIRD) method from blood and urine samples was similar (18–20 mGy) to that measured by TLDs. The beta dose was estimated by the MIRD method from blood activity and testicular volume and ranged between 14 and 31 mGy. **Results:** The total (beta and gamma) doses to testes were 30, 33 and 43 μGy/MBq in the three subjects. **Conclusion:** These values are close to those derived from the ICRP tables (26–37 μGy/MBq $^{131}I$) for euthyroid subjects. The present data indicate that significant irradiation is delivered to the testes after the administration of the $^{131}I$ ablative dose to thyroidectomized patients. The relevance of the radiation absorbed by testes on fertility remains to be established.

**Key Words:** radiation dose; testes dose; $^{131}I$ therapy; differentiated thyroid cancer

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Differentiated thyroid cancer (DTC) may affect subjects in any age group, including children and young subjects. When appropriately treated, DTC is compatible with a normal life expectancy and prospect of paternity. After thyroidectomy $^{131}I$ is used for ablation of thyroid remnants and for destruction of metastases. The $^{131}I$ activity administered in a single dose ranges from 1110 to 5500 MBq and may be given repeatedly when metastatic disease is present. Thus, large amounts of $^{131}I$ may be administered in the course of the illness. In males this may lead to an irradiation dose to the testes that could impair fertility. Variable increases of serum follicle-stimulating hormone (FSH) concentration and depressed spermatogenesis were reported in subjects submitted to $^{131}I$ treatment for DTC in relation to the administered activity (*1,2*). To our knowledge, no data on the absorbed dose in testes after $^{131}I$ treatment have been reported. According to International Commission on Radiological Protection (ICRP) tables (*3*), in euthyroid subjects the radiation dose delivered to the testes ranges from 26 to 37 μGy/MBq and is inversely related to the thyroid uptake. Conceivably, the testicular radiation dose may be affected by several factors. It may be increased in hypothyroidism because of the reduced iodine renal clearance and subsequent prolonged exposure of the testes to relatively high $^{131}I$ levels in blood and urine (*4*). Moreover, the $^{131}I$-labeled iodoproteins released in blood from damaged thyroid remnants or metastatic lesions can also contribute to increase the radiation dose. To clarify this problem the radiation dose delivered to the testes was evaluated in three subjects with DTC who submitted to $^{131}I$ therapy for ablation of the postsurgical thyroid remnants.

## MATERIALS AND METHODS

### Patients

Three men with DTC were studied at the time of their first total body scan after thyroidectomy. Each of them was found to have only a thyroid remnant with no evidence of metastases. After informed consent, each patient provided full cooperation with the

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study. Relevant clinical data of the three patients are reported in Table 1. Blood volume was assessed by red blood cell targeting with the $^{51}Cr$ method. Testicular volume was evaluated by sonography. The 24-h uptake was measured by a 7.6 × 7.6 cm scintillation probe. The volume of the thyroid remnant was also evaluated by sonography. The $^{131}I$ ablative dose was administered and the study was performed for the following 14 d.

## Gamma Dose Evaluation

*Thermoluminescent Dosimeter Measurements.* Thermoluminescent dosimeter (TLD) measurements were performed for 2 wk after $^{131}I$ therapy. The TLDs used in this study contained chips of LiF (Mg, Cu, P), which at present is the most radiation-sensitive phosphor. It has a very low threshold and can measure doses as small as 1 μGy. The TLDs were sealed in a thin polyethylene bag that was inserted into a small pocket sewn into the scrotal portion of an athletic supporter such that the TLD remained proximal to the inferior poles of the testes. Patients were asked to wear these supporters for the entire period of the study and to change the TLD in the pocket at predetermined times (partial TLDs). An additional pocket was sewn into the athletic supporters of patients B and C, in which a second TLD was maintained throughout the entire period (fixed TLD). TLDs were stored in a small lead box that was given to the patients with instructions to avoid any unnecessary proximity. A control TLD for background activity measurement remained in the lead box for the duration of the study. On day 1, patient A had two consecutive partial TLDs, whereas patients B and C had three. The remaining partial TLDs were worn on days 2, 3, 7 and 14 by patient A and on days 2, 3, 4, 5, 7 and 14 by patients B and C.

The value of absorbed dose from γ emission was calculated after subtraction of the background dose from the sum of the single values measured by partial TLDs. In patients B and C, this value was compared with that measured by the fixed TLD. The contribution of β rays emitted from the testes to the total amount of activity measured by TLDs was considered negligible.

TLD measurements had two biases. First, the TLDs were positioned proximal to the lower poles of the testes. The resulting measurements indicated the dose received in the inferior pole of the testes compared with the dose for the entire organ. Second, the testes themselves shielded photons from the upper part of the body. A numerical simulation using the MCNP Monte Carlo code was performed to correct the above biases. This allowed both the $^{131}I$ spectral source and the geometry of the body to be described in accurate detail (*5*). The two main contributors to testes irradiation were assumed to be the blood, uniformly distributed throughout the body, and the urine contained in the bladder. A bottle manikin absorption (BOMAB) phantom mathematical model (*6*) was used to model testes and bladder. The reference equations of the blood and urine were drawn from the ADAMO (*7*) male phantom specifications. Two calculations were performed, which simulated the testes with compensation for data collected only at the inferior pole. In the first simulation, the source was the whole body; in the second simulation, the source was the bladder contents. The ratio between the mean dose absorbed by the testes and the dose absorbed by the TLDs, as calculated by MCNP code, was 1.10 for γ rays emitted uniformly from the whole body and 1.48 for those emitted from the bladder contents. This means that TLD measurements underestimated the dose to the testes, most significantly associated with the component of the bladder contents. These two correction factors were applied to the dose values registered by the TLDs on the basis of the simplifying hypothesis that the sources of gamma dose to the testes are only blood and bladder contents. The relative whole body and bladder contribution to the total gamma absorbed dose by the testes was evaluated by the Medical Internal Radiation Dose (MIRD) method (*8*). Contributions from sources other than whole body and bladder contents, such as the gastrointestinal tract, were not considered. The amount of error caused by the exclusion of the gastrointestinal tract contribution may be considered small because the corresponding correction factor is intermediate between those calculated for whole body and bladder contents.

In patient A, the total gamma dose was calculated as the sum of the partial TLDs. Patients B and C did not wear partial TLDs on days 5 and 8–13. The dose values of these days were interpolated from measured values.

**TABLE 1**
Relevant Clinical Data of Studied Patients at Time of $^{131}I$ Administration

| Data | Patient A | Patient B | Patient C |
|---|---|---|---|
| Age (y) | 37 | 25 | 49 |
| Height (cm) | 188 | 184 | 170 |
| Weight (kg) | 88 | 69 | 60 |
| Blood volume (mL) | 5041 | 4955 | 4671 |
| Total testes volume (mL) | 33 | 36 | 29 |
| FT4 (pg/mL) | 5.6 | 2.0 | <1 |
| FT3 (pg/mL) | 2.5 | 1.3 | 1.0 |
| TSH (μU/mL) | 17.9 | >100 | 80 |
| Remnant volume (mL) | 2 | 3 | <1 |
| Remnant uptake (%) | 40 | 18 | <1 |
| Urinary iodine (μg/L) | 45 | 120 | 34 |
| Creatinine (mg/dL) | 1.10 | 1.20 | 1.38 |
| Administered $^{131}I$ (MBq) | 1394 | 1198 | 1176 |

FT4 = free thyroxine; FT3 = free triiodothyronine; TSH = thyroid-stimulating hormone.

## Beta Dose Evaluation

The beta contribution to the absorbed dose was evaluated by the MIRD method from blood activity and testicular volume data. Blood samples were drawn before $^{131}I$ therapy and at 1, 2, 4, 8, 24, 48 and 72 h after $^{131}I$ therapy: and on days 7 and 14. Blood was diluted in distilled water to obtain 10 mL hemolyzed solution, which was counted with a 7.6 × 7.6 cm NaI(Tl) γ-ray spectrometer. The spectrometric chain was calibrated with a source of $^{131}I$ in 10 mL water certified by the Italian National Institute of Metrology of Ionising Radiation of the Italian Agency for New Technologies, Energy and Environment.

The blood content in the testes was evaluated in each patient using testicular volume, as measured by sonography, following the indication of the ICRP for the reference man (*9*). The testicular specific blood content was assumed to be 0.166 $g_{blood}/g_{testes}$ and the specific gravity was assumed to be 1.044 $g/cm^3$. The following hypotheses were assumed: The blood contained in the testes is the only source of β radiation to the testes, and the β rays emitted in testicular blood are totally absorbed within the testes.

The S factor (the mean absorbed dose in a target organ per unit of cumulated activity in the source organ) for β autoirradiation of the testes was calculated using the decay scheme of $^{131}I$ (*10*). A value of $9.67 \times 10^{-10}$ mSv/(Bq × s) was obtained. This is very close to the MIRD value for total autoirradiation (β and γ): 9.71 ×

$10^{-10}$ mSv/(Bq × s). The result confirmed the hypothesis that γ autoirradiation of the testes is not significant (<0.5% of the total autoirradiation dose).

To validate the values of the beta dose obtained from blood activity, the gamma dose was also evaluated from blood and bladder urine activity using the MIRD method and compared with the values measured by TLDs. It was assumed that the γ radiation to the testes derived mainly from blood and bladder contents (gut contribution could not be evaluated) and that there was no significant contribution from the testes themselves. During the first 3 d after treatment, all urine excreted was collected, and volumes were measured. Twenty-four-hour collections were then obtained on days 7 and 14. Appropriate aliquots were stored until the end of the study and counted in the same γ-ray spectrometer as that used for blood measurements. Tabulated S factors for adults were used, whereas the integrated activities in the blood and bladder contents during the study period were calculated on the basis of blood and urine activity measurements. Six micturitions per day and blood activity uniformly distributed throughout the whole body were assumed.

## RESULTS

### Radiation Dose to Testes

Gamma and beta dose values are reported in Table 2. Two values of gamma dose are reported for each patient: the first derived directly from TLD measurement and the second obtained indirectly by the MIRD method based on blood and urine activities. In general, the two sets of values were in good agreement, except for patient A in whom a slight difference was observed. The values obtained by the MIRD method were slightly lower, possibly because the contribution from the gastrointestinal tract was not considered. Direct measurements by TLDs were used for the assessment of the total absorbed dose. Beta doses were calculated from blood activity and testicular volume using the MIRD method. The total (beta and gamma) doses were calculated as the sum of the beta doses as assessed by the MIRD method and the gamma doses obtained by TLDs. The total dose was also expressed as mGy/MBq of administered unit activity. As shown in Table 2, these values were of the same order of magnitude as those reported in the ICRP tables for euthyroid men. Only minor differences were found, with the highest discrepancy being observed in subject A in whom the measured absorbed dose was 43 μGy compared with the expected value of 26 μGy.

**TABLE 2**
Dose Absorbed by Testes in Three Male Patients After $^{131}$I Treatment for Ablation of Thyroid Remnant

| Method | Dose to testes (mGy) | | |
|---|---|---|---|
| | Patient A | Patient B | Patient C |
| TLD (mGy) | | | |
| Gamma contribution* | 21 | 15 | 15 |
| Corrected value | 29 | 21 | 21 |
| MIRD (mGy) | | | |
| Gamma contribution from urine | 12 | 14 | 16 |
| Gamma contribution from blood | 8 | 4 | 4 |
| Total gamma dose | 20 | 18 | 20 |
| Beta contribution from blood | 31 | 18 | 14 |
| Total absorbed dose (mGy)† | 60 | 39 | 35 |
| Absorbed dose per MBq (μGy) | 43 | 33 | 30 |
| Expected dose from remnant uptake per MBq (μGy), by ICRP‡ | 26 | 28 | 37 |

*Gamma dose as measured by TLDs (in patient A as sum of partial TLDs; in patients B and C as mean value between sum of partial TLDs and fixed TDL). TLD values were corrected for distance of TLD from center of testes and for testes attenuation (see text).

†Total dose is sum of beta absorbed dose (from blood activity) and gamma absorbed dose (from TLD).

‡Expected doses to testes for euthyroid subjects reported by ICRP tables according to value of remnant uptake.

TLD = thermoluminescent dosimeter; MIRD = Medical Internal Radiation Dose; ICRP = International Commission on Radiological Protection.

The gamma dose rate to testes, as measured by TLDs, is illustrated in Figure 1. The dose rate was highest at day 1 in all patients and thereafter decreased sharply in patient A (who had an elevated remnant $^{131}$I uptake) and more slowly in patient C (probably because of the delayed $^{131}$I renal excretion associated with the profound hypothyroidism). On days 4–14 of the study, the gamma dose rate was 6- to 10-fold higher in patient A compared with that in patients B and C. Patient A received 44% of the whole testicular dose in days 4–14 of the study, whereas in the same period patients B and C received 5% and 3% of the whole dose, respectively. The higher dose received by patient A during the last study period might have contributed to the slightly higher total absorbed dose in this patient compared with the expected value from ICRP tables.

### Blood and Urine

As shown in Figure 2, blood activity curve showed a sharp peak 3 h after the $^{131}$I oral administration and declined with no difference in the studied patients in the first 2 d. Thereafter, a second, prolonged and blunted peak was observed at day 5 in patient A (who had high remnant uptake) and to a lesser extent at day 11 in patient B (who had lower remnant uptake with respect to patient A). This was presumably associated with the release of $^{131}$I-labeled iodoproteins from the irradiated thyroid remnants. Patient C, who had no significant $^{131}$I uptake in the thyroid bed, showed no second peak with a progressive decrease in blood activity. In patient A, the peak was one order of magnitude higher than that in patient B. At the end of the study, the blood activity in patient A was double than that in patient B and >70-fold than that in patient C.

As shown in Figure 3, urinary activity was maximal at day 1 in all patients and declined rapidly in patient A and more slowly in the other patients. Urinary activity persisted up to day 14 in both patients who had significant $^{131}$I uptake and was barely detectable in patient C, who had no uptake in the thyroid bed. Urinary excretion was rather slow in patient C in keeping with his profound hypothyroidism.

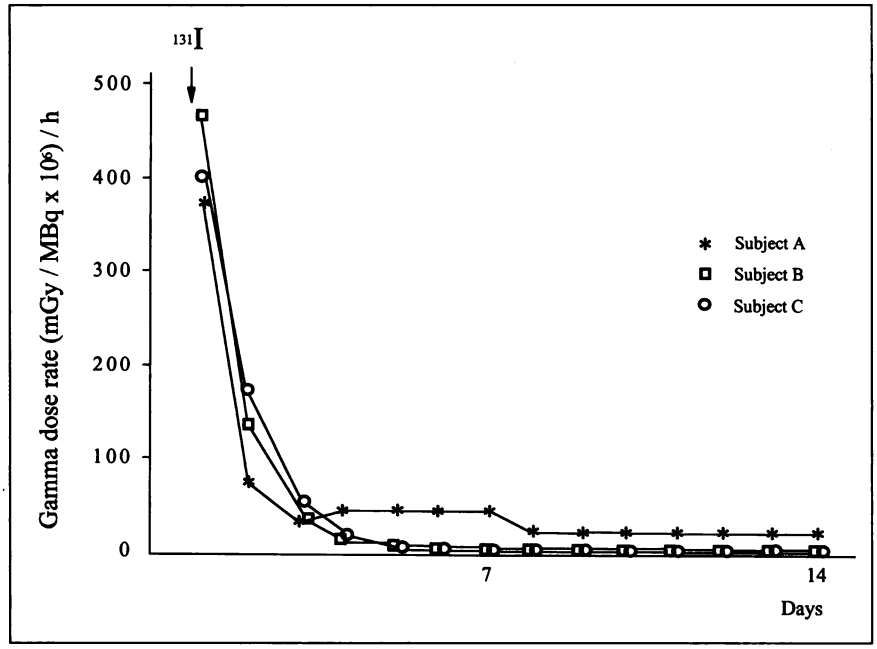


**FIGURE 1.** Gamma dose to testes measured by TLDs after administration of $^{131}I$ ([mGy/MBq × $10^6$]/h).

## DISCUSSION

The radiation dose delivered to the testes by $^{131}I$ therapy for DTC is uncertain. To study this problem, the testicular radiation dose was assessed in three patients with DCT who submitted to $^{131}I$ treatment (mean activity 1260 MBq) for ablation of thyroid remnants after thyroidectomy. The total radiation dose to the testes resulted in 30–43 μGy/MBq of administered $^{131}I$ activity. These values were close to those of the ICRP (from 26 to 37 μGy/MBq $^{131}I$) for euthyroid men.

The question of whether and to what extent the radiation dose to the testes could be influenced by the prolonged high $^{131}I$ blood and urine levels associated with the release of $^{131}I$-labeled iodoproteins from the damaged thyroid remnant and with the reduced renal clearance associated with the hypothyroid status should be considered. Two patients had relatively high uptake values, which is consistent with the fact that these patients were from areas with documented iodine deficiency (*11*). The third patient had no significant thyroid tissue and no uptake in the thyroid bed. Renal function was not studied, but creatinine values, as reported in Table 1, were slightly higher in this patient. Variations in $^{131}I$ kinetics were observed: blood activity had a second peak in the two patients with significant thyroid tissue, whereas renal excretion of $^{131}I$ was slower in the most hypothyroid patient. Despite these variations, the final dose values found

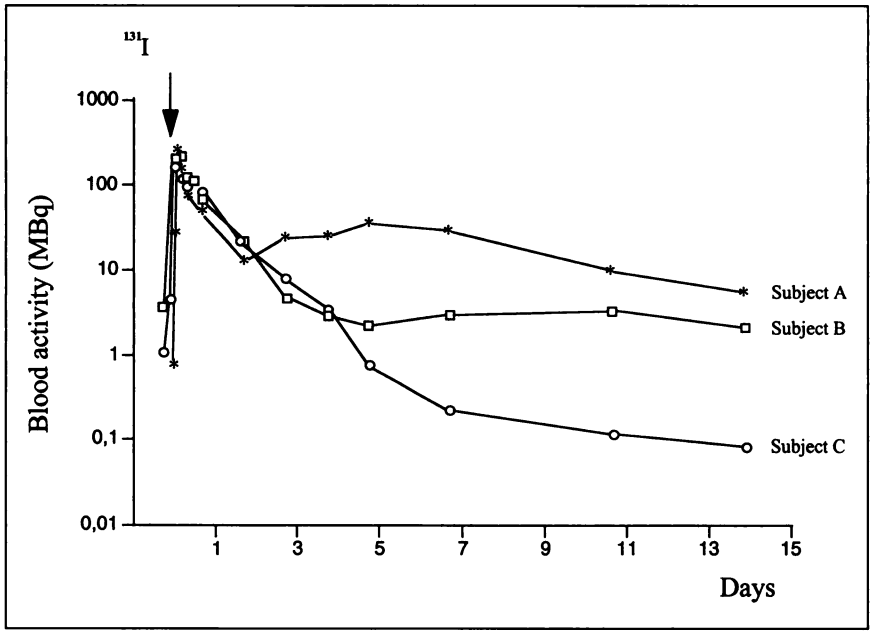


**FIGURE 2.** Changes in blood activity after oral administration of $^{131}I$ occurring in three male patients who submitted to $^{131}I$ therapy for ablation of thyroid remnant.

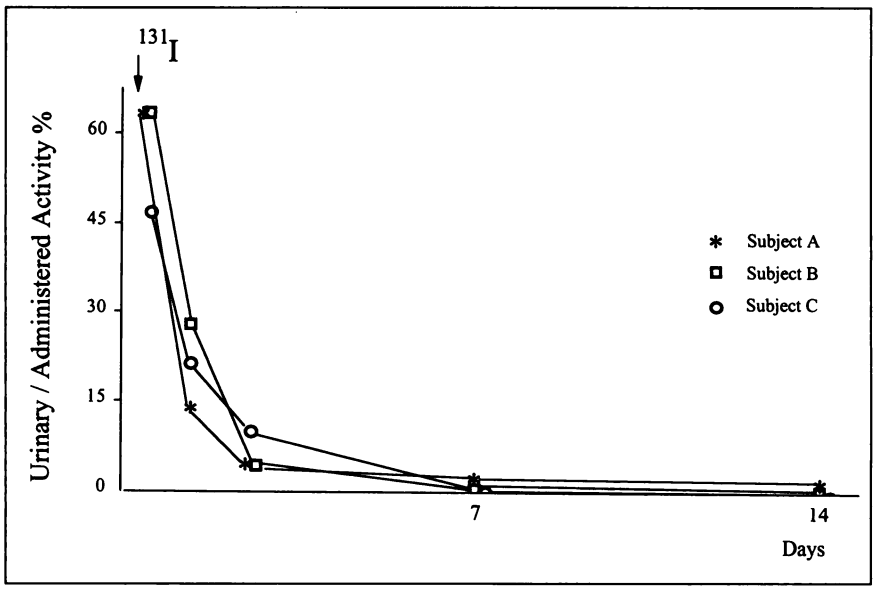


**FIGURE 3.** Urinary $^{131}$I excretion in three male patients after $^{131}$I therapy expressed as percentage of administered activity.

in these patients were rather close. The dose values estimated in our patients were similar to those reported in the ICRP tables for euthyroid men, suggesting that the thyroid status had a limited influence on the absorbed dose in testes. The slightly higher dose value of patient A could reflect the higher $^{131}$I blood levels associated with the $^{131}$I-labeled iodoproteins delivered from the large thyroid remnant (*12*). In fact, as reported in Table 2, this patient received higher beta and gamma doses from blood in comparison with the other two patients. In the studied patients the gamma radiation dose to the testes derived mainly from $^{131}$I present in the blood, bladder urine and gut. The contribution from thyroid remnant could be considered as not relevant because of the large source-target distance (*13*). There were no functioning metastases that could contribute to the gamma dose. This contribution should be considered in subjects with bone metastases in the pelvis, whereas the influence of neck metastases is probably negligible, as in the case of the thyroid remnant. In a retrospective study of women with DTC who submitted to large $^{131}$I amounts for ablation of thyroid remnant, a large variability of the radiation dose to the ovaries was reported, which was largely related to the variability of the body mass (*14*). The limited number of patients in this study does not permit any conclusion on the relevance of the body mass in determining the radiation dose to the testes.

In this study the effect of the $^{131}$I therapy on testicular function was not addressed. A small and transient increase of FSH was previously reported in two male patients with DTC after administration of 1850 MBq $^{131}$I (*1*). In a large series of thyroidectomized patients with DTC treated with about 3700 MBq $^{131}$I, we found a transient increase of serum FSH and a reduction of normokinetic sperm after treatment (*2*). On the basis of the present evaluation, administered activities of $^{131}$I from 1850 to 3700 MBq $^{131}$I would deliver a testes dose ranging from 55 to 160 mGy. Persistent changes of serum FSH were observed in four subjects treated with large cumulative activities in repeated administrations (from 19,240 to 29,600 MBq $^{131}$I) for metastatic disease (*2*). On the basis of the present evaluation the cumulative dose to testes received by these patients, showing persistent germinal epithelium failure, as assessed by FSH assays, could be estimated to range between 557 and 1273 mGy. Thus, it would appear that single administered activities ranging from 1850 to 3700 MBq may cause a transient testicular failure by delivering a radiation dose to testes of 55–160 mGy, whereas cumulative activities from 19,240 to 29,600 MBq may cause permanent testicular failure by delivering a radiation dose to testes of 577–1273 mGy. The impact of $^{131}$I treatment for DTC on testicular function was recently addressed by Maxon (*15*). Based on data derived from external radiation and atomic fallout studies, and assuming a dose to the testes of 140 μGy/MBq (that is 4–5 times higher than that we found), Maxon suggested that permanent sterility can be predicted in <10% of male patients at 11,100 MBq of total ingested activity and in >90% of males at 29,600 MBq. According to Maxon, no permanent sterility may be predicted in women receiving up to 11,100 MBq, whereas sterility may be expected in 60% of those receiving very large amounts of $^{131}$I, such as 29,600 MBq. Controlled studies on the effect of $^{131}$I therapy on fertility in women with DTC are not available, but the absence of significant mutagenic effect has been reported by us and others in large series of subjects submitted to $^{131}$I therapy for ablation of thyroid remnant and metastatic disease (*16,17*).

## CONCLUSION

Evidence has been provided that a significant radiation dose is delivered to the testes after therapy for DTC. The dose values found in patients submitted to $^{131}$I therapy for ablation of postsurgical thyroid remnant were close to those reported in ICRP tables for euthyroid men and were not

significantly influenced by the thyroid status. These data are in keeping with the observation that $^{131}I$ therapy may be followed by transient or permanent impairment of germinal epithelium function depending on the administered activity. The impact of $^{131}I$ therapy on fertility should be further evaluated and considered when planning therapy in young male subjects to be submitted to large therapeutic $^{131}I$ activities.

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