

Detection of short-term chromosomal damage due to therapeutic ^{131}I exposure in patients with thyroid cancer

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ABSTRACT

We evaluated the chromosomal aberration (CA) frequencies in the peripheral blood lymphocytes of ten female patients, age average 43.7 ± 12.9 , with thyroid cancer (TC) who had been exposed to 100-200 mCi therapeutic doses of ^{131}I . The blood samples were obtained before-treatment and at 2 and 24 h after-treatment. Radiation was measured in the samples by means of dysprosium-activated calcium sulfate thermoluminescent dosimetry. The maximum radiation levels were detected in the samples taken 2 h after treatment. A positive correlation was found between the sample-emitted radiation values and the frequencies of CAs ($r = 0.495$; $p < 0.01$). The average baseline frequency of aberrations found in the ten studied patients was 0.009 per cell. Upon application of the ^{131}I therapeutic dose, this frequency increased to 0.04 and 0.02 CAs/cell at 2 and 24 h after-treatment, respectively ($p < 0.05$). Break-type aberrations experienced a peak at 2 h after-treatment, whereas rejoined aberrations, such as dicentric, rings, and radial figures, increased with sampling time. Seven patients with metastases had high amounts of CAs at 2 and 24 h after-treatment, in comparison to three patients without metastases who had a lower frequency of CAs at 24h after-treatment. This difference could be due to the fact that circulating lymphocytes were exposed to a greater cancerous tissue mass, which retains ^{131}I during the diagnostic and therapeutic processes. These results demonstrate the importance of detecting and surgically removing the largest possible amount of thyroid tissue in order to diminish the exposure of normal cells to radiation.

Key words. Chromosomal Aberrations. Human lymphocytes. Radiation. ^{131}I , Thyroid cancer.

Detección de daño cromosómico a corto plazo, debido a exposición terapéutica a ^{131}I en pacientes con cáncer de tiroides

RESUMEN

Se evaluó la frecuencia de aberraciones cromosómicas (CAs) en linfocitos de sangre periférica de diez pacientes femeninas, edad promedio 43.7 ± 12.9 años, con cáncer de tiroides (TC) expuestos a dosis terapéuticas de 100-200 mCi de ^{131}I . Las muestras de sangre se obtuvieron antes del tratamiento, así como 2 y 24 h después del tratamiento. La radiación se midió en las muestras mediante dosímetros termoluminiscentes de sulfato de calcio activados con disprosio. Los niveles más altos de radiación se encontraron en las muestras tomadas 2 h después del tratamiento; se encontró una correlación positiva entre los valores de radiación y las frecuencias de CAs ($r = 0.495$; $p < 0.01$). La frecuencia basal de CAs en los pacientes estudiados fue de 0.009 por célula. Cuando se trataron con la dosis terapéutica de ^{131}I , la frecuencia incrementó a 0.04 y 0.02 CAs/célula a las 2 y 24 h después del tratamiento, respectivamente ($p < 0.05$). Las rupturas cromosómicas tuvieron un pico a las 2 h después del tratamiento, mientras que las aberraciones del tipo dicéntricas, anillos y figuras radiales, incrementaron con el tiempo de muestreo. En siete pacientes se detectaron metástasis y en tres no; los pacientes con metástasis tuvieron frecuencias de CAs a las 24 h después del tratamiento, más altas que los pacientes sin metástasis; esta diferencia podría deberse al hecho de que los linfocitos circulantes se expusieron a una mayor cantidad de tejido canceroso, el cual retiene ^{131}I durante el proceso diagnóstico y terapéutico. Estos resultados demuestran la importancia de detectar y remover quirúrgicamente la mayor cantidad posible de tejido tiroideo para disminuir la exposición de las células normales a la radiación.

Palabras clave. Aberraciones cromosómicas. Linfocitos humanos. Radiación ^{131}I . Cáncer de tiroides.

INTRODUCTION

Thyroid cancer (TC) is an entity that, once suspected clinically, is monitored with thyroid tissue tracking through the application of the ^{131}I radioisotope at diagnostic doses, which range between 100 μCi and 5 mCi. Once the presence of a well-differentiated TC is confirmed, the primary treatment includes the surgical removal of as much cancerous tissue as possible: thyroidectomy and the removal of metastases if they are susceptible to surgical removal. Immediately after surgery, in the majority of patients as an essential part of treatment, ^{131}I is utilized to destroy the remaining tumor cells, in order to reduce the risk of cancer recurrence and increase patient survival. The therapeutic dose of ^{131}I ranges between 25 and 200 mCi for a single dose, but more than one dose is required when there are metastases.¹⁻⁴

Similarly to cold iodine, ^{131}I is taken up by the thyroid gland, incorporated into thyroxine and triiodothyroxine, and stored in the thyroid gland follicular colloid. Other sites that retain ^{131}I are metastases and, at a low proportion, salivary glands and serum albumin. At all of these sites, ^{131}I emits gamma and beta radiation, causing lethal damage to the thyroid tissue and irradiating the peripheral tissues and circulating blood cells. In addition, prior to the ^{131}I concentrating in the glandular tissues, patients are subjected to generalized radiation through the circulation of ^{131}I in the blood.⁴⁻⁶

Secondary and immediate clinical effects of treatment with ^{131}I are generally slight, self-limited, and

comprised of thyroiditis, sialoadenitis, odynophagia, and facial edema.^{6,7} Nonetheless, severe side effects have been reported, such as pulmonary fibrosis, hypothyroidism, bone marrow depression that can be followed by hemorrhage or infection, leukemia and other secondary tumors, as well as alterations in fertility.⁸⁻¹¹ It has been suggested that some of these effects are caused by the interaction of the radiation with the DNA from normal cells, which produces a variety of CAs. These lesions give rise to clastogenic, mutagenic, and carcinogenic effects that can be detected months and even years after therapeutic exposure to ^{131}I .¹²⁻¹⁴ Despite all of these studies, little is known concerning the chromosomal damage generated in the short term, i.e., within the first 24 h after ^{131}I therapy. This is the period that is considered to have the greatest normal cell exposure, due to circulation via the blood-radionuclide pathway.¹⁵ In the present study, we evaluated the clastogenic effects of ^{131}I treatment on the peripheral blood lymphocytes of 10 patients with TC, using chromosome aberration (CA) analysis at three sampling times: before treatment (before-treatment), and 2 and 24 h after treatment (2-after treatment and 24-after treatment), relating to the administration of the first therapeutic dose of the radionuclide.

MATERIAL AND METHODS

Study population and sampling

Inclusion criteria patients, male or female who had TC diagnosed clinically, histologically, and by

Table 1. Clinical data of patients.

| Patient code | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|--|----------|-----------|----------|-------------------------------|-------------------|-------------------|-------------------|-----------------------|-------------------|-------------------------|
| Age (years) | 52 | 53 | 17 | 57 | 55 | 24 | 37 | 50 | 43 | 49 |
| Birth place (residence place) | Chiapas | Chiapas | Chiapas | Mexico City (State of Mexico) | Oaxaca | (State of Mexico) | Hidalgo (Morelos) | Morelos (Mexico City) | (State of Mexico) | Zacatecas (Mexico City) |
| Smoking | negative | negative | negative | negative | positive | positive | negative | negative | negative | positive |
| Drug therapy | negative | captopril | negative | furosemide | DPH | negative | OC | niphedipine | captopril | captopril & OC |
| Other diseases | negative | HTA | negative | HTA | negative | negative | negative | HTA | HTA | HTA |
| Metastases | femur | negative | negative | braquial plexus | 5 lymphatic nodes | 2 lymphatic nodes | 1 lymphatic node | 1 lymphatic node | negative | perithyroid tissues |
| Days between treatment and diagnostic dose (5 mCi) | 19 | 15 | 15 | 15 | 15 | 14 | 15 | 22 | 15 | 16 |
| Therapeutic dose ^{131}I (mCi) | 100 | 100 | 100 | 200 | 100 | 100 | 100 | 100 | 100 | 100 |

HTA: arterial hypertension. DPH: diphenylhydantoin. OC: oral contraceptives.

thyroid tissue tracking with 5 mCi of ^{131}I ; patients treated on the first occasion with therapeutic doses of ^{131}I , and accepted to participate voluntarily. Patients with previous treatment with genotoxic agents or with blood transfusion within the last 6 months were excluded.

The study included ten female patients. All patients were thyroidectomized. All identified metastases were also removed surgically, with the exception of a patient with a metastasis in the femur (patient code 1) and a patient with metastases to the soft tissues (patient code 10). After surgery, patients were treated on the first occasion with therapeutic doses of ^{131}I administered orally at 100 mCi in nine patients and 200 mCi in one patient (Table 1). All patients agreed voluntarily to participate in the study, which was approved by the Institutional Ethical Committee.

Four milliliter samples of peripheral blood were taken from each patient with a heparinized syringe at three sampling times: before-treatment (Pre), 2 h after-treatment (2-Post), and 24 h after-treatment (24-Post). These sampling times were selected based on the fact that maximum peak ^{131}I concentrations in blood have been observed between 2 and 3 h after radionuclide ingestion and diminished by 25% after 24 h.¹⁵ All samples had a thermoluminescent dosimeter (TLD) attached to the side of each sample container and were then transported on ice to the laboratory, where they arrived within 30 min.

Dosimetry

Two days prior to any procedure, the dysprosium-activated calcium and sulfate (CaSO_4 : Dy) TLDs were prepared as follows. To remove all radiation that these might have taken up, they were submitted to thermal treatment at 300° for 30 min and were later placed in an automatic thermal Harshaw TLD System 400 reader (Thermo Fisher Scientific Inc., USA) to ascertain their basic values.

Once samples were obtained, the dosimeters were attached with micropore tape to the plastic sample syringes containing 4 mL of blood. These were removed 24 h later and read within the following 7 days after being removed from the samples. A calibration curve was carried out to convert the values obtained from nanoCoulombs (nC) to Grays (Gy). For this, dosimeters were de-excited with heat and irradiated for different exposure times with Cesium-137 (^{137}Cs) to obtain a pattern curve, which thus allowed the amount of radiation in the samples to be determined.

Chromosomal aberrations

Heparinized whole blood samples were drawn from all subjects, and lymphocyte cultures were performed according to standard procedure. Briefly, 0.5 mL of whole blood was cultured in tubes containing 5 mL modified McCoy 5A medium (Gibco, Grand Island, NY, USA), 0.25 mL phytohemagglutinin (Gibco) and 0.1 mL reconstituted penicillin-streptomycin (Gibco). Cultures were incubated for 72 h at 37 °C, in order to obtain an appropriate number of metaphases; then 0.1 mg/mL of colchicine (Sigma, St. Louis, MO, USA) was added one hour before harvesting to arrest the cells at metaphase, the tubes were centrifuged at 900 g for 10 minutes, the supernatant was removed, the cells were mixed and 5 mL of prewarmed hypotonic solution (0.075 M KCl) was added; the cells were subsequently incubated at 37 °C for 20 minutes, the tubes were centrifuged at 900 g for 10 minutes, the supernatant was removed and the pellet was fixed in 5 ml of fresh fixative methanol (Merck, Darmstadt, Germany) and glacial acetic acid (Merck) (3:1), this fixation procedure was repeated three times and the tubes were centrifuged for the last time; the cell pellet was resuspended in a small volume of fresh fixative. Cells were dropped onto cold clean microscope slides, air-dried, and stained with 10% Giemsa (Merck) and 50% Wright (Merck) in PBS (Gibco). All slides were coded by individuals not involved with the research to ensure blind scoring.

Two hundred metaphases were analyzed per sample. Different structural chromosome-aberration types were recorded, including chromosome breaks, chromatid breaks, centric fragments, acentric fragments, rings, dicentrics, radial figures, and others, with the latter including miscellaneous aberrations. Gaps were not considered.

Statistical analysis

We used non-parametric tests to compare the CA frequencies. Friedman test was used for comparison of CA frequencies among three sample groups. When the pre vs. post values were compared within a specific group, we utilized the Wilcoxon test for dependent samples. Pearson correlation coefficient was used to find the correlation between CA and radiation doses. Multiple lineal regression analysis and analysis of collinearity for independent variables was performed to detect confounders associated with CA frequency; all statistical analysis were done using SPSS package version 14.00. A p-value < 0.05 was considered to be statistically significant.

RESULTS

Patients

The patients' characteristics and clinical data are shown in Table 1. The studied patients were all females, although we did not select by gender, all of them fit for the inclusion criteria. Patients had an average age of 43.7 ± 12.9 years, were from different states throughout the Mexican Republic, and suffered from papillary or follicular TC. All patients were treated at the Instituto Nacional de Cancerología in Mexico City with high in-patient ^{131}I therapy. At two or three weeks prior to the onset of treatment, each patient received a small diagnostic dose of 5 mCi ^{131}I .

None of the patients had histories of any significant radiation or clastogenic exposure prior to this study. During the course of the patients' clinical work-ups, all underwent surgery for the removal of thyroid tissue. Seven patients presented metastases, and five had them removed. Patient 1, with a metastasis in the femur, was under study for possible amputation of the affected limb, and patient 10 had metastases in soft tissues that were removed after the ^{131}I therapy.

Sample Dosimetry

The baseline radiation values before-treatment and the radiation values at 2h or 24h after-treatment in

Table 2. Chromosomal aberration frequencies before and after ^{131}I treatment.

| Patient code (age) | Number of chromosomal aberrations per sampling time | | |
|------------------------|---|----------------------|-----------------------|
| | Before- treatment | 2 h After- treatment | 24 h After- treatment |
| 1 (52) | 2 | 21 | 9 |
| 2 (53)* | 3 | 11 | 6 |
| 3 (17) | 0 | 6 | 0 |
| 4 (57)* | 3 | 12 | 5 |
| 5 (55)+ | 2 | 2 | 6 |
| 6 (24)+ | 2 | 4 | 2 |
| 7 (37) ^o | 1 | 4 | 1 |
| 8 (50)* | 2 | 4 | 2 |
| 9 (43)* | 0 | 2 | 0 |
| 10 (49)+* ^o | 2 | 7 | 14 |
| Total of aberrations | 17 | 73 | 45 |
| Average \pm SD | 1.7 ± 1.05 | 7.3 ± 5.9 | 4.5 ± 4.47 |
| Aberrations/cell | 0.009 | 0.04 | 0.02 |
| (%) | (0.9) | (4) | (2) |

*Medication for hypertension; + Tobacco smoker; ^o Oral contraceptives. 200 cells were analyzed per patient per sampling time. The before-treatment frequency of CAs was different to 2h and 24 h after-treatment (Friedman Test $p < 0.005$).

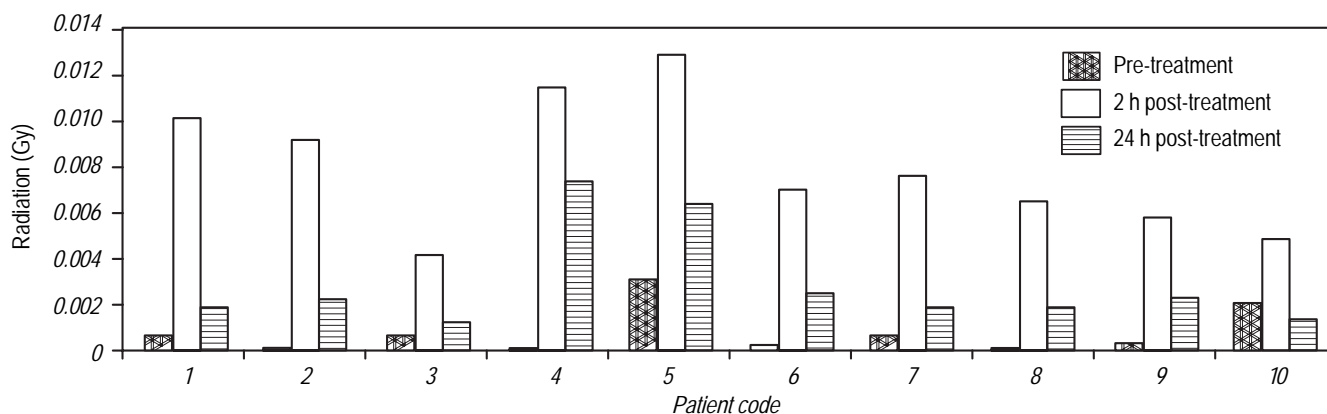


Figure 1. Graphic representation of the amount of radioactivity measured with thermoluminescent dosimeters, in blood samples obtained before-treatment or at 2 h or 24 h after-treatment, in 9 patients who were treated with 100 mCi of ^{131}I and one patient (patient code = 4) who was treated with 200 mCi of ^{131}I .

the samples from ten patients are shown in Figure 1. The sample radiation amount increased significantly at 2 h (Pre vs. 2-Post; paired t , $p < 0.01$) and diminished significantly at 24 h after treatment (2-Post vs. 24-Post; paired t test, $p < 0.01$), although not down to baseline levels in most cases.

Chromosomal Aberrations in Peripheral Blood Lymphocytes

The most frequent CAs at the three sampling times were chromosome and chromatid breaks (75%), followed by radial figures (14%), fragments (6%), and rings and dicentrics (4%). The average before-treatment CA was 0.009 CA/cell, while the average 2-Post was 0.04 CA/cell and that of the 24-Post was 0.02 CA/cell (Table 2). Statistical analysis utilizing the Friedman test for comparing the three groups (Pre, 2-Post, and 24-Post) showed a significant difference among the three values ($p < 0.005$). A positive low correlation ($r = 0.4954$) was found between the CA amounts and the sample radiation doses (Figures 1 and 2).

Two patients showed an absence of CAs in 200 cells analyzed in the samples before and 24 h after-treatment; these same two patients did not present metastases. Thus, data were analyzed according to the presence of metastases (Figure 2). Seven of the ten patients were reported as having metastases, while no metastases were detected in the three remaining patients (Table 1). In the seven patients with metastases, CAs significantly increased at both the 2-Post time and 24-Post time ($p < 0.05$, Fried-

man test). In the patients without metastases, a transitory increase was observed in CA only at the 2-Post time (Pre vs. 2-Post and Pre vs. 24-Post; $p > 0.05$, Wilcoxon test), suggesting that the chromosomal damage in patients with metastases is higher and sustained longer, as compared to patients without metastases (Figure 2). In a multiple lineal regression analysis, collinearity of smoking habit and age of the patients did not show correlation between the independent variables (tolerance = 0.779; 0.866; and VIF = 1.283; 1.155; respectively), and the frequency of CA.

Among the three patients without metastases, two of these exhibited a return to baseline levels of CA, and one patient (patient 2) showed a CA frequency more in agreement with the behavior of those patients in the group with metastases.

DISCUSSION

In this study, we detected CA in peripheral blood lymphocytes of ten patients with TC at three different sample times; before treatment, then 2 and 24 h after *in vivo* administration of ^{131}I for medical management. Two remarkable effects were observed. Firstly. Chromosome breaks showed a peak 2 h after-treatment, while rejoined CA showed a sustained increase throughout the three sampling times. Secondly. Patients with metastases had higher numbers of CA at 24 h after-treatment in comparison to patients without metastases. This difference may be due to the fact that circulating lymphocytes were exposed to a greater cancerous tissue mass (the metas-

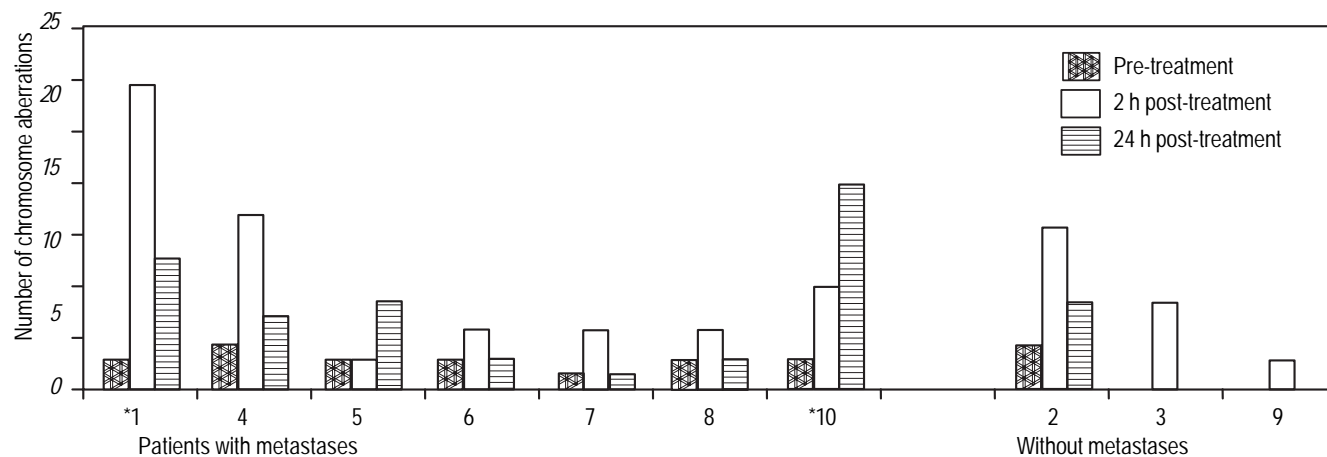


Figure 2. Effect of the presence of metastases on the induction of chromosomal aberrations in lymphocytes from 10 patients with thyroid cancer, before-treatment and after 2 or 24 h of ^{131}I treatment. *Patients with non-removed metastases. The group with metastases had significant differences for the before-treatment vs. 2 h after-treatment and the before-treatment vs. 24 h after-treatment ($p < 0.05$). In the group without metastases, the significant difference for before-treatment vs. 24 h after-treatment disappeared.

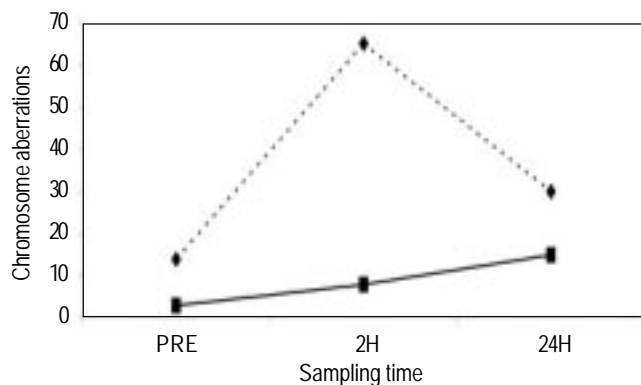


Figure 3. Graphic representation of the total chromosome aberrations according to the status of the lesions. The dashed line represents unrejoined aberrations (breaks), and the continuous line represents rejoined aberrations (dicentrics, rings, translocations, etc). The data is from 2000 metaphases ($n = 10$ patients) per sampling time. PRE = before-treatment; 2H = 2 h after-treatment; 24H = 24 h after-treatment.

tases), which retains ^{131}I during the diagnostic and therapeutic processes.

TLD in patient samples demonstrated that the radiation levels detected in all patients were greater at 2 h than those at 24 h, which were higher than the corresponding baseline values (Figure 1). This is in agreement with the levels that were transmitted through radioisotope circulation, which presented a peak at 2 h after treatment application and elimination of approximately 75% at 24 h. The remaining radioisotope is eliminated during the course of one month, since a part of the radionuclide has accumulated in the thyroid tissue, which can be the remnant of the normal or the cancerous thyroid gland, as well as in the metastases or remnants of these, which are localized in various parts of the body.¹⁵

The baseline CA frequency of the ten patients included in this study lies within the normal range.¹⁶⁻¹⁸ In after-treatment samples, the total CA frequency demonstrated an increase, with a peak at 2-post and a decrease by 24-post (Table 2), without a return to the levels that were exhibited in the before-treatment samples. When the aberrations were classified on the basis of CA types, the unrejoined aberrations, such as breaks and fragments, followed the previously described pattern, whereas the rejoined CAs, such as radial figures, dicentrics, and rings, increased over time (Figure 3). This suggests that even when DNA is repaired at the molecular level, the rejoining of chromosomal segments may be erroneous, generating stable aberrations. These remnants of prior damage become recognizable as rejoined CAs that were observed in increasing numbers with exposure time.

In addition, although there has been no prior report of a group of patients studied at 2 h following the first ^{131}I therapeutic dose, as was performed in the present study, there was a report of one patient in whom CA frequency was higher at 2- than at 24-Post.¹⁶ This is in agreement with our current observations and reflects the exposure due to the circulating radionuclide.

CA after-treatment frequencies, which are reported at different sampling times anywhere from 1 to several days after treatment application, ranged between 0.034 and 0.040,^{17,18} which is in concordance with the 0.04 frequency that we found in our Post treatment groups. In fact, in studies conducted for several weeks or months after treatment and with different radiation dosages and different ages, the CA frequency was maintained or even increased.¹⁹

The number of CAs was not associated with drug intake, age or smoking but it was directly proportional to the radiation amount that was detected in our samples, as reported previously.¹² Nevertheless, this positive correlation detected in our samples is low $r = 0.4954$, and it may be explained because in patients with metastases, the amount of after-treatment CA was high, in fact patient numbers 1 and 10, who were not subjected to metastases extirpation, showed the highest amounts of CA registered at any sampling time (Table 2, Figure 2). In addition, we observed in all patients with metastases, that chromosomal damage did not diminish at 24-post (Pre vs. 2-post $p < 0.05$, 2-post vs. 24-post $p > 0.05$), even when the dosimetry registered a radiation decrease in the samples (Figure 1), which may be due to the fact that the dosimetry value measures the free and circulating radioisotope. The fact that, when there are metastases, the chromosomal damage observed at 24-post does not diminish to the basal level can be explained by the presence of metastases or metastatic remnants in the body of variable localization and extension. This implies that there are a greater amount of cells that are capable of taking up and retaining ^{131}I , which generates a greater radiation emission that is, in turn, taken up by circulating lymphocytes within the organism *in vivo*. Moreover, lymphocytes have the potential to be more intensely irradiated if the ^{131}I is located in the remnant cancerous tissue of bone marrow or lymph nodes.

In two of the three patients without metastases, the damage that was registered at 2-Post was transitory and at 24-Post was similar to that of the before-treatment level. In one of these patients, however, the CAs were maintained, as occurred in

the patients with metastases. The latter suggests that this patient could have had some undetected metastases. It is precisely because of this type of case (in which, due to anatomic impossibility or non-detection, all cancerous tissue is not surgically removed) that ^{131}I treatment is applied after surgery.

Patients without metastases have lower probabilities of having secondary radiation uptake and emission foci. Thus, their lymphocytes are exposed to lower ^{131}I -radiation doses and, consequently, the chromosomal damage is less.

In fact, there are reports in which a greater amount of thyroid tissue correlates with a greater amount of chromosomal damage. Ramirez, *et al.*, utilizing fluorescence *in situ* hybridization (FISH) to detect breakage in a specific 17p region in a group of patients treated with ^{131}I for TC and for hyperthyroidism, found that there was no difference in the group of patients with TC before and after treatment. However, in those patients who had hyperthyroidism, in a manner similar to our patients, the frequency of structural CAs was not modulated by age nor by administered radiation dosage, but rather by the amount of thyroid tissue that took up the ^{131}I *in vivo*. This was because the patients with TC, but not those with hyperthyroidism, had thyroidectomies, and, in those with hyperthyroidism, CA frequency in 17p increased significantly after treatment.²⁰ In the same manner, Gundy found that, in patients with thyrotoxicosis without thyroidectomy, the amount of after-treatment CAs was more than double that in patients with TC with thyroidectomy, although the applied radiation dose was ten times less in the former.²¹

Recently Joseph, *et al.*²² found a significant increase of peripheral blood lymphocytes micronuclei in thyroid cancer patients with metastases, as compared with the patients without metastases, the interval between the ^{131}I radiotherapy and sample collection was < 1 to 126 months. Our study, carried out in patients treated with the same therapeutic ^{131}I dosis, corroborated that the presence of metastases plays a major role in increasing structural chromosomal damage that can be detected from the first hours after treatment. These observations underlie the importance of the remnant thyroid tissue as a source of internal radiation emission. Chromosomal damage in lymphocytes after ^{131}I therapy could be a facilitating factor in the development of secondary neoplasia; it has been reported a 0.1 to 2.0% of leukemia following ^{131}I therapy. Indeed, Im *et al* found four cases of secondary hematologic malignancy in patients previously treated with iodine

therapy for TC after thyroidectomy, three of them presented CA, and the authors found a possible relationship between the iodine therapy and secondary malignancy in all the four cases.²³

The data presented here show the importance of the detection and surgical removal of as much cancerous tissue as possible, because its retention implies an increased risk, not only due to the cancer itself, but also because of the greater exposure of normal cells to radiation that may lead to secondary cancer. In fact, in patients with hyperthyroidism and thyrotoxicosis in whom ^{131}I therapy is applied, it would be beneficial to consider the advantages of removing thyroid tissue prior to treatment, in order to ensure that the normal cells have the least possible exposure to radiation.

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