

Radiotoxicity After Iodine-131 Therapy for Thyroid Cancer Using the Micronucleus Assay

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The purpose of the present study was to evaluate the degree of cytological radiation damage to lymphocytes after ^{131}I therapy using the cytokinesis-blocked micronucleus assay. The chromosomal damage to lymphocytes induced by ^{131}I in vivo should result in augmentation of the cells with micronuclei. **Methods:** We studied 25 patients with differentiated thyroid carcinoma who were treated with 3.7 GBq of ^{131}I . Isolated lymphocytes collected from patients 1 wk after therapy were harvested and treated according to the cytokinesis-blocked method of Fenech and Morley. The micronucleus number of micronuclei per 500 binucleated cells were scored by visual inspection. As controls, lymphocytes from the same patients before therapy were also studied. In an in vitro study, lymphocytes from three patients at least 3 mo after therapy were exposed to doses varying from 0.25 to 1 Gy and studied with the same method. **Results:** The mean number (mean \pm s.d.) of micronuclei after treatment was significantly increased ($p < 0.05$) as compared to control subjects (15.7 ± 2.7 vs. 5.4 ± 1.4). Since there was an interval ranging from 6 to 20 mo (mean 11.8 mo) between the present and the last radioiodine therapy, no significant effect on the frequency of micronucleus with cumulative radiation exposure of ^{131}I to lymphocytes was detected. Internal radiation absorbed doses estimated for 25 patients were 0.33 ± 0.09 Gy in this external irradiation study. **Conclusion:** The relatively low frequency of lymphocyte micronuclei induced by ^{131}I in vivo and lack of significant effect on the frequency of lymphocyte micronuclei with cumulative ^{131}I supported the contention that short-term nonstochastic damage of this therapy with 3.7 GBq of ^{131}I in thyroid cancer patients is minimal and reversible.

Key Words: micronucleus assay; differentiated thyroid carcinoma; radioiodine therapy; radiotoxicity

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The therapeutic application of radioactive ^{131}I was first reported more than 50 yr ago (1), and it has been used widely to treat well-differentiated thyroid carcinoma (2,3). Radioiodine treatment of well-differentiated thyroid carcinoma consists of administering a large amount of radioiodine. Since significant complications may result, radioiodine treatment should be carried out only when there is a reasonable expectation that it will benefit the patient (4).

The usual practice in treating thyroid cancer is to give a standard amount of ^{131}I to all patients. Most laboratories use between 100 and 200 mCi (3.7-7.4 GBq), and the administration of up to 200 mCi has not generally been associated with serious complications (4,5). However, transient bone marrow suppression occurs maximally approximately 6 wk after treatment with radioiodine (3,6). Transient anemia, leukopenia and

thrombocytopenia have been reported (6,7). Therefore, in most patients who are treated with a large amount of ^{131}I , the limiting factor is the radiation dose to the blood and the bone marrow (8). Dosimetric studies have estimated the radiation dose to the blood and bone marrow with a large amount of radioiodine (3). Previous work has been done on cytogenetic changes (9). However, the cytological effects of radiation exposure on the lymphocytes in vivo with large therapeutic doses of radioiodine have not been extensively examined.

The purpose of our study was to evaluate the degree of radiation-induced cytological damage to the lymphocytes in thyroid cancer patients following therapeutic administration of 3.7 GBq ^{131}I using the cytokinesis-blocked micronucleus assay. Chromosomal damage to lymphocytes induced by ^{131}I in vivo should result in augmentation of the cells with the micronucleus. Since micronuclei enclose acentric chromosome fragments or whole chromosomes that have not been incorporated in the main nuclei at cell division (10), a comparison of the frequency of the micronuclei among lymphocytes irradiated in vivo by ^{131}I and in vitro by electrons may allow a cytological assessment of internal radiation absorbed doses.

MATERIALS AND METHODS

Patients

From May 1994 to February 1995, 25 patients (19 women, 6 men; age range 36-72 yr; mean age 58.4 yr) were admitted for treatment with radioiodine for differentiated thyroid carcinoma at the Department of Radiology of Toyama Medical and Pharmaceutical University and the Nuclear Medicine Department of Kanazawa University Hospital, Japan. All patients were diagnosed by biopsy and had total thyroidectomies. After informed consent, 25 patients who received 3.7 GBq ^{131}I were studied. These patients were classified into one of three groups according to the cumulative amount of ^{131}I administered prior to the current therapy, with the most ^{131}I administration at least 6 mo previously: Group 1, consisting of six patients with no prior ^{131}I administration; Group 2, consisting of 11 patients with one prior ^{131}I administration of 3.7 GBq and Group 3, consisting of eight patients with two prior administrations of 3.7 GBq of ^{131}I each. The last treatment was administered more than 6 mo after the first therapy dose.

Lymphocyte Isolation and Culture

Venous blood was collected from each of the 25 patients before therapy and 1 wk after therapy. Serial blood samples were obtained periodically from two patients (Patients A and B) for 2 wk after therapy.

Peripheral blood lymphocytes were separated from whole blood on a lymphocyte separation medium (ICN Biomedicals, Inc., Aurora, OH) with centrifugation, and they were washed twice in Hank's balanced-salt solution and resuspended in McCoy's mod-

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ified medium 5A containing 15% heated inactivated fetal-calf serum. The lymphocytes were cultured according to the method of Fenech and Morley (10) in a 25-ml tissue culture flask at a concentration of 0.5×10^6 cells/ml. An optimum concentration of phytohemagglutinin (PHA) (5 μ /ml, Difco Laboratory, Detroit, MI) was used to stimulate the lymphocytes to transform and divide in the culture. A solution of cytochalasin B (Aldrich Chemical Co., Milwaukee, WI) was added 44 hr after the commencement of the culture at a concentration of 3.0 μ /ml, unless otherwise stated. The cultures were terminated 72 hr after initiation.

In Vitro External Irradiation

In an in vitro study, lymphocytes could be collected from only one patient at 3 mo after ^{131}I therapy and two patients (Patients A and B) at 12 mo after ^{131}I therapy. Lymphocytes were irradiated with external electron beams (300 rad/min, 5 MeV, Metatron, MD 2/40, Toshiba, Tokyo, Japan) with doses ranging from 0.25 to 1 Gy and micronucleus assays were performed.

Micronucleus Assay

The acridine orange fluorescent staining procedure was applied to the micronucleus assay in our study according to the method of Hayashi et al. (11). The prepared lymphocytes were stained with 0.1% aqueous solution of acridine orange. These lymphocytes were then smeared on clean glass slides. An Olympus BH-RFL fluorescent microscope (Olympus Optical Co., Tokyo, Japan) with BG-12 excitation filter and 0-515 barrier filter was used for observation. Micronuclei were stained yellowish-green with green fluorescence. The number of micronuclei per 500 binucleated cells was scored by visual inspection.

Lymphocyte Counting

Hematological parameters, including cell counts and size distribution, were determined with a Coulter counter on the serial blood samples from the same two patients up to 2 wk after therapy. Analysis and classification of white blood cells were based on three simultaneous measurements: individual cell volume, high frequency conductivity and laser light scatter. The number of lymphocytes was also determined with this system.

Statistical Analysis

Data are expressed as mean \pm s.d. The Student's t-test was used to analyze the differences between means. Probability values of $p < 0.05$ were considered significant.

RESULTS

Evaluation of the Cytological Radiation Damage to Lymphocytes After Iodine-131 Therapy

The number (mean \pm s.d.) of micronuclei per 500 binucleated lymphocytes was 5.4 ± 1.4 before and 15.7 ± 2.7 after ^{131}I therapy, a statistically significant increase ($p < 0.05$) (Fig. 1). The respective number (mean \pm s.d.) of micronuclei per 500 binucleated lymphocytes in Group 1 and Group 3 was 4.5 ± 1.2 and 5.7 ± 1.1 before ^{131}I therapy and 16.1 ± 3.5 and 15.2 ± 3.1 after ^{131}I therapy. There was, thus, no significant difference between Group 1 and Group 3 either before or after ^{131}I therapy. The interval between the present and the last radioiodine therapy of Group 3 ranged from 6 to 20 mo (mean 11.8 mo).

For the two patients from whom serial lymphocyte samples were obtained and micronucleus assays were performed, the frequency of micronuclei peaked at 3 days postadministration of ^{131}I and gradually decreased to near baseline (i.e., pre-therapy) levels by 2 wk (Fig. 2).

Evaluation of Number of the Lymphocytes After Therapy

The lymphocyte count had decreased sharply in Patient A at 5 days postadministration of ^{131}I , but it actually increased

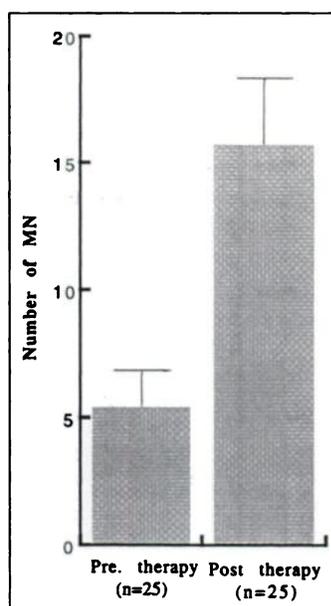


FIGURE 1. Number of micronuclei per 500 binucleated cells before treatment and after treatment. Mean values (columns) and s.d. (thin vertical lines) are shown.

slowly thereafter. In contrast, in Patient B, the lymphocyte count had decreased only slightly at 6 days post-therapy and appeared to decrease further only slightly thereafter (Fig. 3).

Evaluation of the Cytological Radiation Damage to Lymphocytes After External Irradiation

In an external irradiation study, the number of lymphocyte micronuclei in Patients A and B without external irradiation was 6 and 7, respectively, at 12 mo after therapy. It was 5 and 7, respectively, before therapy. The number from one patient was 7 at 3 mo after therapy and 4 before therapy. We could collect lymphocytes from only three patients after this therapy. The number of micronuclei before therapy was 5.4 ± 1.4 in our in vivo study. Therefore, we performed this in vitro study with these lymphocytes. The number of micronuclei per 500 binucleated lymphocytes was observed following electron irradiation doses of 0.25 Gy, 0.5 Gy, 0.75 Gy and 1 Gy, respectively. These data fit a nonthreshold, linear dose-response function ($y = 29.2 \times +5.8$, $r = 0.96$) (Fig. 4). Internal radiation-absorbed doses were calculated compared to the same frequency of lymphocyte micronuclei of external irradiation. Absorbed doses estimated for the 25 patients were 0.33 ± 0.09 Gy.

DISCUSSION

The usual procedure for obtaining human dosimetry is serial whole-body scanning for biodistribution followed by integration of the area under the resulting time-activity curve of an organ region of interest (ROI). An accurate estimate of marrow dose by this method is imprecise due to its widespread distribution in the body and the difficulty in defining a suitable ROI. A sensitive bioassay accurately reflecting marrow damage would be very valuable.

Fenech and Morely (10) developed the cytokinesis-blocked micronucleus assay as a method for measurement of chromosomal damage in mitogen-stimulated human lymphocytes. This assay has been extensively used in routine mutagen/carcinogen screening programs to detect agents that cause chromosomal breakage and spindle dysfunction (12,13). In nuclear medicine, Thierens et al. (14) have evaluated the cytological radiation damage to lymphocytes after in vitro labeling of mixed leukocytes and isolated lymphocytes with $^{99\text{m}}\text{Tc}$ -HMPAO using this assay. Chromosomal damage following radioiodine therapy has been reported (9,15,16). However, only a few studies have been performed to evaluate quantitative biological effect (15,16).

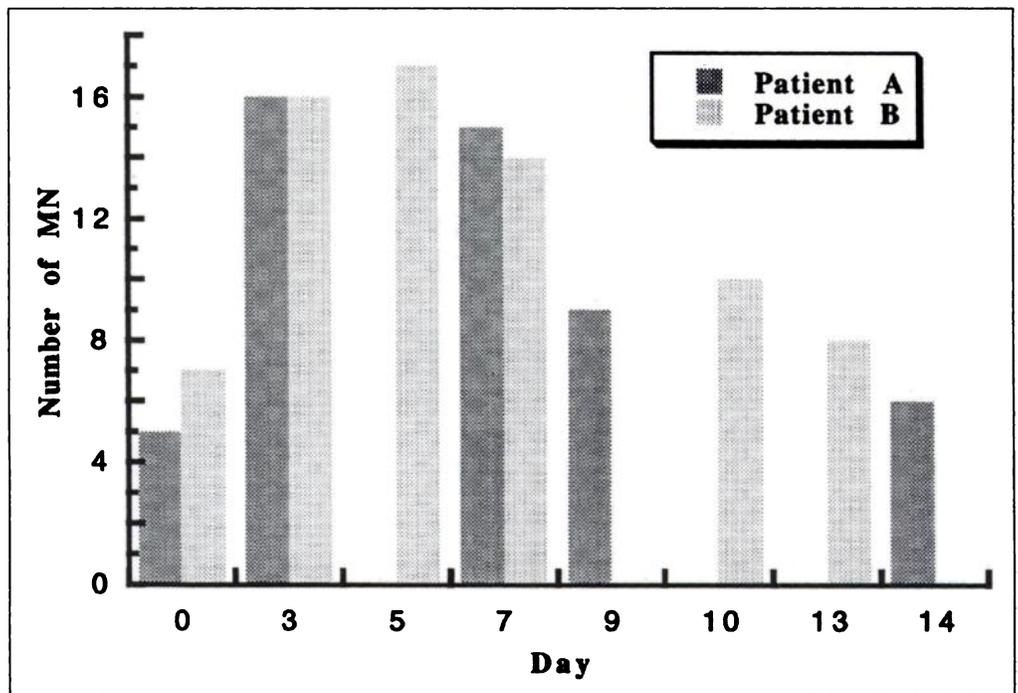


FIGURE 2. Serial change of number of micronuclei per 500 binucleated cells in Patient A and Patient B until 2 wk.

We applied the cytokinesis-blocked micronucleus assay to evaluate the degree of cytological radiation-induced damage to lymphocytes in thyroid cancer patients after therapeutic administration of 3.7 GBq ^{131}I . Our findings showed that the lymphocytes exposed to ^{131}I have significantly higher micronucleus frequencies compared to the controls. Considering the long half-life of lymphocytes, the gradual decrease in the frequency of the micronucleus noted after peak value was attributed to the depletion of lymphocytes from the blood due to internal irradiation, at least up to 2 wk postadministration of ^{131}I . In an *in vitro* study 12 mo after therapy, the frequency of the micronucleus returned to the baseline in both cases examined. Moreover, we could not collect the blood samples from 2 wk to 12 mo from these two patients. Ottesen et al. (17) found that lymphocytes could be separated into two groups: (1) a minor one with a survival time of 3 to 4 days, and (2) a major one with

a survival time of 100 to 200 days. Norman et al. (18) reported that the lifetime of the lymphocytes in hematologically normal women is 530 ± 64 days. The lifetime of lymphocytes is variable. Since there was an interval ranging from 6 to 20 mo (mean 11.8 mo) between the present and the last radioiodine therapy, no significant effect on the frequency of the micronucleus by previous exposure of lymphocytes to ^{131}I should have been detected. Our results suggested that cytological damage to lymphocytes induced by ^{131}I can recover by 12 mo post-therapy. Thus, the micronucleus assay 12 mo after therapy would no longer be useful as a biodosimeter. These results were remarkably close to the findings that any possible genetic damage induced by therapeutic exposure to ^{131}I is eliminated after a period of 1 yr (19). However, using different techniques, M'Kacher et al. (20) reported recently that the biological damage persisted for up to 2 yr after therapeutic exposure to

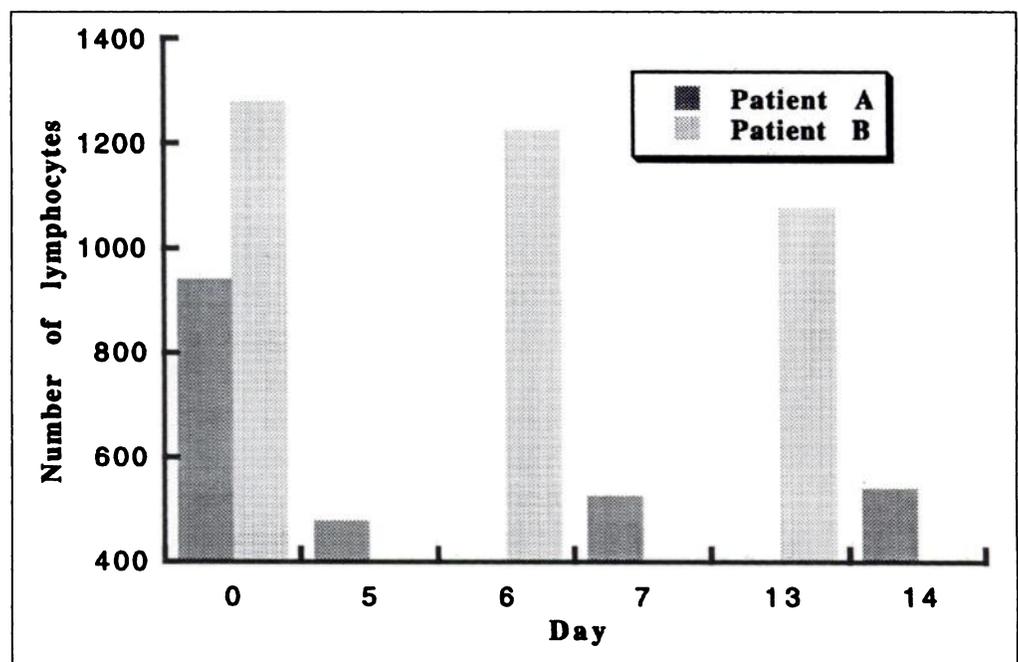


FIGURE 3. A decrease in the number of lymphocytes in Patient A and B until 2 wk.

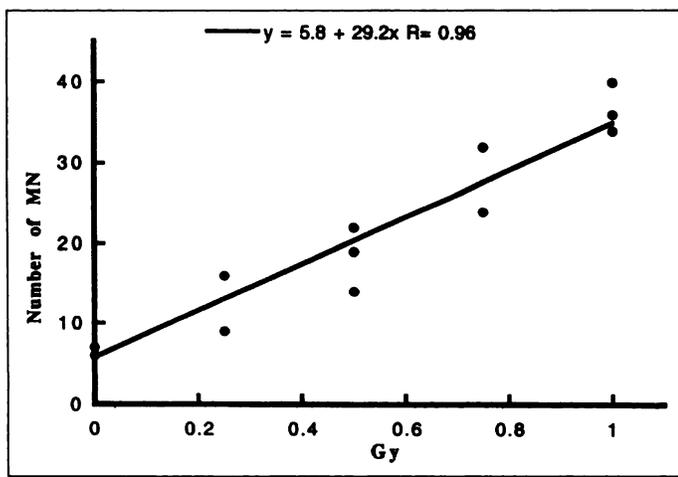


FIGURE 4. Number of micronuclei per 500 binucleated cells after external irradiation in vitro ($n = 3$).

^{131}I . The question of repair of internal radiation damage in lymphocytes in vivo is still moot.

To estimate the effective absorbed radiation to lymphocytes in vivo, we performed an external irradiation study to compare the micronucleus incidence in in vivo and in vitro irradiated lymphocytes. This was done to match the radiation damage in vivo with the radiation cytological damage in vitro and to determine the external radiation dose that produced it by considering that biological types of damage are thought to represent a nonstochastic effect. We demonstrated that the cytological damage to the lymphocytes induced by ^{131}I in vivo may be considered equal to the damage observed after a mean external irradiation of 0.33 Gy in vitro. However, for a radiograph, dose-rate is one of the principal factors for determining the biological consequences of a given dose. As the dose-rate is lowered and the exposure time extended, the biological effect of a given dose is generally reduced (21). Therefore, it may be argued that the total dose in vivo of low dose-rate radiation exposure is considerably underestimated when compared to high dose-rate external radiation exposure in vitro. Our study was designed to clarify the biological estimation of the internal radiation dose with ^{131}I therapy. M'Kacher et al. (22) performed a low dose-rate irradiation study to compare the number of chromosomal aberrations in in vivo lymphocytes 4 days after therapy and in vitro lymphocytes from a normal volunteer after 48 hr irradiation. The estimated dosimetric index was 0.5 Gy, which could also be considered an underestimation because continuous radiation exposure in vivo is much more prolonged. Iodine-131 therapy induced an increased micronucleus frequency in lymphocytes in vivo after 1 wk of low dose-rate chronic radiation exposure. This is very different from high dose-rate acute in vitro irradiation of lymphocytes. However, both the in vivo and in vitro studies used lymphocytes from the same patients under the same conditions and in the same assay system. The biological dose estimation of our study may be relatively underestimated compared to that of M'Kacher et al. (22), although our method can be performed much more conveniently and easily to evaluate the internal radiation exposure of patients.

Blood and bone marrow are the dose limiting organs not only in ^{131}I therapy for thyroid cancer but also in ^{131}I radioimmunotherapy and ^{89}Sr -therapy in bone metastases. The marrow radiation dose calculated from a bone marrow ROI is much higher for these studies, typically in the 0.05 Gy/mCi range (23). Thus, blood and marrow dosimetry is of great interest for

radionuclide therapy, and it has been investigated by a number of researchers (3).

Gunter et al. (24) reported that the radiation doses in 10 subjects receiving 200 mCi ^{131}I for thyroid cancer were 0.0047 Gy/mCi to the blood and 0.0030 Gy/mCi to the marrow. These results were remarkably close to the estimation of McEwan (25) of 0.0044 Gy/mCi to the blood and 0.0032 Gy/mCi to the marrow. However, Benua et al. (7) reported on 59 patients receiving a mean whole-blood radiation dose of 2.67 Gy (range, 0.45 to 7.4 Gy). The estimated radiation dose could be variable. The mean internal radiation exposure estimated for our patients of 0.33 Gy may be in a range similar to these calculated results.

The long-term hazards of treatment of thyroid cancer and induction of leukemia by ^{131}I treatment have been already reported (26,27). We believe, however, that our results suggest a minimum short-term nonstochastic hazard, although a long-term stochastic hazard is still present.

The internal radiation exposure to lymphocytes induced by ^{131}I therapy was thought to be minimal based on the comparative cytological study. Monitoring other radionuclide therapies giving larger marrow doses, such as ^{131}I radioimmunotherapy, may be useful in the future for treatment planning. The method described here is the only one currently available to evaluate radiation-induced chromosomal damage as a routine procedure (28,29).

CONCLUSION

The relatively low frequency of lymphocyte micronuclei induced by ^{131}I in vivo and the lack of significant effect on the frequency of lymphocyte micronuclei with cumulative ^{131}I supported the contention that short-term nonstochastic damage from this therapy with 3.7 GBq of ^{131}I in thyroid cancer patients is minimal and reversible.

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Glucose Metabolism in Human Malignant Gliomas Measured Quantitatively with PET, 1-[C-11]Glucose and FDG: Analysis of the FDG Lumped Constant

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Calculation of the glucose metabolic rate (MRGlc) in brain with PET and 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG) requires knowing the rate of uptake of FDG relative to glucose from plasma into metabolite pools in the tissue. The proportionality factor for this is the FDG lumped constant (LC_{FDG}), the ratio of the volumes of distribution of FDG and glucose multiplied by the hexokinase phosphorylation ratio for the two hexoses, $Km_{Glc} \cdot Vm_{FDG} / Km_{FDG} \cdot Vm_{Glc}$. MRGlc equals the FDG metabolic rate (MRFDG) divided by the LC_{FDG} ; i.e., $MRGlc = MRFDG / LC_{FDG}$ and $LC_{FDG} = MRFDG / MRGlc$. This investigation tested the hypothesis that LC_{FDG} is significantly higher in gliomas than it is in brain uninvolved with tumor. **Methods:** We imaged 40 patients with malignant gliomas with 1-[¹¹C]glucose followed by FDG. The metabolic rates MRGlc and MRFDG were estimated for glioma and contralateral brain regions of interest by an optimization program based on three-compartment, four-rate constant models for the two hexoses. **Results:** The LC_{FDG} , estimated as $MRFDG / MRGlc$, in gliomas was 1.40 ± 0.46 (mean \pm s.d.; range = 0.72-3.10), whereas in non-tumor-bearing contralateral brain, it was 0.86 ± 0.14 (range = 0.61-1.21) ($p < 0.001$, glioma versus contralateral brain). **Conclusion:** These data strongly suggest that the glioma LC_{FDG} exceeds that of contralateral brain, that quantitation of the glioma MRGlc with FDG requires knowing the LC_{FDG} specific for the glioma and that the LC_{FDG} of normal brain is higher than previously reported estimates of about 0.50. 2-Fluoro-2-deoxy-D-glucose/PET studies in which glioma glucose metabolism is calculated by the autoradiographic approach with normal brain rate constants and LC_{FDG} will overestimate glioma MRGlc, to the extent that the glioma LC_{FDG} exceeds the normal brain LC_{FDG} . "Hot spots" visualized in FDG/PET studies of gliomas represent regions where MRGlc, LC_{FDG} or their product is higher in glioma than it is in uninvolved brain tissue.

Key Words: lumped constant; glioma; glucose metabolism; brain neoplasm; PET

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2-[¹⁸F]fluoro-2-deoxyglucose (FDG) with PET is being used clinically in the management of malignant gliomas for grading, planning biopsies and distinguishing recurrent disease from radionecrosis (1-9). These studies have been based on simple visual assessment of FDG uptake (1,9-11), determination of the ratio of tumor FDG uptake to some normal brain reference region (2,4,12,13) or estimation of regional glucose metabolic rate (MRGlc) with FDG, based on the autoradiographic approach of Sokoloff et al. (14), applied with normal brain rate constants (3,6,15-21) or rate constants determined by dynamic imaging (8,22,23). The underpinning of these approaches is the fact that FDG, in a similar manner to glucose, is transported across the blood-brain barrier and phosphorylated by hexokinase (HK) to 2-fluoro-2-deoxy-D-glucose-6-phosphate, which accumulates in the tissue at a rate proportional to the rate of glucose utilization.

Because FDG and glucose differ in their rates of transport and phosphorylation and respective volumes of distribution in brain tissue, calculation of MRGlc from PET with FDG requires a proportionality constant, the FDG lumped constant (LC_{FDG}), in the operational equation (14). The LC_{FDG} represents the ratio of the metabolic rate of FDG (MRFDG) to MRGlc and, as such, is a complex constant that contains the Km and $Vmax$ for FDG and glucose in the HK reaction, the ratios of the volumes of distribution of FDG and glucose (λ) and a ϕ term, assumed to be one, for the proportion of glucose which, once phosphorylated, is further metabolized. Mathematically:

$$LC_{FDG} = (\lambda/\phi)(Km_{Glc} \cdot Vm_{FDG}/Km_{FDG} \cdot Vm_{Glc}). \text{ Eq. 1}$$

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