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EDITORIAL

Genetic Risk Assessment after Iodine-131 Exposure: An Opportunity and Obligation for Nuclear Medicine

All diagnostic and therapeutic modalities should be assessed carefully for the relative benefits and hazards so patients and physicians can make rational decisions. Although this basic principle would seem to be self-evident, the objective, practical evaluation of the pros and cons of ^{131}I therapy is a particularly complex task.

The diagnostic and therapeutic use of ^{131}I for the evaluation of thyroid remnants and regional and distant metastases of differentiated thyroid carcinoma (DTC), the ablation of remnants and the ^{131}I therapy of avid metastases have been routine for decades. It has been half a century since ^{131}I was introduced into medical practice, and a large body of information has been gathered on the diagnostic and therapeutical effectiveness of this modality (*1–4*). Nevertheless, definitive results have yet to be acquired, and the indications for the diagnostic and therapeutic use of ^{131}I are still the subject of dispute (*5,6*). Much of the difficulty arises from the low prevalence of DTC and the unusually long, natural history of the disease which necessitates the assembly of large series which are meticulously followed for decades. While the exact utility of diagnostic and therapeutic ^{131}I remains controversial, the evaluation of the hazards of these applications remains even more controversial and difficult to define. Despite the fact that virtually every paper dealing with ^{131}I treatment of DTC mentions the chance of untoward effects, particularly those proposing more restrictive protocols, the available data on this issue are scant and inconclusive.

Every nuclear physician should have a clear impression from clinical practice that ^{131}I therapy is safe and that the level of risk is smaller than that of other therapeutic modalities routinely used in oncology (e.g., external beam radiotherapy and chemotherapy), but the time has come to support this impression with indisputable data. While the risks are obviously small, fear of the unknown is the worst enemy of the medical use of radionuclides. The accurate and objective evaluation of the risk is thus an important primary task of the nuclear medicine community.

COMPLICATIONS FROM IODINE-131 THERAPY

The most common acute complications of ^{131}I therapy, radiation thyroiditis, sialadenitis, gastrointestinal discomfort and nausea, xerostomia and altered taste sensation are usually mild and self-limiting (*7,8*); in fact, specific treatment is only occasionally required. In the case of commonly used doses of ^{131}I, impairment of gonadal function appears to be a temporary reversible effect (*9,10*). Edema and hemorrhage into the tumor may rarely cause serious problems when metastases are located in the brain or near the airways. Among the late effects, permanent myelosuppression and pulmonary radiation fibrosis are dose dependent, and thus, only the minority of patients treated with very high cumulative doses are at risk. In contrast to these risks, the potential hazards from ^{131}I therapy, which have the greatest impact on the decision to utilize this modality, are the induction of second tumors (*11,12*) and genetic damage (*13–23*). These are considered to be stochastic effects with no threshold; virtually every patient treated with any dose of ^{131}I is exposed to some potential risk. Chromosomal abnormalities and genetic mutations which express themselves in the offspring of exposed subjects are only relevant to fertile individuals of reproductive age.

Nuclear physicians dealing with radionuclide therapy are asked almost daily by patients and referring physicians to define the extent of the risk. Thus, the rare contributions to the literature on this subject, such as that from Schlumberger et al. in this issue of the *Journal* (*24*), are especially valuable and useful in every day clinical practice.

The paucity of available data in the literature on this topic stems from a number of factors. Remarkable methodological difficulties arise when assessing effects that are both infrequent and which have long latent intervals before becoming manifest (years for carcinogenesis and at least a generation for diseases formed from genetic mutations). Tumors and mutations induced by exposure to ionizing radiation for medical purposes are generally indistinguishable from those arising from other causes (e.g., chemicals, viruses and background radiation). Therefore, determining the cause of carcinogenesis and of genetic mutations from ^{131}I exposure is impossible in individual cases (even if these are grouped together), but depends on the

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comparison of the incidences of events in the exposed patients (or their offspring) and appropriately matched control groups. Only those disorders which are single-gene, highly penetrant autosomal dominant or x-linked dominant traits that are uniformly expressed and readily diagnosed near birth (the so-called "sentinel phenotypes") are readily detected with certainty on the first generation of the exposed population and are useful in proving the possible existence of a causative relationship between exposure and mutation. These genetic disorders are much rarer than the common multifactorial anomalies which manifest only later in life in the offspring of exposed subjects or future generations (which decreases the probability of detection). Thus, there are genetic diseases that are either easily recognized but uncommon, or more frequent but difficult to detect.

Another problem is that biological effects of exposure to ^{131}I are linked to the specific absorbed radiation dose (in the case of genetic effects, that to the ovary or testis) in each organ, which is only weakly correlated to administered doses of ^{131}I (*25*). The dosimetry after radionuclide therapy is made difficult by multiple anatomic, physiological and physiopathological variables. Even when all the required parameters are available, the range of error can be wide. Moreover, retrospective analyses often lack complete data, particularly when these have been acquired over long periods of time. Thus, it is not surprising that the estimates of gonadal absorbed radiation doses from ^{131}I treatment for DTC vary greatly in different publications dealing with the evaluation of genetic damage. Casara et al. (*22*), using the MIRD model and recommendations of Smith and Edmonds, reported a mean estimated absorbed dose of 24 ± 13.5 cGy delivered to the ovaries, following a mean total ^{131}I dose of 4.39 ± 25.2 GBq (i.e., approximately 5.46 cGy cGy/GBq). Schlumberger et al. (*24*) used an original approach expressly designed for thyroidectomized patients and found estimated doses approximately twice as large (10.8 cGy/GBq). Despite these difficulties, however, every effort should be made to define individualized dosimetry, as this is the one way to better correlate the cause (gonadal radiation exposure) with the effects (genetic damage).

Awareness of these difficulties should not discourage the efforts of the nuclear medicine community to objectively assess the risks of exposure to ^{131}I, but rather, should encourage us to acquire even more solid and indisputable data. Paradoxically, the very low level of risk from ^{131}I therapy is the principal cause of difficulty in accurately estimating this risk.

The importance of this type of study rests not only with the need to collect data which are useful in the management of patients with DTC, but also for the assessment of the impact of ionizing radiation on human health in general. This issue has increased in importance as societal anxiety about the use of ionizing radiation, particularly radionuclides after the Chernobyl accident, has risen.

The genetic risk of ionizing radiation in humans has been estimated in the offspring of atomic bomb survivors (*26,27*), in populations living in areas of high natural or man made background radiation levels (*28*) and in the descendants of persons exposed to radiation either on the job (*29*) or through diagnostic and therapeutic procedures (*30*). To date, the best available data for the estimation of the genetic risk of human exposure to ionizing radiation are those derived from the offspring of the atomic bomb survivors. The survey of Otake et al. (*27*) examined 70,073 pregnancies, which resulted in 5638 children being born to parents exposed to radiation doses comparable to those from ^{131}I treatment of DTC (doses ranged from 1–2.49 Sv in 916 cases, from 0.5–0.99 Sv in 1404 cases and from 0.1–0.49 Sv in 3318 cases). This information has not demonstrated a statistically significant relationship between radiation dose and the incidence of genetic effects. There is a nonsignificant positive trend between increasing doses and the incidence of genetic effects. This is consistent with previous experimental data on the mutagenic effect of ionizing radiation, but the calculated excess risk above the spontaneous mutation rate is low. The minimal doubling dose for genetic effects was estimated to be approximately 2 Sv for acute exposure (*31*). Based on extrapolation from animal data this figure might be increase by 2–3 times following chronic exposure. Even data from this large survey are fraught with potential errors in the dose calculation given uncertainties as to the location of the survivors at the moment of the explosions, the estimate of the free-in-air kerma dose curves and the evaluation of the energy attenuation by tissues and surrounding environmental materials. The different dose rates and quality of the radiation, as well as different population characteristics and other relevant confounding factors (e.g., socioeconomic status, parental age distributions, effects of other mutagens, fraction of offspring from both exposed parents and hormonal status), all hamper the automatic transposition of these data to patients exposed to ^{131}I for diagnosis or therapy.

Recent controversial reports on an apparent increase in the number of leukemias in young people born to occupationally exposed men working at the Sellafield nuclear reprocessing plant in Northwest England (*32*), and the report of possible reproductive and carcinogenic effects after the Chernobyl nuclear reactor accident (*33–35*) have raised new concern about these effects at low doses. Indeed, the most profound reproductive effect of this accident was a sharp increase in elective terminations of pregnancy in Europe which were often due to unfounded fear following negligible exposures (*35*). Studies in the offspring of the survivors of childhood leukemia and non-Hodgkin's lymphoma appear to demonstrate that inherited abnormal alleles do not play a major role in the etiology of these diseases (*36*), which precludes the potential role of radiation exposure in their induction. Other surveys have failed to confirm significant increases in childhood cancers (*37,38*), congenital malformations (*39*) or chromosomal abnormalities (*40,41*) in those geographical areas that were exposed to increased low dose radiation doses from the Chernobyl fallout. The limitations of descriptive ecological studies for the detection and estimation of the very low risks derived from exposure of less than 1 mSv (natural background radiation being 1–2 mSv) have been superbly summarized by Boice and Linet (*42*).

Nevertheless, these data, especially when reported incorrectly or misinterpreted by the mass media, may increase public anxiety towards any use of radionuclides, with obvious negative effects on the acceptance and adoption of diagnostic and therapeutic nuclear medicine procedures. This is particularly detrimental in those countries in which overregulation (*43*) (often itself derived from misinterpretation of data on the biological effects of radiation) already hampers the optimal medical use of radionuclides. It is thus important to acquire data which extend the knowledge already acquired, but also which better fit the actual scenario of clinical practice. In recent months, a number of papers from several groups in Europe have begun to provide new data on these from somewhat different points of view. Casara et al. (*22*) reported the outcomes of 73 pregnancies in 70 women who were previously treated with ^{131}I doses ranging from 1.85

to 16.55 Gbq (mean ± s.d.: 4.39 ± 25.2 Gbq). Unfavorable outcomes included: two spontaneous abortions during the second month of pregnancy, one case of Fallot's trilogy and three cases of low birth weight. The gonadal absorbed radiation doses, estimated using the MIRD method and the recommendations of Smith and Edmonds ranged from 10 to 63 cGy (mean ± s.d.: 24.0 ± 13.5 cGy) in all cases and from 11 to 20 cGy in those with untoward pregnancy outcome.

In a retrospective study not specifically aimed at the evaluation of genetic effects, but rather seeking to globally assess the most significant untoward late hazards of ^{131}I therapy (i.e. carcinogenesis, effects on female fertility and genetic effect) (*23*), I participated in a study which reported on 65 children born to 49 women treated before pregnancy with ^{131}I in doses ranging from 2.6 to 22.2 Gbq (mean: 6.5 GBq). These pregnancies were compared with 19 offspring from 15 women with DTC who were not treated with ^{131}I. Among the exposed women were two premature deliveries at the seventh month of gestation; three spontaneous abortions and one case of ventricular septal defect and patent ductus arteriosus. For comparison, there was only one spontaneous abortion in the second month in the group of non-exposed women. The birth weights in the two groups were not statistically different. The fertility of the exposed women was also not significantly different from the control group. Unfortunately, it was not possible to calculate actual individual dosimetry, but there was no relationship between the occurrence of second tumors and an estimate of absorbed dose projected from cervical ^{131}I uptake and the cumulative doses of ^{131}I administered.

The article by Schlumberger et al. (*24*) is an outstanding example of how these difficult issues should be handled. The study was carefully planned and the data were collected over approximately 4 yr using expressly designed, structured interviews and not abstracted retrospectively from files. This reduces the possibility of missing cases of adverse pregnancy outcome and might explain the apparent higher incidences of such outcomes (notably miscarriages) in this study compared with those of the two Italian groups. The multicenter nature of the study enabled the authors to collect a substantial body of data (1877 females were interviewed and a total of 2113 pregnancies studied, 122 of which followed exposure to diagnostic doses and 136 therapeutic doses of ^{131}I). There were no significant differences in the incidence of untoward pregnancy outcomes, of thyroid diseases and cancers in the offspring of patients treated with surgery alone and also those exposed to ^{131}I with the notable exception of a significant increase in the incidence of miscarriage (0.4) in the subgroup exposed to therapeutic doses of ^{131}I in the year prior to conception. The authors assume that this finding may be related to suboptimal adjustment of thyroid hormonal status following thyroidectomy. A possible increase in the rate of miscarriages has been reported to occur in women previously irradiated for Wilm's tumor or other cancers (with abdominal doses of 20–30 Gy), but this has been attributed to somatic damage to abdomino-pelvic organs more than to radiation-induced germ cell mutations (*30,44*). Furthermore, miscarriages are not always identified easily, particularly when they occur at the earlier stages of pregnancy. This under-reporting might be less pronounced in the first months following ^{131}I exposure due to heightened patient awareness and stricter medical surveillance for such events.

In the study of Schlumberger et al., the relative risk from exposure to more than 3.7 GBq of ^{131}I had 95% confidence interval from 0.2 to 3.18, assuming a normal distribution. This wide range may imply that gonadal doses of approximately 1 Gy from this type of exposure might increase clinically detectable untoward pregnancy outcomes by a factor of two or three (with a risk similar to that calculated for humans after acute exposure) or on the other hand that the risk is significantly lower than those estimates, as might be assumed for a more prolonged exposure. Even larger samples will be needed to assess and exclude the possible biases due to the many confounding factors (*45*).

Therefore, the numbers in this survey, even if considerable, are not yet sufficient to assess the exact level of genetic risk with sufficient precision. Nevertheless, it is remarkable that the last three papers published on this topic all agree substantially upon the fact that the genetic risks after exposure to ^{131}I are low, even following therapeutic doses, as no excess of malformations, stillbirths and early deaths could be measured.

It will be interesting to verify whether these data on genetic risks after maternal ^{131}I exposure could also be extended to the offspring of exposed males. The authors have announced that such a survey is already in progress. The significantly lower incidence of thyroid cancer in males will make the recruitment of an adequate patient population for that group even more challenging than for women. The profound differences between spermatogenesis and oogenesis could imply different levels of risk in the occurrence of mutations and chromosomal imbalance disorders after radiation exposure in females or males (*46*).

A particular effort should be made to calculate absorbed radiation doses, especially in the gonads, in each patient. The model used should be appropriate for athyreotic patients.

It would be useful if those centers with large series of DTC patients could combine their efforts in assessing the late hazards of ^{131}I therapy in the future. To do so, homogenous methodology would have to be used to make results comparable and to increase the statistical power of the data.

CONCLUSION

The nuclear medicine community has the opportunity to provide itself and the scientific community with its own unique data on the biological effects of ionizing radiation. This is not only an important opportunity, but also an important obligation for our discipline.

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Investigations of Breast Tumors with Fluorine-18-Fluorodeoxyglucose and SPECT

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Methods: We designed a prospective study to investigate the feasibility of combined FDG-SPECT and whole-body acquisition in the diagnostic work-up of breast tumors applying visual analysis. We studied 50 patients with breast tumors of unknown histology. **Results:** All malignant diseases were accurately detected in tumors >2.3 cm, while the smallest FDG-positive lesion was 1.4 cm. In a subgroup of these patients, quantitative evaluation (tumor-to-background ratios) was added, which improved the sensitivity. Lymph node metastases were accurately indicated in 9 of 13 patients, while the detection of distant metastases depended on the location and size. False-positive FDG scans were observed in inflamed tissue, in a rapidly growing phylloides tumor and in supposedly healthy breasts. **Conclusion:** These results are comparable with prior investigations of other groups using PET. Therefore, FDG-SPECT and whole-body acquisition may be an adequate and less expensive technique to meet the increasing demand of FDG examinations.

Key Words: fluorodeoxyglucose; breast tumors; SPECT; whole-body acquisition; radionuclide imaging

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Breast cancer is one of the leading malignant diseases of women in the western hemisphere and is the most frequent cause of death from malignant disease in women (*1*). Prognosis depends on early detection of the primary tumor site and worsens after the development of metastases and disease progression (*2*). Standard imaging methods give accurate information in many patients, but there is concern that mammography results in many unnecessary surgeries to obtain needed histological information (*3*). Small lesions and recurrences after surgery often lead to diagnostic problems. Therefore, an imaging method to detect primary and metastatic malignancies and to distinguish between malignant and nonmalignant disease would be useful.

Recently, some efforts were made to use the glucose analog ^{18}F-fluoro-2-deoxy-D-glucose (FDG) for this purpose (*4,5*).

For several decades, tumor cells have been known to exhibit increased glycolytic activity due to a higher energy demand and changes in the intracellular enzymatic profile (*6,7*). FDG is phosphorylated like glucose by intracellular hexokinase and undergoes no further metabolism, a phenomenon which results in vigorous intracellular accumulation (*8,9*). Several experi-