Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I

Thesis to obtain the degree of Doctor in Medical Sciences.

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Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

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List of abbreviations.

β: Beta
γ: Gamma.
ACC: Activity correction coefficient.
ALARA: As low as reasonably achievable.
APUD: Amine precursor uptake and decarboxylation.
BrDU: Bromo-deoxy uridine.
CT: Computed Tomography.
DIT: Di-iodo tyrosin
DNA: Desoxy ribo nucleic acid.
E. coli: Escherichia coli. A common gut bacteria.
EANM: European Association for Nuclear Medicine
ETAC: European thyroid comittee.
ETBD: Equivalent total body dose.
FISH: Fluorescence in situ hybridisation.
GBq: Giga Becquerel.
Gy: Gray.
HBV: Hepatitis B virus.
HCC: Hepato cellular carcinoma
HLCC: Half life correction coefficient.
I: Iodine.
ICRP: International Commission on Radiological Protection.
ICRU: International Commission on Radiological Units.
INSS: International neuroblastoma staging system.
KCl: Potassium chloride.
KeV: Kilo electron volt.
KI: Potassium iodide.
LET: Linear energy transfer.
LiF: Lithium fluoride
MBq: Mega Becquerel.
MCNP: Monte carlo n particle software program.
MEM: Minimal essential medium;
MIBG: Meta-iodo-benzyl-guanidine.
MIRD: Medical Internal Radiation Dosimetry;
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MIT: Mono-iododotyrosin
MN: Micronucleus.
MRI: Magnetic Resonance Imaging.
MSv: Milli Sievert.
MTC: Medullary thyroid carcinoma.
NIS: Sodium/iodide symporter protein
PET: Positron Emission Tomography.
PHA: Phytohaemagglutinin.
PMMA: Perspex.
R: Correlation coefficient.
RNA: Ribo nucleic acide.
ROI: Region of interest.
RPMI: Roswel Park Memorial Institute.
SD: Standard deviation.
T3: Tri-iodothyronin
T4: Thyroxin.
TB: Total body.
TI: Thallium.
TLD: Thermoluminescence dosemeter.
TSH: Thyroid stimulating hormone.
UNSCEAR: United Nations scientific committee on the effects of atomic radiation.
WCP: Whole chromosome probe.
List of included papers.


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1. Introduction.
1.1 Nuclear medicine.

Nuclear medicine is a medical specialty that uses unsealed radioactive materials (radiopharmaceuticals) for diagnosis and treatment of disease. A radiopharmaceutical is a radionuclide linked to a “target seeking” molecule. Radiopharmaceuticals are administered systemically to the patient and are aimed at specific tissues (bones, tumours…) in the body into which they can adhere or incorporate. The radiopharmaceuticals used in nuclear medicine for diagnostic purposes contain radionuclides that emit gamma rays, which can be detected externally by so called “scintigraphy”, providing information about an organ’s function and structure in a non-invasive way.

![Fig. 1.1. Scintigraphic camera.](image)

In positron emission tomography (PET), the radiopharmaceutical is linked to a positron emitter. A positron will anneal with an electron almost immediately after emission to produce annihilation photons of 511 keV emitted over 180°. Images produced in PET are based on the detection of these photons.
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1.2 Radionuclide therapy.

Although nuclear medicine is commonly used for diagnostic purposes, it also has important therapeutic applications. In radionuclide therapy, large quantities of radiopharmaceuticals, which selectively target the tissue under consideration, are administered to the patient in order to treat disease. For therapeutical purposes, the radiopharmaceutical is usually a $\beta$-emitter. The radionuclide mostly used for this kind of therapy is $^{131}$I (radioiodine).

$^{131}$I has been used for radionuclide therapy since 1942. $^{131}$I emits both $\beta$-rays (maximum energy 606 keV), which travel a maximum distance of 3 mm in tissue and thereby ensure local treatment of the tissue under consideration and 364 keV $\gamma$-rays used for imaging of the patient. Its physical half-life of 8 days enables long-term irradiation of the target tissue. Supplemental advantages of $^{131}$I consist of: the low production cost, it’s easy availability and the long-term expertise that has been gathered for this isotope.

There are also some drawbacks to the use of $^{131}$I. Perhaps the most important one is that because $^{131}$I emits high-energy gamma rays (364 keV), the patient represents a radiation hazard to his surroundings i.e. family members and hospital staff. To avoid irradiation of these persons after administration of high activities of $^{131}$I, the patient has to be hospitalised in a so called “isolation room”. This room is specially designed of lead walls to avoid irradiation to bystanders and allows management of radioactive waste produced by the patient by separate waste collection, storage and disposal after complete decay. In conjunction with its long half-life of 8 days, this means that hospitalisation times can be up to 7 days and waste storage to decay takes at least 6 months.

The imaging by Gamma camera is not ideal for $^{131}$I due to the high energy (364 keV) of the gamma rays. Gamma cameras are designed for imaging of radiopharmaceuticals labelled with $^{99m}$Tc, the most used isotope in diagnostic imaging, with a gamma ray energy of only 140 keV.

The third disadvantage of $^{131}$I is that its beta rays have a rather low energy max. 606 keV, which allows a penetration depth in tissue of only 3 mm. Therefore, the isotope needs to be distributed homogeneously throughout the whole tumour to be effective in oncological applications.
1.3 Radionuclide therapies using $^{131}$I-labelled radiopharmaceuticals.

In the following chapter, a brief overview is given of all pathologies included somewhere into the scientific work of this thesis. In each case, the disease is briefly situated, followed by its therapeutic option involving $^{131}$I-labelled radiopharmaceutical. Other treatment options are not discussed, as they do not form part of this work.

1.3.1. $^{131}$I for hyperthyroidism and thyroid cancer.

Since its first use in 1942 (Hertz S. *et al.* 1942), the most important systemic treatment using ionising radiation is radiiodine ($^{131}$I) treatment for hyperthyroidism and thyroid carcinoma. In Belgium about 14,000 patients are treated every year (data from RIZIV Belgium).

1.3.1.1. Normal thyroid function.

![Anterior view of the thyroid](image)

*Fig. 1.2. Anterior view of the thyroid (Eisenberg, 1991)*

The thyroid is the organ responsible for the production of the hormones T3 (triiodothyronine) and T4 (thyroxine). Microscopically, the thyroid is composed of spherical follicles, each composed of a single layer of follicular cells surrounding a lumen filled with colloid (mostly thyroglobulin).

A daily intake of I (under the form of I') is provided for by regular diets, a minimum intake of 50 µg a day is needed to prevent iodine deficiency goitre (Utiger RD. 2002). In Belgium, slight iodine deficiency exists.
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Although it has been known for decades that I$^-$ transport into the thyroid gland is mediated by a specific Na$^+$ dependent I$^-$ symporter (NIS) gene was cloned just in 1996 (Dai et al., 1996). NIS is a transmembrane protein with 13 transmembrane domains, an extracellular amino terminus and an intracellular carboxyl terminus. The structure of NIS is visualised in figure 1.3. NIS co-transportates two Na$^+$ ions along with one I$^-$ ion, with the transmembrane Na$^+$ gradient serving as the driving force for the I$^-$ uptake. The Na$^+$ gradient providing the energy for this transfer, is generated by the Na$^+$/K$^+$ adenosine triphosphatase (Na$^+$/K$^+$- ATP-ase).

![Fig. 1.3. The NIS protein.](image)

After active transport across the basolateral membrane, I$^-$ is translocated across the apical membrane by pendrin to exocytotic vesicles fused with the apical cell membrane. In these vesicles the I$^-$ is rapidly oxidised and covalently bound to a few of the tyrosyl residues along the thyroglobulin backbone. The thyroid hormones T3 and T4 are synthesized by coupling of two iodo-tyrosine residues and stored in the colloid. All of these steps are stimulated through pituitary derived TSH (thyroid stimulating hormone), which interacts with the TSH receptor located on the basolateral membrane of thyroidal cells. To liberate T4 and T3, thyroglobulin is resorbed into the thyroid follicular cells in the form of colloid droplets. The droplets fuse with lysosomes to form phago-lysosomes, in which the thyroglobulin is hydrolysed to T4 and T3. The hormones are then secreted into the extra cellular fluid and enter the circulation.

In addition to its key role in thyroid physiology, NIS-mediated I$^-$ accumulation in the thyroid gland is a crucial prerequisite for diagnostic scintigraphic imaging as well as for the highly efficient radiiodine therapy of benign and malignant thyroid diseases.
1.3.1.2. Thyroid pathologies treated with $^{131}$I.

On the average, up to 5 to 10 % of the population may suffer from thyroid pathologies during their lifetime. (Johnston, 1995), but there are regional differences depending on factors such as presence or absence of iodine deficiency. In this thesis, we will only focus on the pathologies that can be treated with $^{131}$I: hyperthyroidism and thyroid carcinoma.

1.3.1.2.1. Hyperthyroidism.

Hyperthyroidism is a pathology where the cells of the thyroid have escaped the feedback mechanism of thyroid production in the body resulting in an overproduction of thyroid hormone. The cause of these problems can be threefold: Graves’ disease, toxic adenoma and multinodular goitre.

Graves’ disease.
Graves’ disease is the most common cause of hyperthyroidism in children as well as adults. In Europe the disease is found in about 10 to 50 people in 100.000 (Barker and Philips, 1984). The disease is an autoimmune pathology since spontaneous development of “thyroid stimulating immunoglobulins” (TSAb) that mimic TSH action leads to the excessive production and release of thyroid hormones, resulting in hyperthyroidism. The disease is characterised by diffuse goitre, hyperthyroidism and ophthalmopathy.
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**Fig. 1.5.** $^{99m}$Tc-pertechnetate scan of a patient with Graves’ disease.

**Toxic adenoma and multinodular goitre.**
Toxic adenoma and toxic multinodular goitre are common causes of hyperthyroidism, second only to Graves’ disease. 20 to 80 % of toxic adenomas and some nodules of multinodular goitres have somatic mutations of the TSH receptor gene that confers autonomous hyperactivity (Tonacchera et al., 1998).

A classical clinical presentation for toxic adenoma is a hyperthyroid patient with a palpable nodule that corresponds to an area of increased radiiodine concentration on thyroid scintigraphy. There should also be suppression of radioiodine uptake in surrounding and contra lateral tissue.

Toxic multinodular goitre in comparison, typically presents with one or more focal areas of increased radiiodine uptake, which may or may not correspond to palpable nodules; non-functioning “cold” nodules are present in some patients (see figure).

**Fig. 1.6.** $^{99m}$Tc-pertechnetate scan of a patient with multinodular goitre
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### 1.3.1.2.2. Differentiated thyroid carcinoma.

In about 4 to 5 people in 100,000, a thyroid carcinoma will be diagnosed during life. The disease can be treated well so the death rate due to this kind of carcinoma is only 0.5% of all cancer related deaths (Thompson et al., 1978). 85 to 90% of all thyroid carcinoma’s are differentiated thyroid carcinomas: papillary and follicular carcinoma. Since only the differentiated thyroid carcinomas can be treated with $^{131}$I, only these will be discussed further. The thyroid carcinoma cells usually are less capable to incorporate I and produce thyroid hormones than normal thyroid cells. This at least partly due to a reduction in NIS expression (Lazar et al., 1999) as well as a decrease in TSH receptor positive cells (Caillou et al., 1998).

### 1.3.1.3. Therapeutic modalities using $^{131}$I.

#### 1.3.1.3.1. Hyperthyroidism.

The thyroid cannot differentiate between stable I and $^{131}$I, and will therefore incorporate the $^{131}$I in the precursor for thyroid hormone. The short range (<3 mm) β-rays of the iodine will therefore selectively irradiate the over-productive thyroid tissue, curing the hyperthyroid state of the patient and reduce goitre. $^{131}$I (radioiodine) therapy has become the most widely used therapy for patients with Graves’ disease in the United States. It is the least expensive treatment option and is rarely accompanied by acute side effects. A number of dosing regimens have been proposed, ranging from those based on high precision dosimetry and ultrasound-guided volume determination, to large, fixed doses of $^{131}$I intended to cause hypothyroidism soon after treatment. Whatever the protocol, it is now clear that most Graves’ disease patients ultimately become hypothyroid after $^{131}$I treatment. Possible complications include exacerbation of ophtalmopathy, particularly in patients who smoke.

Patients suffering from a toxic adenoma or multinodular goitre on the other hand are usually euthyroid after $^{131}$I treatment, because the radioiodine preferentially accumulates in the hyper functioning nodules.

For the treatment of hyperthyroidism, typical administered activities are 185 - 1110 MBq. This activity is excreted from the thyroid with a mean half-life of about 4-5 days before it is urinary excreted. The advantages of the therapy are: non-invasiveness, easy (oral) administration and little side effects. The therapy result is known after about 3 months (Murray and Ell, 1994), and therapeutic efficiency is high: 57% to 100% (Delgrange et al., 1994). Approximately 10-20% of patients fail the first administration of radioiodine and require a second treatment. These patients typically have severe hyperthyroidism or large goitres.
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In spite of the high administered activities, no significant increase in the incidence of secondary neoplasms has been reported in the literature (Clarke S.1991; Hall P. et al. 1992; Halnan K. E.1992). So far, studies of children with Graves’ disease have not revealed an increased risk of thyroid neoplasia, but as only 1000 children have been included and results were not followed up long term, caution to treat younger patients remains (Moll and Patel, 1997). Other disadvantages of the therapy are the radiation hazard the patient represents for his family and the medical staff, the radioactive waste he produces and the fact that the therapy results are only known after 3 months.

1.3.1.3.2. Thyroid carcinoma.

The unique property of thyroid follicular cells to trap and concentrate $^{131}$I due to expression of NIS allows effective therapy of differentiated thyroid carcinoma and their metastases by administration of radioiodine, thereby improving the prognosis of thyroid cancer patients significantly and making thyroid cancer one of the most manageable cancers. Therapy with $^{131}$I has been successfully used for over 40 years in the treatment strategy of differentiated thyroid cancer. Recurrence rates are significantly higher in patients treated with surgery and TSH suppression by T4 alone than in those who also receive radioiodine treatment. The efficacy of radioiodine therapy is reflected in the low mortality of patients suffering from metastatic thyroid cancer who are treated with $^{131}$I (3%) compared with those who are not (12%) (Mazzaerri EL, 1996).

A standard activity of 3700 MBq to 7400 MBq is usually administered. These high administered activities are necessary, because only a very small part of the $^{131}$I (about 2% of the administered activity) is retained within the thyroid remnant tissue. The rest is eliminated from the body within a few days after administration by urinary excretion.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I

1.3.2. $^{131}$I-MIBG for neuroendocrine tumours.

1.3.2.1. Neuroblastoma.

Neuroblastoma, which is a tumour of the peripheral nervous system arising from the neural crest, is the most common extra cranial solid tumour of childhood and has an incidence of 1/70000 children under the age of 15. (Young and Miller, 1975). Depending on local extension of tumour and on presence of metastases, several stages can be defined in neuroblastoma and an overview figure of all different stages is given below.

![INSS staging of neuroblastoma](image)

**Fig 1.7. (Brodeur et al., 1988)**

INSS (international neuroblastoma staging system) staging of neuroblastoma: Stage 1: localised tumour confined to the area of origin. Stage 2a: unilateral tumour, no lymph node involvement. Stage 2b: unilateral tumour with regional lymph node involvement. Stage 3: tumour and/or lymph node metastases infiltrating across the midline. Stage 4: dissemination of tumour to distant lymph nodes, bone, bone marrow, liver and/or other organs. Stage 4-S: localised primary tumour as defined for stage 1 and 2 with dissemination limited to liver, skin and/or bone marrow.

Analysis of prognostic factors at the time of diagnosis is essential for selecting appropriate therapy. In general, risk groups can be defined by clinical stage of disease, age, N-Myc gene amplification and DNA ploidy of the tumour, histopathology and serum markers at diagnosis. Approximately 60% of children with neuroblastoma are at high risk for developing fatal progressive disease (Reynolds et al., 1990). This group includes patients with stage 4, disease who are diagnosed after one year of age, and patients whose tumours have N-Myc amplification, regardless of stage of disease or age at diagnosis.
1.3.2.1.1. \(^{131}\)I-MIBG therapy.

Neuroblastoma cells actively take up nor-adrenalin via an uptake-1 system. The \(^{131}\)I-marked molecule meta-iodo benzyl guanidine (MIBG) has a similar molecular structure and is taken up and stored in the cell in the same way as nor-adrenalin.

\[
\text{Noradrenalin} \quad \text{MIBG}
\]

\[\text{Fig 1.8. Molecular structures of nor-adrenalin and }^{131}\text{I-MIBG}\]

Since its first scintigraphic use, in 1981 (Sisson et al., 1981), \(^{131}\)I-MIBG has played an important role in the diagnosis and staging of neuroendocrine tumours. With a cumulative sensitivity of 92% and specificity of 100% in 779 patients with neuroblastoma (Hoefnagel et al, 1994), \(^{131}\)I MIBG scintigraphy has established itself as the most sensitive technique for detection, staging and follow-up of this disease. Diagnostic images are nowadays usually made with \(^{123}\)I-labeled MIBG. The purely \(\gamma\)-emitting radionuclide \(^{123}\)I possesses better imaging qualities than \(^{131}\)I with a \(\gamma\)-ray energy of 159 keV as compared to the 364 keV of \(^{131}\)I.

\[\text{Fig 1.9 }^{131}\text{I-MIBG scintigraphy of a stage 4 neuroblastoma patient.}\]
Since 1984, $^{131}$I-MIBG has also been used therapeutically in neuroblastoma (Hoefnagel et al., 1987; Hoefnagel, 1991). In 1991, the cumulative experience in 276 children with neuroblastoma indicated an objective response rate (improvement in disease status, reduction of pain, patient resumes normal life) of 35% (Hoefnagel, 1994; Troncone and Galli, 1991). Most of these patients had, progressive and intensely pre-treated stage 4 disease as they were only treated with $^{131}$I-MIBG after chemotherapy had failed. In addition, $^{131}$I-MIBG provided adequate palliation and improved quality of life for many children. Usually a fixed dose of 3700 to 7400 MBq of $^{131}$I-MIBG is infused intravenously over a 2h to 4h period.

**Fig 1.10. Neuroblastoma patient receiving $^{131}$I-MIBG therapy in an isolation room of the Netherlands Cancer Institute.**

**Fig 1.11. Set-up of $^{131}$I-MIBG infusion system.**
1.3.2.2. Carcinoid tumours.

Carcinoid tumours are the most common occurring gut endocrine tumours. The incidence of carcinoid tumours is estimated to be approximately 1.5 cases per 100000 of the general population. Nonetheless, they account for 13-34% of all tumours of the small bowel and 17-46% of all malignant tumours of the small bowel (Buchanan et al, 1986). They are derived from a totipotent stem cell in the gut wall, capable of differentiating into any one of a variety of cells, which may be responsible for the clinical syndrome. Carcinoids usually appear in the gut, but are also found in the pancreas, the rectum, the ovary, the lungs and elsewhere. The tumours grow slowly and are often clinically silent for many years before becoming manifest, usually when metastases have occurred. They frequently metastasise to the regional lymph nodes, the liver and less common to bone. The age distribution of carcinoids is Gaussian in nature and the peak incidence occurs in the sixth and seventh decade.

1.3.2.2.1 $^{131}$I-MIBG therapy.

Since carcinoids are neuroendocrine tumours, they also selectively take-up MIBG. The first report of $^{131}$I-MIBG imaging of a carcinoid tumour was that of Fisher and co-workers in 1984 in which hepatic metastases, that were seen as photopenic areas on a $^{99m}$Tc-phytate liver scan, concentrated $^{131}$I-MIBG (Fisher et al. 1984). Since this initial description, $^{131}$I-MIBG has been used for successful imaging of carcinoid tumours. Reported results reveal that 70% of carcinoids in 275 patients concentrate this tracer (Hoefnagel, 1994). The overall sensitivity is calculated to be only 55%, because MIBG is taken up by a large variety of neuroendocrine tumours.

For therapeutic use of $^{131}$I-MIBG to treat metastatic carcinoid disease, results were available for 52 patients in 1991, revealing on the one hand an objective response of only 15% but on the other hand palliation, which may be very meaningful and long lasting, in 65% (Hoefnagel, 1991). As for neuroblastoma, usually a fixed dose of 3700 to 7400 MBq of $^{131}$I-MIBG is infused intravenously over a 2h to 4h period.

1.3.2.3. Medullary thyroid carcinoma and pheochromocytoma.

Both Medullary thyroid carcinoma and pheochromocytoma are neoplasms of endocrine organs and are linked together by at least two major considerations. Firstly, the tumours arise from the so called “amine precursor uptake and decarboxylation” (APUD) cells which constitute the diffuse system of neuroendocrine cells distributed throughout the body (Pearse, 1968; Pearse and Polack, 1974). The APUD acronym denotes the capacity of these
cells to synthesize and/or secrete biogenic enzymes formed through activity of the enzyme L-dopa decarboxylase. The second feature linking these particular neoplasms is that they can occur in individual patients as a consequence of autosomal dominant genetically transmitted disorders. Inherited genetic defects affect different groups of APUD cells and lead to neoplastic development of related cell types in diverse anatomic regions (Baylin, 1990).

Medullary thyroid carcinoma (MTC) is an uncommon tumour representing 5-10% of all thyroid cancers. It is a neoplasm of the calcitonin secreting C-cells, which are sparsely distributed in the thyroid gland. The only known etiological factors for occurrence of this neoplasm are the autosomal dominant genetic disorders MEN 2a, MEN 2b and non-MEN syndromes which account for 20 % of patients with MTC. Otherwise, MTC arises as a sporadic tumour, equally distributed among both sexes and different ethnic groups. The peak onset for the sporadic form of MTC is around the age of 50-60, while the tumour represents much earlier in life in the MEN syndromes (Alexander and Norton, 1991).

Pheochromocytoma describes a neoplasm of chromaffin cells found in the adrenal medulla or elsewhere in the sympathetic paraganglionic axis. Pheochromocytomas occur infrequently and are found in approximately 0.1-0.5% of hypertensive patients (Scott and Halter, 1984). 90% of Pheochromocytomas occur sporadic and 10% are associated with familial syndromes MEN2a and MEN2b. Familial Pheochromocytomas typically follow a benign course, but because of their potential for causing significant morbidity and mortality, they must be diagnosed or removed. Only 10% of Pheochromocytomas are malignant and the overall 5-year survival in this case is about 44%.

1.3.2.3.1. $^{131}$I-MIBG therapy.

30-40% of MTC cells concentrate MIBG although the mechanism of uptake is not understood (Troncone et al., 1991). Treatment protocol consists of repeated high activity $^{131}$I-MIBG infusions at 2-8 month intervals. The results of 22 patients treated with $^{131}$I-MIBG are variable. 50-100% of patients derived some kind of relief from the treatment. Response was indicated as symptom palliation, reduced calcitonin secretion or tumour regression. Complete remission is rare, although partial response with disease stabilisation is reported in 30-80% (Hoefnagel et al., 1991).

95% of Pheochromocytomas concentrate MIBG, which can therefore be used for targeted radiotherapy. The $^{131}$I-MIBG retention within the cell is rather low so the treatment has to be
repeated several times in order to have a manifest effect (Shapiro and Fig, 1989). The cause for this insufficient uptake of MIBG by chromaffin neoplasms is not fully understood, but it may be due to the fact that these neoplasms may have a less differentiated amine uptake and storage phenotype compared to benign and normal chromaffin cells. In 1994, results were available for 99 patients and are listed in the table below.

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<td><strong>21</strong></td>
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<td><strong>11</strong></td>
</tr>
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1.3.3. $^{131}$I-lipiodol for hepato cellular carcinoma (HCC).

1.3.3.1. Hepato cellular carcinoma.

HCC has one of the greatest geographical variations of any major cancer. While rare in the US and Western Europe, liver cancer is one of the most common neoplasms in eastern Asia and Sub-Saharan Africa. Due to the large population sizes in these areas, HCC ranges as one of the most common cancers in the world. It is responsible for an estimated one million deaths annually. (London, 1981). The survival time among patients with irresectable HCC is extremely short and may be as low as 1-2 months. (Novell and Hilson, 1994).

Also the peak age incidence has geographical variability. In South Africa the peak incidence occurs between the ages of 35 and 45 years. In Asia the peak occurs ten years later and in the US the peak is ten years later yet (Kew et al., 1984 ). The male/female ratio among cases of HCC is heavily biased towards males with ratios between 4/1 (low incidence area’s) to 9/1 (high incidence area’s). The male preponderance can be explained by a number of factors, including the male bias towards hepatitis B virus carriers, genetic susceptibility, androgenic steroids, and higher body iron stores.

The relationship between chronic hepatitis B virus (HBV) and HCC has been established over more than 30 years: those areas in the world that have high incidences of HCC also have high infection rates of HBV. Epidemiological research in low and moderate incidence areas has shown a relationship between alcohol consumption and HCC (as well as liver cirrhosis).

Fig 1.12. T2-MRI scan of a patient with a 4 cm HCC nodule in the liver and the resected nodule.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I

1.3.3.1. $^{131}$I-lipiodol therapy

Of the approaches available for treating irresectable HCC, much interest is currently focused on the improved results achieved with arterially delivered therapies using iodised oil as a vehicle (Bhattacharya et al., 1994). Lipiodol consists of mono-, di- and tri-iodinated ethyl esters of linoleic, oleic and stearic acids. It naturally contains up to 38% of iodine. In 1979, Nakakuma et al. (Nakakuma et al., 1979) established the selective retention of iodised oil in the foci of HCC, following its injection into the hepatic artery. It is now well established that lipiodol is retained by HCC for periods ranging from several weeks to over a year, while it is cleared from the normal liver parenchyma within 7 days (Ohishi et al., 1985; Okuyasu et al., 1988). Coupling lipiodol with chemotherapeutic agents (such as doxorubicin or cisplatinum) allows in-situ chemotherapy (Takayasu et al., 1987). Intra-arterial infusions of emulsions composed of lipiodol and anticancer agents in combination with gel-foam embolisation (so called “chemo-embolisation” treatments) that stops blood flow to the affected parts of the liver, increased therapeutic efficiency (survival rates of 89% at 6 months and 69% at 1 year (Ohishi et al., 1985), 48% after 6 months (Raoul et al., 1994), but a drastic increase in side effects, due to necrosis of part of the liver, was seen as well.

Internal radiation therapy can be achieved, when some of the iodide present in the lipiodol is substituted by $^{131}$I using a nuclidic exchange reaction. The clinical results of patients treated with $^{131}$I-lipiodol are at least as good as with the chemo-embolisation method; moreover the patients experience less side effects (Raoul et al., 1994, Raoul et al., 1997) since liver necrosis is prevented.

However, $^{131}$I-lipiodol treatments are not only used for palliation. The treatment can be curative when the $^{131}$I-lipiodol is given neo-adjuvant before liver transplantation and/or after resection of hepatocellular carcinoma (Lau et al., 1999). It is believed that the adjuvant administration of $^{131}$I-lipiodol will clear up the micrometastases that form due to HCC cells that are inevitably left in the body after tumour or liver resection.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I

**References to chapter 1.**


Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I


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Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I


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Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

Myriam Monsieurs

2. Aim of the study.
2.1. Introduction.

In Nuclear Medicine, target-finding molecules coupled to a radioisotope (radiopharmaceuticals) are injected into the patient to enable physiological imaging (diagnosis) or therapeutic effects (radionuclide therapy). For radionuclide therapy, high activities (several GBq) of radiopharmaceuticals are administered to the patient in order to have a significant therapeutic effect. Although the injected radiopharmaceuticals mainly target the tissue under treatment, inevitably the rest of the body is also irradiated to some extent. This is partly due to the circulation of the radiopharmaceutical in the body before it is incorporated into the target tissue, or is excreted, and partly by the long-range $\gamma$-rays emitted from the radiopharmaceutical inside the target tissue. Since radionuclide therapies are often repeated several times for the same patient and can be considered as curative in the treatment of some tumours, it is important to determine the radiation dose to the patient as measure of the mutagenic effect of the therapies and the risk for development of fatal cancers. Ideally, bone marrow dose data for a specific patient should be known prior to the planned radionuclide therapy, so the amount of administered activity can be prescribed accordingly.

In this work biological and physical dosimetry methods were used.

A second problem occurring from the long-range $\gamma$-rays emitted from the radiopharmaceutical inside the patient is the radiation hazard they pose for their surroundings, especially their relatives. Based on a revision of the epidemiological data on the incidence of cancer and leukaemia in populations exposed to ionising radiation (UNSCEAR, 1994), EURATOM 96/29 (1996) has recommended reducing the limit for members of the public for exposure to ionising radiation from 5 mSv/yr. to 1 mSv/yr. This recommendation has been included into the Belgian legislation, issued on 31 July 2001. It is therefore necessary to determine what safety measures have to be taken to ensure that the dose to the relatives does not exceed this new dose limit.

In this work the patient dose and the dose to the relatives has been determined for different radionuclide therapies using $^{131}$I-labelled radiopharmaceuticals.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

2.2. Determining the patient effective dose and the dose to specific organs using physical dosimetry methods.

Physical dosimetry methods in nuclear medicine are based on the MIRD (Medical Internal Radiation Dosimetry) formalism:

$$D_T = \sum A_S \cdot S_{(T-S)}$$

Where: $D_T =$ Absorbed dose to target organ $T$

$A_S =$ Cumulated activity in the considered source organ $S$

$S =$ the organ specific $S$ factor: Dose in the target organ per unit of cumulated activity present in the source organ.

The cumulated activity values are determined by means of a set of biplanar scans taken at various intervals after administration of the therapeutic activity.

2.2.1. Can the patient dose after radionuclide therapy be determined before administration of the therapeutic activity?

Since a high total body dose to the patient can cause severe side effects such as long lasting pancytopenia, ideally, dose data for a specific patient should be known prior to the planned radionuclide therapy, so the amount of administered activity can be prescribed accordingly. In the case of $^{131}$I-MIBG therapy, the dose limiting organ is the bone marrow. In practice, the whole body absorbed dose is used as an adequate representation or index of bone marrow toxicity. To predict the whole body dose prior to therapy, one must measure the retention of a tracer dose of MIBG.

Pre-therapeutic MIBG scans can be performed using either $^{123}$I-MIBG or $^{131}$I-MIBG. Since the $^{123}$I-MIBG data reflect predominantly the blood clearance phase while the delayed timing of the $^{131}$I-MIBG scans reflects predominantly the second slower component of clearance, neither type of scan reflects both components. Therefore we decided to combine the" best of both worlds" and use the information of the combination of $^{123}$I-MIBG pre-therapy scans and $^{131}$I-MIBG post therapy scans as the gold standard to determine the total body dose to the patient after $^{131}$I-MIBG therapy. The aim of the present study was to evaluate the feasibility of this combination and to determine how much information about the $^{131}$I-MIBG therapy can be gathered from $^{123}$I-MIBG pre-therapy scans alone.
2.2.2. What are the differences for the absorbed dose to the organs and the effective
dose to the patient between calculations by means of the MCNP® Monte Carlo code
and the MIRDOSE® program?

Although some bio distribution studies have been performed (Raoul et al., 1988; Madsen et
al., 1988; Nakajo et al., 1988), data on patient dosimetry for the $^{131}$I-lipiodol treatment are
scarce. Therefore, the aim of the present study was to determine the effective dose to
patients treated with $^{131}$I-lipiodol.

In order to use the MIRD formalism to calculate the absorbed dose to each organ and the
effective dose to the patient, the “cumulated activity” and the “S-factor” have to be
determined. In this work, the S factors have been determined in two different ways:

- Derived from the MIRDOSE software program, based on phantoms, sex- and age
matched to the patient.
- In a more patient specific way by calculating S factors using the Monte Carlo code
MCNP program. The anatomy of the specific organs can be derived from CT or MRI
images of the patient and is inserted into a sex and age matched phantom of the
patient in the Bodybuilder software program. Using the $^{131}$I emission spectrum, the S-
factors can then be derived for all source and target organs.

The results of the patient specific Monte Carlo calculations were compared to the output of
the MIRDOSE-3® program.

2.3. Determining the mutagenic effects directly after therapy using cytogenetic
dosimetry methods.

In a healthy population, the mutagenic potential of a certain treatment or drug can be
determined by cytogenetic biodosimetry as the in vitro cytokinesis-blocked micronucleus
assay (Ramatilo et al., 1995; Thierens et al., 1995; Thierens et al., 1999). In nuclear
medicine therapy however, biological dosimetry by means of the micronucleus assay has
only been carried out for $^{131}$I-therapy for thyroid carcinoma (Wuttke et al., 1996) and $^{89}$Sr
therapy for palliation of painful bone metastases (Watanabe et al., 1998). For
hyperthyroidism as compared to thyroid carcinoma, a lower activity is administered to the
patient, but the patient is exposed to the radiation for a longer time due to the higher
percentage of $^{131}$I uptake and half-life in the thyroid. For patients treated with $^{131}$I-MIBG and
$^{131}$I-lipiodol, high administered activities are given and the therapy is usually repeated, but no
biological dosimetry data are available.
2.3.1. How do the results of a biological dosimetry method such as the *in vitro* micronucleus assay compare to a physical dosimetry method based on bi-planar scans?

In this work we report the results of studies on biological dosimetry using the *in vitro* micronucleus assay for patients treated with $^{131}$I and $^{131}$I-MIBG. For $^{131}$I treated hyperthyroidism patients, results were compared to thyroid carcinoma patients. From the increase in micronuclei, the ETBD was calculated and correlated to the administered activity and the activity retained in the thyroid. For patients treated with $^{131}$I-MIBG, the comparison was made between the ETBD determined by the micronucleus assay and the results of a purely physical dosimetry method based on the MIRD formalism. The obtained results can be interpreted within the framework of cancer mortality assessment for radionuclide therapies.

2.3.2. What is the effect of multiple radionuclide therapies on the micronucleus yield?

In this study, 6 patients treated with multiple $^{131}$I-MIBG therapies (4 patients had 2 subsequent therapies while one patient had as many as 5 subsequent therapies) and 1 patient treated with 3 subsequent $^{131}$I-lipiodol therapies were followed over time. For each therapy, the micronucleus yield was determined in a blood sample taken before the therapy and 1 week after administration of the activity. The obtained micronucleus yield in each blood sample was plotted versus time and from these results the mean lymphocyte half-life was calculated.

2.3.3. What is the residual damage after radionuclide therapy one year after treatment?

Stable chromosome aberrations have a very long half-life and are therefore better indicators of the mutagenic potential at long term. Therefore, we investigated the incidence of translocations induced by $^{131}$I therapy in hyperthyroidism patients one year after the administration of the radiolabeled compound. Tricolour FISH with chromosome 2, 4 and 8 whole chromosome probes was used for the scoring of the translocations. From the genomic translocation frequencies, whole body doses were calculated based on the *in vitro* dose response.
2.3.4. Can $^{131}$I treatment be considered as an *in vivo* conditioning dose leading to an *in vivo* adaptive response?

No statistically significant increase in leukemia or solid tumors has been reported in the literature (Clarke, 1991; Hall et al., 1992; Huysmans et al., 1996) after $^{131}$I-therapy for thyroid disease, in spite of the therapy’s frequent use since 1942. The risk for late detrimental effects after $^{131}$I therapy is estimated to be less than 1% over lifetime (Hall et al., 1992; Huysmans et al., 1996; M’Kacher et al., 1996; Watanabe et al., 1998). Exposure to low levels of ionizing radiation (conditioning dose) can stimulate the DNA repair system, resulting in less genetic damage after subsequent high levels of ionizing radiation (challenge dose). This phenomenon has been called adaptive response because it is similar to the induced repair described in *E. Coli* (Samson and Cairns, 1977). The existence of an *in vivo* adaptive response in humans is a possible explanation for the fact that the incidence of cancer in some populations exposed occupationally is lower than expected as suggested by the results of some epidemiological studies recently reviewed by Pollycove (1995) and Van Wijngaerden and Pauwels (1995).

Therefore the aim of this study was to assess whether or not an adaptive response *in vivo* could be observed in peripheral blood lymphocytes of patients treated with $^{131}$I for thyroid disease.

2.3.5. Are there specific problems for biodosimetry of cancer patients?

In a healthy population, the mutagenic potential of a certain treatment or drug can be determined by cytogenetic techniques, such as the *in vitro* cytokinesis-blocked micronucleus assay (Rimalho et al., 1987; Thierens et al., 1995; Thierens et al., 1999). For patients treated with $^{131}$I-MIBG and $^{131}$I-lipiodol, the effect of the malignant disease status and previous treatments on the feasibility of cytogenetic biodosimetry were investigated. For $^{131}$I-MIBG treated patients, the *in vitro* dose response relationship was compared to the response of a control population (Thierens et al., 2001).
2.4. Determining the radiation burden to relatives of patients treated with $^{131}$I.

Based on a revision of the epidemiological data on the incidence of cancer and leukaemia in populations exposed to ionising radiation (UNSCEAR, 1994), EURATOM-29 (1996) has recommended to reduce the limit for members of the public for exposure to ionising radiation from 5 mSv/y to 1 mSv/y. Due to the high activities administered to patients treated with $^{131}$I and the high energy (364 keV) $\gamma$-radiation emitted from the patient, it may be difficult for the relatives of these patients to comply with this new dose limit. In Belgium about 14000 patients are treated with radioactive iodine every year (RIZIV, 2003).

The practical consequences of the EURATOM-29 (1996) regulations, should be investigated by studies measuring the real-life radiation burden of family members of patients treated with $^{131}$I for thyroid disease (O'Doherty et al., 1993). However, because of logistic or practical problems, most studies published so far, are based on dose rate measurements of $^{131}$I-treated patients upon leaving the hospital and extrapolations of time spent at varying distances to the patient (Mountford PJ, 1987; Culver and Dworkin, 1992; O'Doherty et al., 1993; Wasserman and Klopper, 1993; Mountford and O'Doherty, 1994; Weber and Castronovo, 1996; Demir et al., 1996; Zanzonico et al., 1997; Guanasekera et al., 1997). The major drawback in these studies is the use of occupancy models for calculation of the doses, which may be inaccurate (Greaves et al., 1996). A number of studies measuring the “real life” radiation burden to family members using film badges, TLD dosimeters or digital dosimeters have been carried out (Harbert and Wells, 1974; Barrington et al., 1993; Thomson et al., 1993a; Thomson et al., 1993b; Barrington et al., 1995; Monsieurs et al., 1996; Mathieu et al., 1996; Barrington et al., 1997. Mathieu et al., 1997). But most of these studies report results on small groups of patients and each individual study uses a separate set of guidelines.

2.4.1 What is the radiation burden of relatives of patients treated with $^{131}$I for thyroid diseases when implementing different sets of guidelines?

We report the results of a multicentre study, carried out in 8 centres of Flanders (Belgium), where a total of 65 $^{131}$I-treated patients and 94 of their relatives were monitored up to 14 days after the patient returned home, using wrist TLD measurements. Each participating centre advised its own routine guidelines to their patients. The real-life radiation burden of the patient’s relatives, measured under different sets of guidelines, is compared to the EURATOM-29 (1996) dose limit. Conclusions are drawn regarding the guidelines for patients treated with $^{131}$I.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

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Aim of the study 2.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

Myriam Monsieurs

3.1. Cytogenetic dosimetry methods.

3.1.1. Introduction.

When ionising radiation passes through matter, it ejects electrons from this matter leaving positively charged ions. In cytogenetics, the matter under consideration is the DNA of the cell nucleus. The induced damage to the DNA can either be repaired, resulting in an apparently normal DNA strand, be misrepaired to form a DNA exchange or remain unrepaired, resulting in a break in the DNA strand.

The DNA damage will increase with increasing dose (since more molecules can be hit). Also the LET (linear energy transfer) of the radiation will determine the biological effect of the radiation. The higher the LET, the more interactions will arise with the DNA strands for the same distance travelled and the more damage will be inflicted upon the DNA.

The aberrations scored in the lymphocytes are interpreted in terms of absorbed dose by reference to a dose response calibration curve. This curve is produced by in vitro exposure of blood to well known doses of ionising radiation.

The dose response relationship for low LET radiation (as studied in this work) has a linear quadratic shape (fig. 3.1):

\[
\text{Number of aberrations} = \alpha D^2 + \beta D + \gamma
\]

Where D = dose.

For low LET radiation, low doses do not create many aberrations, as mostly single strand DNA breaks will be inflicted that can be repaired quite easily. The higher the radiation dose becomes however, the higher the chance of double strand breaks (resulting form multiple single strand DNA breaks) that are more difficult to repair and therefore lead to aberrations.

For high LET radiation, the number of interactions with matter over a short distance is so high that even for a low dose, double strand breaks will be inflicted upon the DNA. Therefore the dose to aberrations relationship has a linear shape (fig. 3.1):

\[
\text{Number of aberrations} = \alpha D + \gamma
\]

Where D = dose.
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In cytogenetics, the aberrations are scored in peripheral blood T-lymphocytes. The dose value obtained by referring a measured yield of aberrations to a calibration curve represents an averaged absorbed dose to the lymphocytes. This approximates to an averaged whole body dose because lymphocytes are widely distributed over the body (both in the peripheral blood and in the organs) and migrate. Thus, with the lymphocyte test system, the observed chromosome aberrations are induced in lymphocytes in the peripheral blood itself and in lymphocytes distributed in different organs throughout the body (Bogen, 1993). Most of the peripheral T lymphocytes are in the “resting” stage of the cell cycle (G₀) while chromosomal aberrations can be observed in DNA at metaphase, thus during cell division. It is therefore necessary to stimulate the lymphocytes to divide. The lymphocytes can be initiated to undergo \textit{in vitro} mitosis by the introduction of phytohaemagglutinin (PHA), a protein derived from the bean plant \textit{Phaseolus vulgaris} (Nowell, 1960).

\textbf{Fig 3.1. Dose response curve}

In cytogenetics, the aberrations are scored in peripheral blood T-lymphocytes. The dose value obtained by referring a measured yield of aberrations to a calibration curve represents an averaged absorbed dose to the lymphocytes. This approximates to an averaged whole body dose because lymphocytes are widely distributed over the body (both in the peripheral blood and in the organs) and migrate. Thus, with the lymphocyte test system, the observed chromosome aberrations are induced in lymphocytes in the peripheral blood itself and in lymphocytes distributed in different organs throughout the body (Bogen, 1993). Most of the peripheral T lymphocytes are in the “resting” stage of the cell cycle (G₀) while chromosomal aberrations can be observed in DNA at metaphase, thus during cell division. It is therefore necessary to stimulate the lymphocytes to divide. The lymphocytes can be initiated to undergo \textit{in vitro} mitosis by the introduction of phytohaemagglutinin (PHA), a protein derived from the bean plant \textit{Phaseolus vulgaris} (Nowell, 1960).
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3.1.2. *In vitro* micronucleus assay on peripheral blood lymphocytes.

3.1.2.1. Short description of the method.

Micronuclei (fig. 3.2) are small, round cytoplasmic bodies containing chromatin. They originate when radiation or chemicals disrupt the DNA and chromosome fragments fail to incorporate in the nucleus during subsequent cellular division.

![Fig. 3.2. Binucleated cell containing micronuclei](image)

To understand how micronuclei are formed, one has to know how normal cell division takes place. The process is visualised in figure 3.3.

First the cell will double the existing amount of DNA, so all DNA is copied (1). The chromatin condenses into the well known shape of chromosomes (2), the nuclear membrane dissolves and the copies are arranged in the midplane of the cell. A “spindle” is formed linking the centromere of each chromosome to one of the cell poles (3) and the chromosomes are drawn to the poles of the cell (4). Around both groups of chromosomes a nuclear membrane is formed so we essentially have a “binucleated” cell at this stage (5). The chromosomes start to decondense and finally the cytoplasm of the cells divides to form two new cells (6).

When radiation has led to DNA breakage, the chromosome fragment will not be included into the spindle formation and is left behind. In the binuclear state of cell division, these fragments can be seen as small nuclei or “micronuclei” as can be seen in figure 3.4.
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Fig 3.3. Normal cell division

Fig 3.4. Cell division after DNA damage due to ionising radiation with formation of a micronucleus

In order to block the cell cycle in the binuclear state to allow scoring of the micronuclei, Cytochalasin B is added to the culture medium as described by Fenech and Morley (1985). The dose dependent induction of micronuclei in lymphocytes has been well characterised after exposure to various kinds of radiation (Fenech and Morley, 1985; Prosser et al., 1988; Gantenberg et al., 1991; Huber et al., 1992; Thierens et al., 1992; Huber et al, 1994; Vral et al., 1994; Wuttke et al., 1994). A good agreement between in vitro and in vivo induced micronucleus frequencies was obtained after total-body irradiation and partial body irradiation (Thierens et al., 1995), indicating that micronuclei in lymphocytes are a reliable non-invasive tool to estimate radiation damage for purposes of biological dosimetry.
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### 3.1.2.1. General study protocol.

Details of the exact study protocol can be found in the papers of chapter 4. In general, for each patient two blood samples were taken. The first was taken immediately before administration of the therapeutic activity, the second 7 days post-administration. These time points were taken since they corresponded with scheduled check-ups for the patient and the normal blood sampling routine.

For patients treated with $^{131}$I and $^{131}$I-MIBG, the first blood sample was divided in three fractions to determine an individual *in vitro* dose-response curve. Since the scoring of the micronucleus yield was done manually and requires at least 1000 binucleated cells to be scored per blood sample in order to gain statistical significance, only three dose points could be taken. In this way results could be reached within a reasonable time frame for all patients.

![Fig. 3.5. Study protocol for biodosimetry based on the *in vitro* micronucleus assay.](image)

For patients treated with $^{131}$I-lipiodol the first blood sample was not irradiated *in vitro* due to the expected cell culture problems related to the hypersplenism. For this patient the dose-response relationship determined by Thierens et al. (1999) was used:

$$Y_{MN} = (23.3 \pm 6.6) + (81.1 \pm 0.3)D + (19.5 \pm 0.5)D^2$$

Where: $Y_{MN}$ = micronucleus yield after therapy  

$$D = \text{Dose (Gy)}$$
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Using the individual or general dose response curve, the equivalent total body dose (ETBD) was derived from the increase in micronucleus yield between the blood sample before and after therapy. The ETBD is the dose of ionising radiation, which, if received homogeneously by the whole body would produce the same increase in micronucleus yield as observed after radionuclide therapy.

3.1.2.3. Adaptive response

The in vitro micronucleus assay can also be used for another purpose: the search for the in vivo existence of an "adaptive response". Exposure to low levels of ionizing radiation ("conditioning dose") can stimulate the DNA repair system in certain individuals, resulting in less genetic damage after subsequent high levels of ionizing radiation ("challenge dose"). This phenomenon has been called adaptive response because it is similar to the induced repair described in E. Coli (Samson and Cairns, 1977). An “adaptive response” differs from “natural selection” in that it is not related to the selection of cells that are already better suited to withstand the genetic damage inflicted by a mutagen, but that it involves active biochemical changes inside the cell after the “conditioning dose” of the mutagen has been distributed. These biochemical changes do not consist of a mere up-regulation of proteins involved in DNA repair, but in de novo synthesis of DNA repair proteins as was determined by Weichselbaum et al. (Weichselbaum et al., 1991).

To investigate the existence of an in vivo adaptive response, only a slight change in the micronucleus protocol was necessary. In this case, also the second blood sample (after therapy) was divided into three fractions and irradiated in vitro with the same protocol as the blood sample before therapy, as is visualized in figure 3.6.
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The increase in micronucleus yield after *in vitro* irradiation of the blood samples taken before and after $^{131}$I therapy was compared. An adaptive response exists when the increase in micronucleus yield *in vitro* is significantly less in the blood sample taken after therapy than the increase in the blood sample taken before therapy.

### 3.1.3. Scoring translocations in peripheral blood lymphocytes.

#### 3.1.3.1. Short description of the method.

There are several chromosome aberrations that can be formed after DNA damage by ionising radiation. Chromosome aberrations that allow for all DNA to be passed through to the next generation of cells are called “stable”. When acentric fragments are formed, these aberrations are called “unstable”, since they can not be incorporated into the daughter cells that will consequently miss pieces of genetic information and are therefore not viable.

The most common unstable chromosome aberrations are dicentrics (fig. 3.7). Dicentrics are formed when two centromere containing DNA fragments are linked. Another unstable chromosome aberration is a ring chromosome (fig. 3.8), formed when two parts of the same chromosome containing a centromere are linked. In both cases the other chromosome fragments recombine into an acentric fragment.
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The only stable aberrations are translocations (fig. 3.9). Translocations are formed when a centric and an acentric chromosome fragment combine, forming a “longer” and a “shorter” chromosome. The daughter cell still contains all information (although some genetic information is now moved to another place).

In order to study long term DNA genotoxic effects, the micronucleus assay is not appropriate since micronuclei are essentially unstable chromosome aberrations and will slowly disappear with time after irradiation. On the other hand, a lot of data indicate that translocations are an efficient tool to study the long term DNA genotoxic effects after irradiation (Lucas et al., 1996; Snigiryova et al., 1997; Lindholm et al., 1998). Therefore, translocations were studied in order to investigate long term effects of radio-iodine treatment on thyrotoxicosis patients.

Translocations are scored by staining different chromosomes with different fluorescent DNA probes (harlequin staining). A translocation is then visualised as a monocentric chromosome with more than one colour (fig 3.10). The technique used is called FISH, short for “fluorescent in situ hybridisation”.
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3.1.3.2. General study protocol

Blood samples were taken immediately before therapy and at about one year after therapy, when the patient reported to the endocrinologist for his scheduled check-up. Blood cultures and FISH analysis were performed by V. Lambert of the “Laboratoire ORME” of the University of Liege (Belgium). Harlequin staining with whole chromosome probes for chromosomes 2, 4 and 8 was used. The frequencies of translocations for the painted chromosomes were extrapolated for a frequency for the whole genome using the formula of Lucas et al. (1999):

$$F_p = 2.05 (f_{p2} (1-f_{p2}) + (f_{p4} (1-f_{p4}) + f_{p8} (1-f_{p8})) - f_{p2} f_{p4} - f_{p2} f_{p8} - f_{p4} f_{p8}) F_G$$

$$F_p = \text{frequency of translocations for the 3 chromosomes}$$

$$f_{px} = \text{length of each individual chromosome relative to the whole genome.}$$

The equivalent total body dose was determined from the observed $F_G$ using a previously determined in vitro calibration curve (Thierens et al., 1999):

$$F_G = (0.050\pm0.013)D^2 + (0.031\pm0.004)D + (0.02\pm0.007)$$

Where: $D = \text{dose (Gy)}$

A detailed description of the method used can be found in chapter 4.
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### 3.2. Physical dosimetry methods.

#### 3.2.1. **Patient dosimetry based on bi-planar total body scans and the MIRD formalism.**

##### 3.2.1.1. Short description of the method.

In physical dosimetry using the Medical Internal Radiation Dose (MIRD) principle, the body is considered as a collection of organs and tissues that homogeneously contain a radionuclide ("source organs") and other organs ("target organs") that do not contain any activity themselves, but are irradiated by radiation emitted from inside source organs. So irradiation from source organs can deliver dose to target organs. Target and source organs can be the same. Some examples of source and target organs depending on the radiopharmaceutical are given in the figure below (fig. 3.11).

![Fig. 3.11. Examples of source and target organs depending on the administered radiopharmaceutical](image)

The “total body dose” is determined by considering the whole body as source and target organ. When the “effective dose” to the total body needs to be calculated, the body is divided into different source and target organs and the effective total body dose is than calculated as a weighted sum of the absorbed doses for all organs inside the body. These weighting factors take into account the radiosensitivity of the organs with respect to late effects.
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3.2.1.1. **Cumulated activity.**

In order to calculate the dose in a target organ, one first has to know the cumulated activity inside the source organ. The cumulated activity is the time integrated activity inside the source organ from the time it entered the source organ until the activity can be neglected. The amount of activity in any organ depends on the time after administration. Activity is usually taken up from the blood and decreases partly by physical decay inside the organ (physical half-life) and partly by biological excretion from the organ (biological half-life). In practice, ROIs (regions of interest) are drawn around the relevant structures visualized on the scan, and the amount of activity inside each ROI is calculated. The evolution of the activity in the organ can be visualized when several sequential scintigrams are taken from the patient.

![Diagram of cumulated activity](image)

*Fig. 3.12. Determination of cumulated activity*
Attenuation correction.

When simply comparing the number of counts on the gamma camera from a known activity in a ROI to the number of counts from inside an organ, the activity inside the organ measured in this way is usually too low. Simply put: the more tissue along the route of the radiation, the more radiation is lost along the way. This process is called attenuation. Nowadays, attenuation correction is usually done by measuring an “attenuation map” of the patient, by putting a moving point- or line source or a steady flood source under the patient and measuring the percentage of radiation penetrating through the patient’s body. The map constructed in this way is then applied to correct the activity measurement of the actual patient scan. In order to do so, either the gamma camera has to be capable of measuring two different radionuclide energies at the same time (dual isotope scanning) or it is necessary to make two subsequent scans of the patient. The first scan (transmission scan) is of the patient with the flood source placed underneath, the second scan (emission scan) is taken in the exact same position with the radiopharmaceutical of interest injected into the patient. In this way, the imaging time is of course much longer.

Since the camera used in our studies (GE Elscint) can not measure two different energies at the same time, dual isotope scanning was not possible for our patients. We also could not to take a transmission scan of the patients, since most of our patients were children. It was hard enough to keep them from moving for the duration of one scan, let alone two.

We therefore had to resort to a simpler method, using a homogeneous correction factor for the whole body, based on the patient equivalent thickness of perspex. Attenuation correction curves giving correction factors for the measured activities of $^{123}$I and $^{131}$I were determined experimentally in Perspex phantoms with increasing thickness with a syringe containing a known activity of $^{123}$I (respectively $^{131}$I) in the middle, on the GE Helix camera. In figure 3.13 the correction factor versus the Perspex equivalent patient thickness relative to the standard phantom of 6 cm thickness is shown.

The purpose of correlating everything to the 6 cm Perspex phantom is that the measured activity in the scans can be corrected for using the same correction factor since the attenuation of the patient remains the same for all subsequent scans.
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The activity inside the organ at each point in time is plotted, and the best fitting curve is drawn through the data. When the uptake of activity in the organ is instantaneous, the curve can usually be represented by a sum of two exponentials: a "bi-exponential" best fitting curve. The cumulated activity is calculated by time integrating this curve.

### 3.2.1.1.2. S factors and dose calculation.

The next step is to determine what the dose in the target organ will be per unit of cumulated activity emitted from the source organ. The result is given as Gy/MBq.s, the so called “S-factor”. The kind of radiation and its energy will determine how far the radiation will penetrate into the tissue e.g. for $^{131}$I, the β-rays can only penetrate 3 mm of tissue and will therefore not contribute significantly to the dose to most organs other than the source organ, while the 364 keV γ-rays will irradiate all other organs and therefore contribute to their dose. The emission spectrum of each radionuclide can be found in ICRP tables (ICRP report 38).

The distance between organs depends upon the age and gender of the patient. The MIRD Committee has developed several age and gender specific phantoms determined as “standard” humans. For all phantoms the S-factors have been determined by Monte Carlo simulations and are tabulated for common radionuclides used in nuclear medicine.
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The dose to each organ can be determined by simply multiplying the cumulated activity of the source organ with the specific S factor between source and target organ, and is then summed over all source organs. The dose to the total body is the sum of all absorbed organ doses. The MIRD formalism can therefore be described as follows:

\[ D_{\text{org } n} = \sum_{m} \tilde{A}_{\text{org } m} \cdot S_{\text{org } n\rightarrow \text{org } m} \]

Where: \( \tilde{A}_{\text{org } m} = \) cumulated activity in the considered source organ m
\( S_{\text{org } n\rightarrow \text{org } m} = \) The specific S factor for radiation from organ m to organ n,

In this work, the doses have been obtained using two different methods:

**The MIRDOSE-3® software package.**
MIRDOSE-3® (Stabin MG., 1996) is a commercially available software program and holds a number of gender and age specific phantoms (with standard organs) and a number of listed S-factors for different radionuclides. Calculations are therefore always for the phantom that comes closest to the anatomy of the patient, but are never patient specific.

It is possible to calculate selfdose to the tumour using the “nodule module”. The tumour is then modelled as a sphere of specific diameter (several available in the program) and the S factor can be inserted (after calculation) or taken from the program depending on discrete intervals of the diameter of the nodule chosen. It is not possible to calculate dose from this nodule to other organs or dose to the nodule from other organs.

**MCNP-4B® calculations on a modified Bodybuilder® phantom.**
This method could only be used for the patients treated with $^{131}$I-lipiodol since CT or MRI scans were not always available for the $^{131}$I-MIBG treated patients.

The Bodybuilder® (J. Briessmeister, 1997) software program lists a variety of gender and age specific phantoms including organs that can be adapted in size and shape. For each patient, in the best fitting phantom volume and location of the liver and of the tumour within the liver were modelled according to patient’s CT or MRI scans.

Using the MCNP-4B® (Monte Carlo n Particle version 4B) (J. Briessmeister, 1997) software, organ specific S factors (“absorbed dose” in Gy/MBq,s) were derived for each organ. Estimated relative errors of the calculated S factors were less than 1%. The organ doses were then calculated using the MIRD formula.
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To calculate the effective dose, all organ contributions were summed according to their weighting factors as determined in the ICRP publication number 60 (ICRP, 1990). By this method it is possible to use patient specific S factors for the liver and tumour, and to calculate dose to the tumour from all other organs (mainly the liver) and dose from the tumour to all other organs (mainly the liver).

3.2.1.2. General study protocol:

A detailed description of each protocol can be found in chapter 4.

3.2.1.2.1. Total body scans.

In our studies, the cumulated activity was always derived from a set of 180° bi-planar total body scans on a GE Helix camera. In each scan, along with the patient a syringe, containing a known activity of the radionuclide administered to the patient, in a 6 cm Perspex phantom was scanned to allow calculation of the activity.

On the Helix XPERT® system (GE) or the HERMES® software system (Nuclear Diagnostics, Sweden), conformal regions of interest (ROIs) were drawn by eye around the organs of interest and the syringe, along with suitable background regions. The activity in each ROI was determined by comparing to the known activity in the syringe taking into account the attenuation correction described above. Every scan was evaluated three times and the mean activity calculated from these evaluations was used. In all cases the SD/mean was less than 5%. Using this methodology, the mean error in calculated activity in phantom studies was 18 % (SD: 4%)

Since we did not have CT or MRI scans for the $^{131}$I-MIBG treated patients, attenuation correction had to be carried out for the whole body as a whole.
Since the first $^{123}$I-MIBG scan was taken immediately after administration of the $^{123}$I-MIBG, the total activity in the body is known. However, due to attenuation in the patient’s body, the activity measured from the scan is lower than the administered activity and should be corrected for using the following correction factor:
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

$$F_{123I} = \frac{A_{\text{actual}}}{A_{\text{measured}}}$$

Where: $A_{\text{actual}}$ = the decay corrected administered activity.

$A_{\text{measured}}$ = the activity determined by comparing to the activity in the syringe.

From this correction factor, the patient equivalent Perspex thickness can be found figure 3.13. For the $^{131}$I-MIBG post-therapy scans, the $^{131}$I attenuation correction factor corresponding to the patient equivalent Perspex thickness determined above, can also be found in figure 3.13. The total body activity, corrected for attenuation was plotted versus time. Best fitting curves to the data sets were applied in 3 different ways:

1) For the post-therapy $^{131}$I-MIBG scans, a single exponential best fit was drawn through the 3 obtained data points.
2) For the pre-therapy $^{123}$I-MIBG scans, the $^{123}$I-MIBG data were first corrected for the difference in half-life and administered activity between $^{123}$I-MIBG and $^{131}$I-MIBG, following the detailed description in chapter 4. A single exponential best fit was then drawn through the obtained corrected data points.
3) By combining the corrected pre-therapy $^{123}$I-MIBG data points (0h–24h) and $^{131}$I-MIBG data points (2-10 days) a bi-exponential best fit was drawn through the resulting 6 data points using SPSS.

For patients treated with $^{131}$I-lipiodol, the thickness of the patient’s trunk, as determined by his CT or MRI scan, was converted into the equivalent thickness of Perspex. The activity inside liver and tumour were than corrected for, using the obtained attenuation correction factor of figure 3.13.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}\text{I}$.

3.2.2. Dosimetry of relatives based on TLD dosimetry.

3.2.2.1. Short description of the method:

In our study, thermoluminescent dosemeter (TLD) measurements were used to measure the radiation burden to relatives of patients treated with $^{131}\text{I}$. The study was carried out in 8 centers of Flanders. Each participating center advised its own routine guidelines to their patients. The real-life radiation burden of the patient’s relatives, measured under these different sets of guidelines, is compared to the EURATOM-29 (1996) doselimit.

In order to facilitate comparison between results of centers using different sets of guidelines, the guidelines of the 8 participating centers were divided in 3 categories according to the difference of the duration each centre advised the patient to sleep separately.

The principle of a thermoluminescent (TLD) crystal is based upon delayed fluorescence. Within a crystal, electrons can exist in only two energy states: low energy (valence band), which is a stable state, and high energy (conduction band), which is an unstable state. Between both energy levels there is a band of “forbidden” energy levels, which means that the electrons cannot exist in these energy states.

By the introduction of small impurities into the crystal, so called “trapping” energy levels will be introduced into the “forbidden” band in which the electron energy can exist in a semi stable way.

![Fig 3.14. Principle of a TLD crystal](image)

When the electrons from the valence band interact with ionising radiation, they will absorb energy and rise to the conduction band levels. Since this is an unstable state, the electrons will quickly try to dissipate energy and fall back to the stable valence band levels or to the semi
stable trapping levels. The semi stable state means that when a small amount of energy is introduced to the irradiated crystal (eg. by heating the crystal), the electrons in the trapping energy levels will absorb this energy and are able to fall back completely to the stable valence band energy level, thereby dissipating the excess energy in the form of visible light. The more radiation hits the crystal, the more electrons populate the trapping levels, and therefore while heating the crystal in a glow plate, the more light flashes can be detected. When TLD crystals (usually LiF with Ti impurities) are irradiated and afterwards heated in a standardised way in an instrument containing a photo electric cell (the “reader”), the light intensity seen at different temperatures can be converted into the dose received by the crystal. The level of accuracy of the dose determination can be up to 2.5 %.

3.2.2.2. General study protocol:

The dose received by the patient’s relatives was measured by thermoluminescent dosimeters (TLD 100).

Relatives were given two TLD’s to be worn sequentially during one week each on the wrist. This was done in order to enhance co-operation and because sequential data were preferred. In addition, some TLD dosimeters were located on the patient’s bedside table in order to measure the dose their partner would receive during the night if they had been sleeping together. To validate guidelines, the data on doses received by the in-living relatives were split-up for discussion according to the patient’s diagnosis (thyroid carcinoma or thyrotoxicosis), the treatment regimen (hospitalised or ambulatory) and the relative’s relationship to the patient (partner, child or parent).

A detailed description of the method used can be found in chapter 4.
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References to chapter 3.


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4. Results.
4.1. Determining the patient effective dose and the dose to specific organs using physical dosimetry methods.


PATIENT DOSIMETRY FOR $^{131}$I-MIBG THERAPY FOR NEUROENDOCRINE TUMORS BASED ON $^{123}$I-MIBG SCANS.

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Patient dosimetry for $^{131}$I-MIBG therapy for neuroendocrine tumours based on $^{123}$I-MIBG scans

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Abstract. Pre-therapeutic metaiodobenzylguanidine (MIBG) scans can be performed using labelling with either iodine-123 or iodine-131. $^{123}$I-MIBG scans provide better image quality and count statistics, while $^{131}$I-MIBG allows registration of tracer kinetics over a longer period. The aim of this study was to determine how much information about the $^{131}$I-MIBG therapy total body dose according to the MIRD formalism can be gathered from $^{123}$I-MIBG pre-therapy scans. Thirty-eight $^{131}$I-MIBG therapies administered to a total of 15 patients suffering from neuroblastoma ($n=6$), carcinoid tumours ($n=5$), phaeochromocytoma ($n=3$) and medullary thyroid carcinoma ($n=1$) were included. The mean administered activity was 5.3 GBq (SD 2.4 GBq). Three biplanar $^{123}$I-MIBG total body scans were taken only once before a series of therapies while three biplanar $^{131}$I-MIBG scans were taken after each therapy. Attenuation correction was performed taking into account the difference in attenuation between $^{123}$I and $^{131}$I. Using the MIRD formalism, the total body dose to the patient was calculated on the basis of: (1) a single exponential fit drawn through the data from the $^{123}$I-MIBG pre-therapy scans, (2) a bi-exponential fit through the combined data of $^{123}$I-MIBG pre-therapy and $^{131}$I-MIBG post-therapy scans. The mean total body dose calculated in our study was significantly higher for patients suffering from neuroblastoma (mean±SD 0.37±0.21 mGy/MBq) than for patients suffering from phaeochromocytoma (0.08±0.02 mGy/MBq), carcinoid tumours (0.07±0.01 mGy/MBq) and medullary thyroid carcinoma (0.09 mGy/MBq). The correlation coefficient between the dose calculated on the basis of the $^{123}$I-MIBG pre-therapy scans and the subsequent $^{131}$I-MIBG therapy was 0.93 when a correction factor of 1.26 was taken into account. When considering all following therapies, the correlation was 0.85 and the correction factor, 1.20. Our results show that it is feasible to use data from pre-therapy $^{123}$I-MIBG scans to calculate the total body dose of the subsequent $^{131}$I-MIBG therapy.

Keywords: $^{131}$I-MIBG – $^{123}$I-MIBG – Dosimetry – $^{131}$I-MIBG therapy

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Introduction

Since 1984, iodine-131 metaiodobenzylguanidine ($^{131}$MIBG) has been used therapeutically in neuroblastoma [1, 2]. The cumulative experience in 276 children with neuroblastoma, published in 1991, indicated an objective response rate of 35% [3, 4]. Also in that year, results in 52 patients with metastatic carcinoid disease revealed an objective response rate of only 15% but on the other hand showed that palliation was obtained in 65% and was sometimes very significant and long lasting [1]. In 1997, Loh et al. [5] reviewed 116 phaeochromocytoma patients treated with $^{131}$I-MIBG. Their results showed an overall response rate of 30% in the three mixed patient groups, and toxicity was found to be much lower than after chemotherapy.

As $^{131}$I-MIBG therapy is not exclusively used for palliation but can also have a curative effect and as the therapy is usually repeated, the radiation dose to the patient should be determined. We have previously reported the results of a study on neuroblastoma patients in which the total body dose determined by the MIRD formalism based on data from post-therapy total body scans was compared with the total body dose determined from biological dosimetry based on the micronucleus assay [6]. The two approaches yielded comparable results. However, this kind of dosimetry can only be performed after the therapy has been given to the patient.

Ideally, bone marrow dose data for a specific patient should be available prior to $^{131}$I-MIBG therapy, so that
the amount of administered activity can be prescribed accordingly. In practice, the whole body absorbed dose is used as an adequate representation or index of bone marrow toxicity. To predict the whole body dose prior to therapy, one must measure retention of a tracer dose of MIBG.

Pre-therapeutic MIBG scans can be performed using either $^{123}$I-MIBG or $^{131}$I-MIBG. $^{131}$I-MIBG allows the measurement of the bi-exponential pattern of whole body clearance because of its long half-life (8.02 days). On the other hand, $^{123}$I-MIBG is more suitable for tumour dosimetry because $^{123}$I possesses better image quantification properties than $^{131}$I owing to its gamma ray energy of 159 keV ($^{131}$I has a gamma ray energy of 364 keV). An ideal scenario for a pre-treatment investigation would include both $^{123}$I-MIBG and $^{131}$I-MIBG data, but it would be cumbersome (and more expensive) to undertake such complex evaluations before each therapy.

Since the $^{123}$I-MIBG data reflect predominantly the blood clearance phase while the delayed timing of $^{131}$I-MIBG scans means that they reflect predominantly the second slower component of clearance, neither type of scan reflects both components. Therefore we decided to combine the “best of both worlds” and use the information obtained by the combination of $^{123}$I-MIBG pre-therapy scans and $^{131}$I-MIBG post-therapy scans as the gold standard for determination of the total body dose to the patient after $^{131}$I-MIBG therapy. The aim of this study was to evaluate the feasibility of this combination and to determine how much information on $^{131}$I-MIBG therapy can be gathered from $^{123}$I-MIBG pre-therapy scans alone.

Materials and methods

Patients

This prospective study included 38 $^{131}$I-MIBG therapies given to a total of 15 patients treated for neuroblastoma (six patients), phaeochromocytoma (three patients), carcinoid tumours (five patients) and medullary thyroid carcinoma (one patient). The patients included seven children with a mean age of 7.5 years (range 2–13 years) and eight adults with a mean age of 54 years (range 28–68 years).

Patients were treated three times on average, but one patient had as many as six therapies. The mean interval between the pre-therapy scan and the subsequent first therapy was 2 weeks (range 1–7 weeks). The overall mean interval between the pre-therapy scan and any given therapy was 11 weeks (range 1–59 weeks).

The overall mean (±SD) administered activity for therapy was 5.3±2.4 GBq. The highest mean activities (7.8±1.2 GBq) were given to patients treated for carcinoid tumours while the mean administered activities were somewhat lower (6.9±1.6 GBq) for patients treated for phaeochromocytoma and much lower (3.4±1.5 GBq) for patients treated for neuroblastoma. The patient suffering from medullary thyroid carcinoma received an activity of 7.4 GBq.

All patients gave their informed consent prior to their inclusion in the study.

Total body scans

$^{123}$I-MIBG pre-therapy scans. $^{123}$I-MIBG scans were obtained only once before a series of therapies. The mean administered activity was 138 MBq (SD 59 MBq).

Biplanar total body scans of the patient were taken shortly after, 5 h after and 24 h after $^{123}$I-MIBG administration with an Elscint Helix camera using medium-energy collimators. Scan speed was 10 cm/min. A 5-ml syringe, containing a known activity of $^{123}$I in a 6-cm-diameter Perspex phantom, was scanned along with the patient.

$^{131}$I-MIBG post-therapy scans. After each $^{131}$I-MIBG therapy, biplanar total body scans were taken at days 3, 6 and 10 with an Elscint Helix camera using high-energy collimators. The scan speed for each of these scans was, respectively, 30 cm/min, 20 cm/min and 10 cm/min to avoid overflow. A 5-ml syringe, containing a known activity of $^{131}$I in a 6-cm-diameter Perspex phantom, was scanned along with the patient.

Determining the measured activity. On the Helix XPERT system, for the first scan of the series of three, irregular regions of interest (ROIs) were drawn over the total body, the syringe containing a known activity of either $^{123}$I or $^{131}$I and the background. These ROIs were then copied (and moved when necessary) for each sequential scan and mirrored to the posterior image. The geometric mean of the counts per pixel was calculated in each ROI. In the EXCEL software, the total net counts within each ROI were converted to the activity within the ROI on the basis of the known activity in the syringe.

Attenuation correction for the measured activity. Attenuation correction curves giving correction factors for the measured activities of $^{123}$I and $^{131}$I were determined experimentally in Perspex phantoms of increasing thickness with a syringe containing a known activity of $^{123}$I (or $^{131}$I) in the middle, on the Elscint Helix camera. A best fit was drawn through the $^{123}$I and the $^{131}$I data and is shown in Fig. 1 as the correction factor versus the Perspex equivalent patient thickness relative to the standard phantom of 6 cm thickness. The purpose of correlating everything to the 6-cm Perspex phantom is that the measured activity in the scans can be corrected for using the same correction factor since the attenuation of the patient remains the same for all subsequent scans.

From these curves, a general attenuation correction can easily be carried out by the following procedure:

- Step 1: Since the first $^{123}$I-MIBG scan was taken before the patient had urinated after administration of the $^{123}$I-MIBG, the total activity in the body equals the administered $^{123}$I-MIBG activity. However, due to attenuation in the patient’s body, the measured activity is lower than the administered activity and should be corrected for by using the following correction factor:

$$F = \frac{A_{\text{actual}}}{A_{\text{measured}}}$$

where $A_{\text{actual}}$ = the decay-corrected administered activity, and $A_{\text{measured}}$ = the activity determined by comparison with the activity in the syringe.

Since the attenuation of the patient remains the same for all subsequent $^{123}$I-MIBG scans, the measured activity in these scans can be corrected for using the same correction factor.

- Step 2: To determine the correction factor for the $^{131}$I-MIBG post-therapy scans, first the thickness of the Perspex phantom
corresponding to the attenuation of $^{123}$I in the patient's body can be found in Fig. 1. The $^{131}$I attenuation correction factor corresponding to the determined Perspex thickness can then be derived from the $^{131}$I attenuation curve of Fig. 1.

The attenuation correction curves given in Fig. 1 correspond to the data measured on our Elscint Helix camera system.

**Determining the cumulative activity.** The attenuation-corrected total body activity was plotted versus time. Best fitting curves to the data sets were applied in three different ways:

1. For the post-therapy $^{131}$I-MIBG scans, a single exponential best fit was drawn through the three obtained data points.
2. For the pre-therapy $^{123}$I-MIBG scans, the $^{123}$I-MIBG data were first corrected for the difference in half-life and administered activity between $^{123}$I-MIBG and $^{131}$I-MIBG. For the $^{123}$I-MIBG data points:
   \[
   y_{123} = A_{123} \cdot R(t) \cdot \exp(-\lambda_{ph123} \cdot t)
   \]
   where $y_{123}$ is the activity of $^{123}$I in the body at time $t$, $A_{123}$ is the administered activity of $^{123}$I-MIBG, $\lambda_{ph123}$ is the physical decay constant of $^{123}$I and $R(t)$ is the retention function of the MIBG in the body. Accordingly, the fit was changed into:
   \[
   y_{131} = A_{131} \cdot R(t) \cdot \exp(-\lambda_{ph131} \cdot t)
   \]
   where $y_{131}$ is the activity of $^{131}$I in the body at time $t$, $A_{131}$ is the administered activity of $^{131}$I-MIBG, $\lambda_{ph131}$ is the physical decay constant of $^{131}$I and $R(t)$ is the retention function of the MIBG in the body.

The following adjustments were needed:

1. Activity correction coefficient (ACC): $\text{ACC} = A_{131}/A_{123}$
2. Half-life correction coefficient (HLCC):
   \[
   \text{HLCC} = \exp((-\lambda_{ph123} - \lambda_{ph131}) \cdot t)
   \]

By multiplying the ACC and the HLCC with the true activity function of the $^{123}$I-MIBG ($y_{123}$), the corrected fit through $^{123}$I-MIBG data points was obtained:

\[
\begin{align*}
   y_{131} &= y_{123} \cdot \text{ACC} \cdot \text{HLCC} \\
   &= y_{123} \cdot A_{131}/A_{123} \cdot \exp((-\lambda_{ph123} - \lambda_{ph131}) \cdot t)
\end{align*}
\]

A single exponential best fit was then drawn through the obtained corrected data points.

3. By combining the corrected pre-therapy $^{123}$I-MIBG data points (0–24 h) and $^{131}$I-MIBG data points (2–10 days), a bi-exponential best fit was drawn through the resulting six data points using SPSS.

**Calculating the total body dose.** By time integrating over the resulting curve, the cumulative activity was calculated. Dividing by the administered activity, the residence time was obtained and combined with the (gender- and age-matched, total body $\rightarrow$ total body) $S$ factors as determined by the MIRDose3 software [7], resulting in the total body dose for the patient (mGy/MBq):

\[
D = \tilde{A} \times S_{(TB \rightarrow TB)}
\]

where $\tilde{A}$ is the cumulative activity in the total body of the patient and $S_{(TB \rightarrow TB)}$ is the age- and gender-matched $S$ (total body to total body) factor.

**Statistics**

Mean values, standard deviations, single-exponential best fits and their correlation coefficients were calculated by means of Excel. The bi-exponential best fits, as well as their correlation coefficients, and the Mann-Whitney tests were calculated using the SPSS software. Wilcoxon tests were performed using Medcalc.

**Results**

An overview of the results is given in Table 1, which includes patient number and age, diagnosis, gender, the interval between the pre-therapy $^{123}$I-MIBG scans and the $^{131}$I-MIBG therapy, administered activity, dose calculated on the basis of a single exponential fit through the $^{123}$I-MIBG data, dose calculated on the basis of a single exponential fit through the $^{131}$I-MIBG data and dose calculated on the basis of a bi-exponential fit through the combination of $^{131}$I-MIBG and $^{123}$I-MIBG data. Means and standard deviations are shown for the patient population as a whole as well as for all patient groups.

The mean (±SD) total body dose calculated on the basis of a single exponential fit through the data of the $^{123}$I-MIBG pre-therapy scans was 0.69±0.38 Gy. The mean total body dose calculated on the basis of a single exponential fit through the $^{131}$I-MIBG data and dose calculated on the basis of a bi-exponential fit through the combination of $^{131}$I-MIBG and $^{123}$I-MIBG data. Means and standard deviations are shown for the patient population as a whole as well as for all patient groups.

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The mean (±SD) total body dose calculated on the basis of a single exponential fit through the data of the $^{123}$I-MIBG pre-therapy scans was 0.69±0.38 Gy. The mean total body dose calculated on the basis of a single exponential fit through the $^{131}$I-MIBG data and dose calculated on the basis of a bi-exponential fit through the combination of $^{131}$I-MIBG and $^{123}$I-MIBG data. Means and standard deviations are shown for the patient population as a whole as well as for all patient groups.
Table 1. Overview of results

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<td>12</td>
<td></td>
<td>1,221</td>
<td>0.12</td>
<td>0.16</td>
<td>0.13</td>
<td></td>
</tr>
</tbody>
</table>

NB, Neuroblastoma; CA, carcinoid tumour; PHAEO, phaeochromocytoma; MTC, medullary thyroid carcinoma; M, male; F, female; SD, standard deviation

\(^a\) The number indicates the patient while the letter indicates the therapy number for that patient

\(^b\) Interval: Interval in weeks between the pre-therapy uptake scan and the therapy

\(^c\) Gy bi: The total body dose in Gy calculated on the basis of a bi-exponential fit through the pre- and post-therapy scanning data together

\(^d\) Gy post: The total body dose in Gy calculated on the basis of a single exponential fit through the post-therapy \(^{131}\)I-MIBG scanning data only

\(^e\) Gy pre: The total body dose in Gy calculated on the basis of a single exponential fit through the pre-therapy \(^{123}\)I-MIBG scanning data only
For all methods of calculating the total body dose, the mean total body dose was highest for patients suffering from neuroblastoma, being 0.86±0.39 Gy, 1.36±0.73 Gy and 1.14±0.57 Gy for the pre-therapy, post-therapy and bi-exponential dose, respectively. The mean total body dose was significantly (P<0.01) lower for patients suffering from phaeochromocytoma (0.58±0.37 Gy, 0.70±0.21 Gy and 0.56±0.19 Gy, respectively) and for those suffering from carcinoid tumours (0.42±0.12 Gy, 0.66±0.16 Gy and 0.52±0.13 Gy, respectively).

Based on the bi-exponential fit through the data, the dose per MBq administered activity was also highest for patients suffering from neuroblastoma (0.37±0.21 mGy/MBq) than for patients suffering from phaeochromocytoma (0.08±0.02 mGy/MBq) and carcinoid tumours (0.07±0.01 mGy/MBq).

The correlation between the total body dose calculated on the basis of the 123I-MIBG pre-therapy scans and the bi-exponential fit through the combined data of the 123I-MIBG pre-therapy scans and the first scans following 131I-MIBG therapy was R=0.93, P<0.0001 (Fig. 2), while the linear best fit was:

\[
\text{Bi-exponential dose (Gy)} = 1.26 (\sigma=0.069) \times 123\text{I-MIBG pre-therapy dose (Gy)}
\]

The correlation coefficient was still high when all following therapies were taken into account: R=0.85, P<0.0001 (Fig. 3), while the linear best fit was:

\[
\text{Bi-exponential dose (Gy)} = 1.20 (\sigma=0.056) \times 123\text{I-MIBG pre-therapy dose}
\]

**Discussion**

Although previously published studies [8, 9] have compared pre- and post-therapy dosimetry in patients treated with 131I-MIBG, our study is the first in which a series of total body scintigrams in the same patients have been compared before (123I-MIBG) and after (131I-MIBG) therapy under the same circumstances, thereby combining “the best of both worlds”. Geiger-Müller total body retention measurements (as used by Fielding et al. [8]) allow rapid evaluation of the activity remaining in the body and are less cumbersome for the patient. However, since it is difficult to attain the same geometry for each measurement, a lot of data are required and absolutely no information is obtained about the distribution of the 131I-MIBG in the body. Planar images of the main tumour region (as used by Fielding et al. [8] and Tristam et al. [9]) probably render better count statistics for defined areas, while a total body dose is necessary as an indication of the dose to the bone marrow.

Since the Elscint Helix camera is not equipped for dual-isotope scanning, acquisition of separate transmission and emission scans to correct for attenuation was considered too cumbersome. Furthermore, we wanted our method to have the widest possible applicability.

Taking into account a factor of 1.20, our results show a good correlation (R=0.84) between the dose calculated on the basis of the 123I-MIBG pre-therapy scans and that calculated on the basis of the 131I-MIBG post-therapy scans. When the dose calculated on the basis of 123I-MIBG pre-therapy scans was compared with the dose calculated on the basis of a bi-exponential fit combining pre-therapy scans and the first scan following post-therapy data points, the correlation was R=0.93 (shown in Fig. 2) and the correction factor, 1.26.

There has been much discussion in the literature as to whether or not the kinetics of a tracer activity of 123I-MIBG and a therapeutic activity of 131I-MIBG are the same. Wafelman et al. [10] stated that clearance of therapeutic 131I-MIBG is faster because of increased cell damage during therapy. Smets et al. [11] suggested that diagnostic studies probably overestimate the loading ca-
pacity of phaeochromocytoma and certainly underesti-
mate that of neuroblastoma owing to differences in
intracellular MIBG concentration. Fielding et al. [8] con-
cluded that the only difference between therapeutic and
tracer doses of MIBG is the higher amount of carrier
present in the therapeutic doses, which may affect the
kinetics of the radiopharmaceutical. These consider-
ations tend to suggest that dose calculation based on $^{123}$I
pre-therapy uptake values may represent an overesti-
mation of the dose actually received during $^{131}$I-MIBG
therapy.

In fact, our results show the exact opposite: the dose
calculated on the basis of the $^{123}$I-MIBG scans leads to a
systematic underestimation in comparison with the dose
calculated on the basis of a combination of $^{123}$I-MIBG
scans and $^{131}$I-MIBG scans (32 therapies out of 38). This
observation is attributable to the short half-life (13.2 h)
of $^{123}$I. The single exponential curve fitted through the
$^{123}$I-MIBG pre-therapy data to a large extent represents
the fast clearance of $^{123}$I-MIBG from the blood. On the
other hand, the post-therapy $^{131}$I-MIBG scans only start
at 48 h after administration of the therapeutic activity, so
the longer retention of the $^{131}$I-MIBG in the body is pri-
marily visualised. The bi-exponential fit through the
combined data from pre- and post-therapy scans (six data
points) takes into account both components and yields an
intermediate total body dose that may be considered the
most accurate.

The difference in half-life between $^{123}$I (13.2 h) and
$^{131}$I (8.02 days) is an argument raised against using $^{123}$I-
MIBG scans as a predictor of $^{131}$I-MIBG therapy [9].
However, our results ($R=0.93$) show that it is accessible
to benefit from the better count statistics and the better
image resolution of $^{123}$I in order to calculate the total
body dose, taking into account a factor of 1.26. There-
fore, in keeping with Shapiro and Gross [12], who also
performed $^{123}$I scintigraphic studies, we assumed similar
biokinetics, independent of the activity of MIBG.

In the present study, patients were also followed over
time. The mean number of therapies in our study was
three, while one patient had as many as six consecutive
therapies. The correlation between pre-therapy total
body dose and the total body dose based on a bi-expo-
nential fit through a combination of the data was some-
what lower ($R=0.85$) when all subsequent therapies were
considered (correction factor =1.20). This observation is
in keeping with the results of Tristam et al. [9], stating
that the pattern of $^{131}$I-clearance remains constant for a
given patient over time if tumour burden and/or tumour
function do not change. Therefore, a new set of pre-ther-
apy scans would only be necessary after a dramatic in-
crease in tumour load. We would therefore suggest that
the overall correction factor of 1.20 be taken into ac-
count when calculating the dose for $^{131}$I-MIBG therapy
based on $^{123}$I-MIBG pre-therapy scans.

For all methods of calculating the total body dose, the
mean total body dose was highest for patients suffering
from neuroblastoma ($\text{mean} \pm \text{SD} 0.37 \pm 0.21 \text{ mGy/MBq}$)
while it was significantly ($P<0.01$) lower for patients suf-
fering from phaeochromocytoma ($0.08 \pm 0.02 \text{ mGy/MBq}$)
and carcinoid tumors ($0.07 \pm 0.01 \text{ mGy/MBq}$). A similar
observation has been made previously [6], and the find-
ings can be explained by the mean age of the patients: 8
years for neuroblastoma patients as compared with 33
years for patients suffering from phaeochromocytoma
and 53 years for patients with carcinoid tumours. The
mean calculated total body dose for neuroblastoma pa-
tients ($0.37 \text{ mGy/MBq}$) in our study is very similar to the
results obtained by Fielding et al. [8] and Lashford et al.
[13] ($0.33 \text{ mGy/MBq}$), but is double the result obtained
by Tristam et al. [9] ($0.16 \text{ mGy/MBq}$) and even triple that
reported by Ertl et al [14]. ($0.11 \text{ mGy/MBq}$). However,
most of the patients included in the latter two studies
were adults, resulting in a lower total body dose.

In our study, for neuroblastoma patients, a mean value
of 6.4 h (range 0.2–23.7 h) was found for the mean total
body half-life for the fast excretion component and
47.6 h (range 16.8–106.0 h) for the longer retention com-
ponent. These results concur with the results obtained by
Fielding et al. [8] (mean 6.8 h and 35–95 h) and Tristam
et al. [9] (9 h and 25 h). For patients suffering from
phaeochromocytoma, the mean half-lives were 16.1 h
(range 0.7–41.8 h) and 35.9 h (range 21.5–78.1 h), re-
spectively. These results also concur with the results ob-
tained by Tristam et al. [9] (13 h and 30 h, respectively).
For patients suffering from carcinoid tumours, the mean
half-lives for the fast and slow components obtained in
the study were 16.4 h (range 10.7–20.6 h) and 102.3 h
(36.0–192.0 h), respectively. The half-lives for both the
fast and the slow component for neuroblastoma patients
were significantly different than those for the other pa-
tient groups ($P=0.018$ and $P=0.001$ for the phaeo-
chromocytoma and carcinoid tumour patients, respec-
tively). There were no significant differences in half-
lives for either component between patients suffering
from phaeochromocytoma and those with carcinoid tu-
mours ($P=0.414$).

In conclusion: The $^{131}$I-MIBG therapy dose can be
predicted from a single set of $^{123}$I-MIBG dosimetric
scans for all following $^{131}$I-MIBG therapies, taking into
account a correction factor of 1.20 ($R=0.85$). $^{123}$I-MIBG
pre-therapy scans do not need to be repeated before each
therapy, except when the biodistribution of $^{131}$I-MIBG
is expected to change rapidly. Combination of the
$^{123}$I-MIBG pre-therapy data and $^{131}$I-MIBG post-therapy
data to obtain a bi-exponential fit is feasible.

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hoek Hospital, Department of Nuclear Medicine, Amsterdam, the
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PATIENT DOSIMETRY FOR $^{131}$I-LIPIODOL THERAPY.

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Abstract. Patient dosimetry data for intra-arterial iodine-131 lipiodol therapy for hepatocellular carcinoma (HCC) are scarce. The aim of this study was to determine the absorbed dose (D) to the tumour and healthy tissues, as well as the effective dose (E), by different methods for 17 therapies in 15 patients who received a mean activity of 1.9 GBq (SD 0.2) 131I-lipiodol. Eight patients received thyroid blocking by potassium iodide (KI). Patient dosimetry was performed based on bi-planar total body scans using the Monte Carlo simulation program MCNP-4B and the MIRDOSE-3 standard software program. CT images of each patient were used to determine liver and tumour volume and position. The total body dose to the patient was also determined by biological dosimetry with the in vitro micronucleus (MN) assay. From the increase in micronucleus yield after therapy, the equivalent total body dose (ETBD) was calculated. Results for D and E were comparable between MCNP and MIRDOSE (liver: mean 7.8 Gy, SD 1.8, lungs: 6.8 Gy, SD 2.9, E: 2.01 Gy, SD 0.58). MIRDOSE gave a systematic overestimation for the tumour dose, especially for tumours <3 cm (15%). The MCNP method is more accurate since the dose contributions from tumour to organs and vice versa can be accounted for. The absorbed dose to the thyroid was significantly lower for patients who received KI (7.2 Gy, SD 2.2) than for the other patients (13.8 Gy, SD 5.0). MN yields could be obtained for only 12 of the 17 therapies due to hypersplenism. A mean ETBD of 1.66 Gy (SD 0.73) was obtained, but the MN results showed no correlation between the ETBD and the total body dose values of the physical dosimetry. Also, in all except one of the patients, no further reduction in the number of thrombocytes was observed after therapy, probably due to the existing hypersplenism. It is concluded that in view of the high E values, patient dosimetry is necessary for patients receiving 131I-lipiodol therapy. Except in the case of the smaller tumours, comparable results were obtained with MCNP and MIRDOSE. Due to hypersplenism, biological dosimetry results based on the MN assay are not reliable.

Keywords: 131I-lipiodol therapy – Dosimetry – Monte Carlo simulations – MIRD – Micronucleus assay

Introduction

Primary hepatocellular carcinoma (HCC) is one of the most common malignant tumours in the world. It is responsible for an estimated one million deaths annually. The tumour often presents late, which, with the underlying cirrhosis, makes surgery difficult or impossible in many patients. The median survival of patients with unresectable HCC may be as low as 1–2 months [1].

Of the approaches available for the treatment of unresectable HCC, arterially delivered therapies using iodised oil as a vehicle are attracting much attention owing to the improved results that have been achieved. Lipiodol consists of mono-, di- and tri-iodinated ethyl esters of linoleic, oleic and stearic acids. It naturally contains up to 38% iodine. In 1979, Nakakuma et al. [2] established the selective retention of iodised oil in the foci of HCC following its injection into the hepatic artery. It is now well established that lipiodol is retained by HCC for periods ranging from several weeks to over a year, while it is cleared from the normal liver parenchyma within 7 days [3]. Coupling lipiodol with chemotherapeutic agents (such as doxorubicin or cisplatin) allows in situ chemotherapy. Intra-arterial infusions of emulsions composed of lipiodol and anticancer agents are frequently associated with embolisation, thereby increasing therapeutic efficiency (survival rates of 89% at 6 months and 69% at 1 year have been reported [3]), but increasing side-effects as well.
Internal radiation therapy is possible when some of the iodide present in the lipiodol is substituted by iodine-131 using a nuclidic exchange reaction. The results in patients treated with 131I-lipiodol are at least as good as those achieved with the chemo-embolisation method, and patients experience fewer side-effects [4]. Furthermore, 131I-lipiodol treatments are not only used for palliation. The treatment can be curative when the 131I-lipiodol is given neo-adjuvantly before liver transplantation and/or after resection of HCC [5]. Therefore dosimetry is important not only in studying the direct effects on the organs but also in evaluating the occurrence of late effects after irradiation.

Although some biodistribution studies have been performed [6, 7, 8], data on patient dosimetry for the 131I-lipiodol treatment are scarce [8]. Therefore, the aim of this study was to determine patient dose using bi-planar total body scans and Monte Carlo techniques. The results of these calculations were compared with the output of the MIRDOS-3 program. The total body absorbed dose was also determined by a completely independent biological dosimetry method: the cytokinesis-blocked micronucleus assay.

### Materials and methods

#### Patient population

This study comprises a total of 17 131I-lipiodol therapies carried out on 15 adult patients (six women and nine men) with a mean age of 61 years (SD 11). Patients received a mean activity of 1,883 MBq (SD 200) of 131I-lipiodol administered intra-arterially into the liver artery by catheterisation. Sixteen of the patients received a single therapy: only patient 1 received three consecutive therapies, over a period of 8 months. The mean administered activity for this patient was 1,820 MBq (SD 240).

Patients were divided into two groups: the first group consisted of eight patients (eight therapies) who did not receive any thyroid blocking before therapy and the second group consisted of eight patients (nine therapies) who received thyroid blocking in the form of stable potassium iodide capsules at a dose of 100 mg per day starting 2 days before therapy and continuing until 2 weeks after therapy. Patient 1 did not receive thyroid blocking during the first therapy, while his thyroid was blocked for both subsequent therapies. The administration of the potassium iodide was verified during hospitalisation in isolation from day 1 until day 6 after therapy.

#### 131I-lipiodol uptake based on total body scans

In all except two patients, a set of two total body 180° biplanar scans were taken after therapy. For patients 8 and 10, only one scan could be taken because they returned home immediately after their 7-day stay in isolation. All scans were acquired using a GE Helix double-head gamma camera fitted with high-energy parallel-hole collimators. The first scan was performed on day 7 and the second on day 14 after administration. The medical condition of the patients did not allow the acquisition of more scans.

A syringe containing a known activity of 131I in a PMMA syringe phantom (diameter 6 cm) was placed at the patient’s feet. The thickness of the trunk as determined by CT or MRI was converted into the equivalent thickness of Perspex. The factor of difference was then calculated between the patient-equivalent thickness of Perspex and the 6-cm Perspex phantom that housed the syringe containing a standard activity. 131I attenuation correction factors between the patient-equivalent thickness of Perspex were measured in phantom experiments. The activity inside liver and tumour were then corrected for attenuation using this factor.

On the HERMES software system (Nuclear Diagnostics, Sweden), conformal regions of interest (ROIs) were drawn by eye around the syringe, the total body, the liver, the tumour, the lungs and the thyroid. Suitable background regions were selected as follows: the normal liver for the tumour, the upper leg for the organs, and along but outside the body for the syringe and the total body. ROIs were mirrored to the posterior image and copied (and moved) to the subsequent scan. For each ROI the geometric mean of the total counts was calculated after subtraction of background counts. The activity in each ROI was determined by comparison with the known activity in the syringe, taking into account the attenuation correction described above. Each scan was evaluated three times and the mean activity calculated from these evaluations was used. In all cases the SD/mean was less than 5%. Using this methodology, the overall uncertainty for calculated activity in phantom studies was less than 13%.

The activity in each ROI was then plotted versus time, and a mono-exponential function, assuming instantaneous uptake of the activity, was fitted through the dataset. The exponential function was integrated to infinity in order to calculate the cumulated activity.

#### Calculation of the absorbed dose per MBq h based on Monte Carlo simulations

A gender- and age-specific phantom layout of the body was made using the Bodybuilder (Oak Ridge Associated Universities) software. The following organs were assumed to contain 131I homogeneously: tumour, liver (excluding the tumour), lungs and thyroid. The volume and location of the liver and of the tumour within the liver were modelled according to the patient’s CT or MRI scans. Organs were modelled using their true composition as described in the ICRU report 44 [9]. Using the MCNP-4B (Monte Carlo n Particle version 4B) software, organ-specific S factors (“absorbed dose” per MBq) were derived for each organ. Estimated relative errors of the calculated S factors were less than 1%. Since direct image fusion was not possible between CT or MRI images and biplanar total body scans, only tumours with a diameter of more than 2 cm were taken into account. Tumour volume was measured on CT or MRI scan. Activity in the tumour was determined from biplanar scans. The absorbed dose to each organ was then calculated using the MIRD principle:

\[
D_{\text{org}} = \sum_{n} A_{\text{org}n} \cdot S_{\text{org}n-\text{org}} + A_{\text{tumour}} \cdot S_{\text{org}n-\text{tumour}}
\]

where: \(\text{org} = \text{organ}, D_{\text{org}n} = \text{absorbed dose to target organ } n, \text{org} m = \text{source organ other than or same as target organ}, \ A = \text{cumulated activity in the considered source organ, and } S = \text{organ-specific S factor, calculated by means of MCNP.}

Finally, to calculate the effective dose, all organ contributions were summed according to their weighting factors as determined in the ICRP publication number 60 [10].

#### Calculation of the absorbed dose based on MIRDOS-3

The cumulated activity in each organ (MBq h) was divided by the administered activity (MBq) in order to calculate the residence time. The residence times were inserted into the MIRDOS-3 (oak Ridge associated Universities) software program and the absorbed doses...
were then calculated. The “self dose” to the tumour was determined by using the “nodule module” by linear interpolation for the correct tumour diameter between the given S values for discrete sphere diameters. To calculate the effective dose, two dose calculations were performed in MIRDPOSE: a first where the tumour activity was added to the liver activity for the calculation of the absorbed dose to all organs except the liver, and a second where the activity of the tumour was subtracted from the liver to give the absorbed dose to the normal liver. The effective dose was then manually calculated using the appropriate weighting factors for all organs.

Micronucleus assay. The first heparinised 5-ml blood sample was taken immediately before administration of the $^{131}$I-Lipiodol therapeutic activity. This blood sample served as the non-irradiated control. A second heparinised blood sample of 5 ml was taken 7 days post administration.

Whole blood cultures were incubated following the protocol described by Vral et al. [11]. Micronuclei were scored based on the criteria summarised by Fenech [12].

The equivalent total body dose (ETBD) is the absorbed dose of ionising radiation, which, if received homogeneously by the whole body, would produce the same yield of micronuclei as observed in the patients. The ETBD was derived from the increase in micronucleus yield in the blood sample of each patient 1 week after administration of the activity, using the dose-response relationship of Thierens et al. [13]. This value was then corrected for the $^{131}$I remaining in the body after the first week by multiplying with a factor of 1.71. This factor was experimentally calculated by dividing the absorbed total body dose derived from Monte Carlo calculations to infinity by the absorbed total body dose derived from Monte Carlo calculations for the first week only.

Thrombocyte counts. Blood samples were taken for every patient before administration of the radiopharmaceutical and at least once after therapy in order to allow follow-up of the thrombocyte count after therapy.

Statistics. Statistical analysis was performed by means of SPSS. Differences for the mean were investigated by means of non-parametric two-tailed Mann Whitney U tests. Correlations were investigated by means of the Pearson correlation test.

Results

An overview of the results obtained is given in Tables 1 and 2.

Based on the data from the total body scans, the mean decay-corrected percentage of $^{131}$I uptake in the total body at 7 days after administration was 72.8% (SD 13.6). At the same time the uptake in the normal liver, the tumour and the lungs was, respectively, 26.1% (SD 8.3%), 17.2% (SD 7.5%) and 11.7% (SD 5.4%). The uptake in the thyroid was significantly ($P=0.027$) lower in the patient group who received thyroid blocking (mean 0.36%, SD 0.18%) than in patients who did not receive thyroid blocking (mean 0.57%, SD 0.18%). For patient 1, the percentage uptake in the thyroid was halved in the second and third treatments, in which thyroid blocking was administered.

The percentage uptake in the total body at the time of the second scan (14 days after therapy) had decreased to 53.1% (SD 13.8%). The percentage uptake for the normal liver, the tumour and the lungs at the time of the second scan was 14.4% (SD 4.3%), 14.5% (SD 6.4%) and 7.4% (SD 4.1%), respectively. The uptake in the thyroid at the time of the second scan was also significantly lower ($P=0.018$) in the patient group who received thyroid blocking (mean 0.27%, SD 0.13%) than in the patients who did not receive thyroid blocking (mean 0.50%, SD 0.17%). Mean tumour to total liver activity ratio was 40% (SD 15%) at the time of the first scan and reached 49% (SD 11%) at the time of the second scan.

The effective half-life, calculated from the single exponential fit through the data, was 5.2 days (SD 0.8) for the total body and 4.3 (SD 0.9), 5.8 (SD 0.9), 4.5 (SD 1.0) and 6.0 days (SD 1.3) for the normal liver, the tumour, the lungs and the thyroid, respectively. There was no significant ($P=0.82$) difference between the half-life in the thyroid of patients who received thyroid blocking and that in the thyroid of those who did not receive it: mean 5.8 (SD 1.4) and 6.2 (SD 1.0) days, respectively.

Based on an exponential fit through the data and the S factors determined by the MCNP software, the following absorbed doses were obtained: normal liver 7.8 Gy (SD 1.8, range 4.0–11.8), tumour 129.5 Gy (SD 58.2, range 68–246) and lungs 6.8 Gy (SD 2.9, range 2.2–11.3). The absorbed dose to the thyroid was significantly ($P=0.005$) lower for the patients receiving thyroid blocking by potassium iodide (mean 7.2 Gy, SD 2.2, range 3.4–10.7) than for those who did not receive thyroid blocking (mean 13.8 Gy, SD 5.0, range 8.0–21.9). For the total body dose, a mean value of 0.95 Gy (SD 0.18, range 0.58–1.18) was obtained. The mean effective dose for the patient calculated from the weighted contributions of the organs was 2.01 Sv (SD 0.58, range 0.83–2.70).

The absorbed dose based on the bi-planar scans calculated according to the MIRDPOSE program for the total body was 0.97 Gy (SD 0.23, range 0.65–1.27). The mean absorbed dose was 6.70 Gy (SD 1.88, range 3.05–11.08) for the normal liver, 144.4 Gy (SD 68.5, range 69–288) for the tumour and 6.5 Gy (SD 3.4, range 0.8–11.6) for the lungs. The absorbed dose to the thyroid was significantly ($P=0.005$) lower for the patients receiving thyroid blocking by potassium iodide (mean 8.0 Gy, SD 2.4, range 3.8–11.9) than for those who did not receive thyroid blocking (mean 15.5 Gy, SD 5.7, range 8.9–24.6). The mean total body dose was 0.93 Gy (SD 0.18, range 0.56–1.16). The mean effective dose for the patient calculated from the weighted contributions of the organs was 2.05 Sv (SD 0.59, range 0.93–2.94).

Figure 1A provides an overview of the mean absorbed dose to all source organs according to Monte Carlo simulations and the MIRDPOSE-3.1 program. In Fig. 1B, the mean absorbed doses to all other organs are given.
Table 1. Results regarding data from the scans and the cell cultures

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Pt, Patient number (patient 1 had three therapies: a, b and c); KI, blocking of thyroid by potassium iodide: Y, yes; N, no; Y, patient age (in years); G, patient gender (M, man; F, woman); GBq, administered activity (GBq); %, percentage uptake (%1: at 7 days after therapy; %2: at 14 days after therapy); T, half-life of the $^{131}$I in each organ (TB, total body; Li, normal liver; Tu, tumour; T/L, tumour to liver ratio; Lu, lungs; Th, thyroid); MN, micronucleus yield in 1,000 binucleated cells (MN pre: before therapy; MN pst: after therapy); SD, standard deviation
The mean equivalent total body dose at 1 week after therapy based on the cytokinesis-blocked micronucleus assay could be determined for 12 of the 17 therapies and was 0.94 Gy (SD 0.52). When the results were corrected for the 131I remaining in the body after the first week post therapy, an ETBD value of 1.66 Gy (SD 0.73 Gy) was obtained.

Information about the thrombocyte count was available for 10 of 15 patients. The evolution in thrombocyte count versus time post administration is depicted in Fig. 2.

### Table 2. Calculated doses

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Pt, Patient number (patient 1 had three therapies: a, b and c); R Tu, diameter of the tumour (cm) as determined by CT; D, absorbed dose in the organ (Gy) calculated by MCNP (Tu, tumour; Li, liver; Lu, lungs; Th, thyroid); D Tu MIRD, absorbed dose in the tumour (Gy) calculated by MIRD; TB, total body dose (Gy) (MC: calculated by MCNP; MIRD: calculated by MIRDOSE); E, effective dose (Sv) (MC: calculated by MCNP; MIRD: calculated by MIRDOSE); ETBD, equivalent total body dose (Gy) obtained by the in vitro micronucleus assay; SD, standard deviation.

**Fig. 1.** A Comparison of the absorbed dose to all source organs according to Monte Carlo simulations and the MIRDOSE program. Thyroid KI: patients receiving thyroid blocking by potassium iodide (KI). Thyroid no KI: patients not receiving thyroid blocking by potassium iodide (KI). Open squares: MCNP; filled squares: MIRD. B Comparison of the absorbed doses to all non-source organs according to Monte Carlo simulations and the MIRDOSE program. Open squares: MCNP; filled squares: MIRD. ULI, Upper large intestine; LLI, lower large intestine.

**Fig. 2.** Evolution of the thrombocyte count in ten patients post administration of 131I-lipidol therapy.

The mean equivalent total body dose at 1 week after therapy based on the cytokinesis-blocked micronucleus assay could be determined for 12 of the 17 therapies and was 0.94 Gy (SD 0.52). When the results were corrected for the 131I remaining in the body after the first week post therapy, an ETBD value of 1.66 Gy (SD 0.73 Gy) was obtained.

Information about the thrombocyte count was available for 10 of 15 patients. The evolution in thrombocyte count versus time post administration is depicted in Fig. 2.
Discussion

The $^{131}$I-lipiodol uptake percentages for the liver and the lungs obtained in this study support the results reported by several authors [6, 7, 8], indicating that, aside from the tumour, $^{131}$I-lipiodol is taken up mainly in these organs.

The average $^{131}$I effective half-lives of 5.2 days (SD 0.8) for the total body, 4.3 days (SD 0.9) for the liver and 4.5 days (SD 1.0) for the lungs compare very well with the results obtained by Raoul et al. [6]. The long retention of $^{131}$I in the body justifies the patient's relatively long (6–7 days) stay in the isolation ward. Nakajo et al. [8] calculated a somewhat lower half-life in the total body (varying between 3.7 and 4.8 days) and the normal liver (3.7 days, SD 0.6). These lower half-lives were likely due to the fact that, in their study, scans were only taken up to 8 days post injection of the $^{131}$I-lipiodol.

As can be seen in Fig. 1, the mean absorbed dose for the most relevant organs was comparable between the MCNP calculations and MIRDSE. Our result for the normal liver is comparable to the absorbed liver dose calculated by Raoul et al. [14] (5.5 Gy, SD 8.7), although their absorbed dose to the lungs was lower, with a maximum of 2.9 Gy (SD 2.2). Direct effects after therapy were never observed even though some of our patients were treated with $^{131}$I-lipiodol up to 5 times.

None of the early authors [6, 7, 8], described any significant $^{131}$I uptake in the thyroid. In fact, the guidelines of the European Association of Nuclear Medicine [15] do not recommend any special precautions. Thyroid uptake has only recently been described systematically for 31 patients by Toubeau et al. [16]. The reason for this iodine uptake in the thyroid remains unclear since non-ionic contrast media injected during the procedure contain free inorganic iodide and the amount of stable iodide injected should saturate the thyroid iodine uptake mechanism.

In our study, we calculated a significantly lower mean absorbed dose to the thyroid of 7.2 Gy for patients who received thyroid blocking compared with the other patients (13.8 Gy). Also for patient 1, the dose to the thyroid of 21.3 Gy for the first therapy (without thyroid blocking) was double the values found for the two subsequent therapies (10.7 Gy and 7.6 Gy respectively), in which thyroid blocking was administered. Since our patient group is relatively small for the comparison of two treatment schedules, a larger (68 therapies) randomised prospective study [17] was undertaken. The results of that study confirmed the halving of the absorbed dose to the thyroid when thyroid blocking was administered. Toubeau et al. [16] calculated a lower mean absorbed dose of 6.9 Gy (range 1.5–13.0 Gy) for patients who did not receive thyroid blocking, but their scans were taken at later times than ours: up to 35 days after therapy. Since thyroid blocking is well tolerated and $^{131}$I-lipiodol treatment is usually repeated so that the thyroid will be irradiated several times, we now systematically give KI to all patients.

In our study, only tumours with a diameter of more than 2 cm on CT or MRI images were considered because direct image fusion between CT or MRI scans and biplanar total body scans was not possible. For these tumours, a mean of 40% (first week), rising to 49% (second week), of all the activity present in the liver was contained within the tumour. The increase was due to the fact that $^{131}$I-lipiodol was retained for longer in the tumour (mean 5.8 days, SD 0.93) than in the liver (mean 4.3 days, SD 0.93). The mean half-life in the tumour was comparable to the results of Nakajo et al. [8], obtained in five patients.

The mean absorbed dose to the tumour calculated with the MCNP software was 129.5 Gy (SD 58.2, range 68–246 Gy). Madsen et al. [7], calculated a mean absorbed dose of 65 mGy/MBq, corresponding to 121 Gy for the mean activity administered in our study. When the dose to the tumour was calculated by means of MIRDSE, a mean tumour dose of 144 Gy (SD 68.5, range 69–288) was obtained. The MIRDSE results were systematically higher than the MCNP values. The difference was due to the linear interpolation that is necessary between the tabulated discrete sphere sizes (and corresponding S factors) tabulated in the “nodule module” of MIRDSE. The difference is particularly large (mean 15%) for smaller tumours (<3 cm). For the larger tumours (>3 cm) included in this study, the differences in the calculated tumour S values are within the 5% margin.

The MCNP value is more accurate since the liver and tumour are patient specifically introduced into the Bodybuilder program and from there on calculated by MCNP for the actual tumour diameter. By including the tumour in the geometry, additional S factors (e.g. $S_{\text{tumour-liver}}$, $S_{\text{liver-tumour}}$, $S_{\text{lungs-tumour}}$) could be calculated, which is impossible with MIRDSE. Additionally, in our MCNP calculations, the contribution of the electron dose deposited outside the tumour was included. This is not the case in the MIRD formalism. Due to the medium energy of the $\beta$ rays, the contribution of the additional S factors to the dose is not important. Such would not be the case, however, were high-energy beta emitters (such as rhenium-188) to be considered. Even though the Monte Carlo simulations are more time consuming, for tumour dosimetry in metabolic radiotherapy, the MCNP method should be used instead of the MIRDSE-3.0 program.

In our study the ratio of the absorbed dose to the tumour to the absorbed dose to the liver was 18.24 (SD 7.90) calculated by MCNP and 24.24 (SD 11.07) calculated according to MIRDSE. According to Raoul et al. [6], on average activity within metastases is 2.4 times the level achieved in normal tissue and in HCC it is 4.3 times that in surrounding normal tissue. The ratio between tumorous and non-tumorous hepatic areas can even exceed 5.3 [4]. However, their method of determining ratios was to compare ROIs with the same surface...
around the tumour and around the normal hepatic tissue, while our ratio was between the absorbed dose to the tumour and absorbed dose to the normal liver.

Overall, a good correlation ($R=0.93$) was obtained between the effective dose calculated by Monte Carlo simulation techniques (mean 2.0 Gy) and the effective dose calculated by MIRDOSE (mean 2.1 Gy). For 15 out of 17 therapies, the effective dose calculated by MCNP was somewhat lower than the effective dose calculated by MIRDOSE. This was due to the activity present in the tumour that was modelled as such in the MCNP program, while we performed two dose calculations in MIRDOSE: a first where the tumour activity was added to the liver activity for the calculation of the dose to all organs except the liver, and a second without the activity of the tumour included to give the dose to the normal liver. The effective dose was then manually calculated using the appropriate weighting factors for all organs. The MCNP result was therefore more accurate.

To estimate the risk that patients would develop lethal secondary neoplasms induced by the irradiation received during the $^{131}$I-lipiodol therapy, a risk factor of 2% per Sievert [10] had to be taken into account, considering the mean age of this patient group. On this basis, the risk was estimated as 5% following the MCNP calculations.

We realise that an exponential fit drawn through only two (organs) or three (total body) data points may have introduced uncertainty into our results. Performance of more than one scan between 7 and 14 days after therapy was not possible owing to the medical condition of the patients. None of the other biodistribution studies [6, 7, 8] have included scans obtained later than 8 days after therapy, and while Toubeau et al. [16] performed a second scan at 35 days after therapy, they only reported results for the thyroid.

Only 12 of the 17 therapies could be evaluated by the in vitro micronucleus assay owing to the low number of peripheral blood lymphocytes and a reduction in their proliferation capacity. The problem is a consequence of the hypersplenism occurring in many of these patients. Akimaru et al. [18] reported that splenic enlargement was found in 20% of their HCC patients, resulting in hyperplenism in many of them. The enlarged spleen together with reduced liver function (as a result of HCC) causes impaired detoxification of the body and a shortened half-life of all blood cells in the patient, resulting in pancytopenia [19].

When the mean ETBD of 0.95 Gy after 7 days was corrected for the remaining $^{131}$I in the body (mean factor of 1.71, calculated by dividing the absorbed total body dose derived from Monte Carlo calculations to infinity by the absorbed total body dose derived from Monte Carlo calculations for the first week only), a mean ETBD of 1.66 Gy (SD 0.73) was obtained. Unlike in patients treated with $^{131}$I-metaiodobenzylguanidine, in whom a good correlation has been found to exist between biological and physical dosimetry techniques ($R=0.83$) [Monsieurs M et al., unpublished work], there was no correlation between the ETBD and the total body dose calculated either by MCNP or by MIRDOSE for the patients treated with $^{131}$I-lipiodol. The lymphocytes in HCC patients clearly no longer show the normal in vivo behaviour of lymphocytes and therefore results obtained by biological dosimetry have to be treated with caution.

The generally low number of blood cells for $^{131}$I-lipiodol patients was reflected by the low number of thrombocytes present in all except one of the patients before therapy (Fig. 2). With effective doses calculated between 1.6 and 2.5 Gy, normally a 50% decrease in thrombocytes would be expected within 30 days after therapy [20]. In fact only the patient (patient 1) with the normal thrombocyte count before therapy showed the expected halving of the initial thrombocyte count, while the others showed only a non-significant reduction in their thrombocyte count after therapy. This result was probably also due to the existing hyperplenism.

**Conclusion**

The high value of the patient’s effective dose obtained in this study points to the need for dosimetry after radionuclide treatments. MCNP calculations taking into account the patient’s specific data for tumour and liver are preferable to MIRDOSE calculations for assessment of the absorbed dose to the tumour. Biological dosimetry by means of the in vitro micronucleus assay is not advisable in these patients since the lymphocytes no longer show the normal in vivo behaviour due to the existing hyperplenism.

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**References**


Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

4.2. Determining the mutagenic effects directly after therapy using cytogenetic dosimetry methods.


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ESTIMATION OF RISK BASED ON BIOLOGICAL DOSIMETRY FOR PATIENTS TREATED WITH RADIOIODINE.

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**Key words:** $^{131}$I therapy, thyrotoxicosis, thyroid carcinoma, biological dosimetry.

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Estimation of risk based on biological dosimetry for patients treated with radiiodine

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Summary
A multicentre study was undertaken to assess the cytogenetic damage to peripheral blood lymphocytes in 31 patients treated with $^{131}$I for thyrotoxicosis using the cytokinesis-blocked micronucleus assay. The results were compared to those for eight thyroid carcinoma patients using the same method. For each patient, blood samples were taken immediately before and 1 week after iodine administration. The first blood sample was divided into three fractions and each fraction was subsequently irradiated in vitro with 0.05 and 1 Gy $^{60}$Co gamma rays, respectively. After blood culture for 70 h, cells were harvested, stained with Romanowsky-Giemsa and the micronuclei scored in 1000 binucleated cells. For both patient groups, a linear-quadratic dose-response curve was fitted through the data set of the first blood sample by a least squares analysis. The mean increase in micronuclei after $^{131}$I therapy (second blood sample) was fitted to this curve and the mean equivalent total body dose (ETBD) calculated. Surprisingly, in view of the large difference in administered activity between thyroid carcinoma patients and thyrotoxicosis patients, the increase in micronuclei after therapy (mean ± s.d.: 32 ± 30 and 32 ± 23, respectively) and the equivalent total body dose (0.34 and 0.32 Gy, respectively) were not significantly different ($P > 0.1$). The small number of micronuclei induced by $^{131}$I therapy (32 ± 29), compared with external beam radiotherapy for Hodgkin’s disease (640 ± 381) or cervix carcinoma (298 ± 76) [1], gave a cancer mortality estimate of less than 1%. This also explains why late detrimental effects in patients after $^{131}$I treatment have not been reported in the literature. (© 1999 Lippincott Williams & Wilkins)

Introduction
Since its first therapeutic use in 1942 [2], radioiodine ($^{131}$I) has played an important role in the treatment of thyrotoxicosis patients and patients suffering from differentiated thyroid carcinoma. For the treatment of thyrotoxicosis, $^{131}$I therapy is cost-effective and its safety is well-documented [3, 4]. An activity of 185–1110 MBq (per os) is usually administered. In the treatment of differentiated thyroid carcinoma, the additional administration of $^{131}$I following surgical resection of the thyroid has been shown to improve prognosis [5], with a standard activity of 3700–7400 MBq usually being administered. In spite of the high administered activities, no significant increase in the incidence of secondary neoplasms has been reported in the literature [3, 6, 7]. However, there is still some reluctance to treat thyrotoxicosis patients under 40 years of age with $^{131}$I, because of concern about the radiation burden and subsequent late side-effects. The radiation burden to the body is mainly due to iodine circulating in the bloodstream, in addition to irradiation from the thyroid or thyroid remnant source.

The aim of this study was to determine the cytogenetic damage to peripheral blood lymphocytes in 31 patients receiving $^{131}$I as therapy for thyrotoxicosis using the
cytokinesis-blocked micronucleus assay. For a comparison, eight patients with thyroid carcinoma were also studied. A multicentre setting was favoured to allow the inclusion of a statistically significant number of patients over a relatively short period of time.

Micronuclei are small, round cytoplasmic bodies containing chromatin. They originate when radiation or chemicals disrupt the DNA and chromosome fragments fail to incorporate in the nucleus during subsequent cellular division. The dose-dependent induction of micronuclei in lymphocytes has been well characterized after exposure to various kinds of radiation [8–16]. Good agreement between in-vitro and in-vivo induced micronucleus frequencies was obtained after whole-body irradiation and partial body irradiation [1], indicating that micronuclei in lymphocytes are a reliable non-invasive tool to estimate radiation damage for the purpose of biological dosimetry. Based on individual dose–response curves, determined by in-vitro irradiation with $^{60}$Co gamma rays of a blood sample taken before $^{131}$I therapy, individual in-vitro radiosensitivity was investigated. For thyrotoxicosis patients, the correlation between the increase in micronuclei as a result of the administered activity and the activity retained in the thyroid was investigated. From the general dose–response curve for thyrotoxicosis patients and for thyroid carcinoma patients, a mean equivalent total body dose (ETBD) was determined for both groups. Based on the results of a similar study of patients treated with external beam radiotherapy for Hodgkin’s disease or cervix carcinoma [1], and on epidemiological data in this population [17–19], the results obtained can be interpreted within the framework of cancer mortality assessment of $^{131}$I therapy for thyrotoxicosis.

**Methods**

**Patients**

We studied a group of 39 patients, referred by their endocrinologist to the nuclear medicine department of one of the participating hospitals for treatment with $^{131}$I for thyroid disease. All patients provided informed consent. Thirty-one patients with a mean age of 60 years (range 25–82 years) were treated for thyrotoxicosis. Most were women (27 women, 4 men), as is the case naturally with this benign disease. They received a mean activity of 703 MBq (range 295–1295 MBq).

Another eight patients (3 men, 5 women) with a mean age of 49 years (range 9–78 years), with non-metastatic differentiated thyroid carcinoma, were included as a comparison with the thyrotoxicosis patients. They received a standard activity of 3700 MBq $^{131}$I, except one patient aged 9 years who received 2220 MBq $^{131}$I.

**Blood sampling and irradiation**

A heparinized blood sample (5 ml) was taken immediately before administration of the $^{131}$I therapeutic activity. A second heparinized blood sample (5 ml) was drawn 7 days post-therapy in 33 patients. For practical reasons, six patients treated for thyroid carcinoma at the University Hospital of Gent had their second blood sample taken 10 days post-therapy, at the time they reported for their post-therapy total-body scan.

**Micronucleus assay**

According to the method of Fenech and Morley [8], whole-blood cultures were incubated at 37°C for 70 h in a 5% CO$_2$ (95% dry air) atmosphere. The culture medium consisted of RPMI 1640 with 2 mmol·l$^{-1}$ L-glutamine and Hepes buffer (Gibco) supplemented with 15% fetal calf serum and antibiotics. Phytohaemagglutinin (Difco) at a concentration of 40 μg·ml$^{-1}$ was used to stimulate cell division. Cytochalasin B (3.5 μg·ml$^{-1}$ in DMSO; Sigma) was added 42 h after culture initiation to block cytokinesis. After incubation for 70 h, the cells were harvested, treated with a hypotonic solution of 0.075 molar KCl, and fixed with a mixture of methanol: glacial acetic acid (8:1) following the protocol described by Vral et al. [20]. The slides were stained with Romano–Sky-Giemsa and the micronuclei scored in 1000 binucleated cytokinesis-blocked cells under a light microscope with a magnification of 400×, based on the criteria summarized by Fenech [21].

**Equivalent total-body dose**

The equivalent total body dose is the in-vitro $^{60}$Co gamma radiation dose, which produces the same yield of micronuclei in a blood sample as that induced in vivo by the $^{131}$I treatment.

The number of micronuclei, obtained after in-vitro irradiation, was averaged over the thyrotoxicosis patient group and over the thyroid carcinoma patient group and plotted against the $^{60}$Co gamma radiation dose. A linear-quadratic dose–response curve was derived by a least squares fit to the data. The linear-quadratic nature of the dose–response relationship for induction of micronuclei has been studied previously [1, 3]. The ETBD was calculated by fitting the mean increase in micronuclei after $^{131}$I therapy for each patient group to the dose–response curve.

For the thyrotoxicosis patients, the ETBD obtained was corrected for the dose retained in the body after the second blood sample using the effective half-life determined from the pre-therapy uptake curve. When this information was not available ($n = 11$), an average value of 4.5 days for the effective half-life was adopted.
Estimation of risk based on biological dosimetry

Fig. 1. Number of micronuclei before and after $^{131}$I therapy for each patient. Patients are grouped by diagnosis. The error bars represent the standard deviation based on the Poisson distribution. Solid bars = number of micronuclei before therapy; stippled bars = number of micronuclei after therapy; $\diamondsuit$ = patients not showing a statistically significant difference in the number of micronuclei before and after $^{131}$I therapy.

Measurement of $^{131}$I uptake and retention in the thyroid of thyrotoxicosis patients

$^{131}$I retention in the thyroid 7 days post-therapy was measured using a ‘Nardev-Babylone 81’ ionization chamber mounted in lead shielding. A PVC neck cuff extended from the shielding to ensure a standard distance to the patient’s neck of 8.5 cm. This distance permitted a field of view 12 cm in diameter. The probe was calibrated with $^{131}$I-NaI dissolved in 20 ml of water in a neck phantom. For the calibration, three different activities were used: 41, 87 and 218 MBq.

Statistical analysis

Statistical analysis was performed using MedCalc®. Chi-square was used to test for normal distribution of the data sets. Differences in the mean were evaluated using paired or unpaired two-tailed Wilcoxon tests, where applicable. Correlations were investigated by means of the Spearman rank or Pearson correlation test. In Fig. 1, the error bars represent the standard deviations based on the Poisson distribution.

Results

An overview of the results is given in Table 1. In Fig. 1, the number of micronuclei per 1000 binucleated cells before and after therapy was compared for all patients in the study. Except in six patients, a statistically significant increase ($P < 0.05$) in the number of micronuclei was observed after therapy (mean $\pm$ s.d.: before 26 $\pm$ 14; after 50 $\pm$ 29).

The mean increase in micronuclei after $^{131}$I therapy was higher for the patients with differentiated thyroid carcinoma (32 $\pm$ 23) than for those with thyrotoxicosis (23 $\pm$ 21). When corrected for the activity remaining 1 week after $^{131}$I administration, the mean increase in the number of micronuclei for the thyrotoxicosis patient group was 32 $\pm$ 30. For the thyroid carcinoma patients, no correction was applied because of the rapid washout of $^{131}$I from the body ($0.75 \pm 0.01$ days [22]). The number of micronuclei due to $^{131}$I therapy for the thyrotoxicosis patient group (corrected) and the thyroid carcinoma patient group was not significantly different ($P > 0.1$). No significant correlation ($R = 0.23$) was found between
Table 1. Overview of the results.

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<th>MBq ret.</th>
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<th>MN after therapy</th>
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Thyroid carcinoma

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Note: MBq adm. = administered activity (MBq); MBq ret. = activity retained in the thyroid 7 days post-therapy; MN = micronuclei per 1000 binucleated cells; % uptake = maximum percent uptake as determined by the pre-therapy uptake curve; T_{1/2} = effective half-life of ^131I in the thyroid as determined by the pre-therapy uptake curve.

the administered activity and the increase in micronuclei after ^131I therapy. In contrast to the average increase in micronuclei seen in this study, an abnormally large increase after therapy

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(121 micronuclei) was noted for patient #30. Based on the in-vitro increase in micronuclei (an increase of 66 micronuclei for 0.5 Gy and an increase of 153 micronuclei for 1 Gy), this patient can be considered to have a high radiosensitivity.

Based on the linear-quadratic fit to the mean number of micronuclei after in-vitro irradiation of the blood sample for all thyrotoxicosis patients and for all thyroid carcinoma patients, the ETBD was determined from the mean increase in micronuclei after therapy. No significant difference ($P > 0.1$) in ETBD values was noted between the patients treated for differentiated thyroid carcinoma (mean 0.32 Gy, interval 0.07–0.55) and patients treated for thyrotoxicosis (mean 0.34 Gy, interval 0.16–0.55).

For the 18 thyrotoxicosis patients for whom a retention measurement was performed, the mean activity retained in the thyroid 7 days after therapy was 162 MBq (range 56–324 MBq). No significant correlation ($R = 0.21$) was noted between the activity retained in the thyroid 7 days post-therapy in the thyrotoxicosis patients and the increase in the number of micronuclei.

**Discussion**

In the present study, the cytokinesis-blocked micronucleus assay was used to assess the cytogenetic damage in patients after $^{131}$I therapy. Surprisingly, in view of the large difference in administered activity (mean 3515 MBq for thyroid carcinoma patients and mean 703 MBq for thyrotoxicosis patients), the increase in micronuclei for thyrotoxicosis patients ($32 \pm 30$) was not significantly different from that of the thyroid carcinoma patients ($32 \pm 23$). The absence of a difference in radiation damage could be due to the small size of the remnant tissue, the low iodine uptake and the rapid washout of $^{131}$I from the body in thyroid carcinoma patients compared with the thyrotoxicosis patients [22].

For the thyrotoxicosis patients, the mean increase in micronuclei was greater in the present study (mean 32 micronuclei) than in a similar study of thyrotoxicosis patients carried out by Gutierrez et al. [23] (mean 9 micronuclei). In their study, the increase in micronuclei was only significant in patients receiving more than 500 MBq $^{131}$I. However, their patients received a lower mean activity of $^{131}$I (mean 582 MBq) than the patients in the present study (mean 703 MBq).

For the thyrotoxicosis patients, no correlation was found between the increase in micronuclei and the administered activity; nor did Gutierrez et al. [23] find a correlation between these variables. That no correlation was found between the increase in micronuclei and the activity retained in the thyroid 7 days post-therapy in the present study illustrates the important contribution of $^{131}$I circulating in the patient’s bloodstream to the total radiation burden of the patient.

For the thyroid carcinoma patients, the increase in micronuclei after $^{131}$I therapy (mean 32 micronuclei) was quite similar to values (17–40 micronuclei) published previously [24–27]. The mean ETBD in the present study of 0.32 Gy is similar to that of 0.33 Gy calculated by Watanabe et al. [28] and somewhat lower than the 0.54 Gy calculated by M’Kacher et al. [29] after $^{131}$I treatment for thyroid carcinoma. The dispersion in the increase in micronuclei within the thyroid carcinoma patient group in the present study might be explained by the differences in $^{131}$I retention between patients.

The cytokinesis-blocked micronucleus assay has also been used previously to determine the cytogenetic damage in peripheral blood lymphocytes of patients treated with fractionated partial-body radiation therapy with external beams [1, 11, 30]. Using the same method as in the present work, the mean increase in micronuclei in the study of Thierens et al. [11] was 298 ± 76 for cervix carcinoma patients and 640 ± 381 for patients with Hodgkin’s disease. In the present study, the mean increase in micronuclei after $^{131}$I therapy for thyrotoxicosis ($32 \pm 30$) was 10–20 times less than that obtained after external beam radiotherapy.

After radiotherapy for cervix carcinoma, a two-fold mean increase in leukaemia was reported by Boice and Hutchinson [17] and Boice et al. [18]. Kleinerman et al. [20] reported that curative external beam radiotherapy for 49,828 patients with cervical cancer resulted in 3750 patients surviving for more than 30 years, but developing secondary cancers very late in life. Boice et al. [31] calculated a cancer mortality of 10% after irradiation for cervix carcinoma.

Taking into account these data on cancer mortality after external beam radiotherapy for cervix carcinoma (10%) and the ten-fold lower yield in micronuclei after $^{131}$I therapy, the cancer mortality after $^{131}$I therapy for thyrotoxicosis can be estimated to be about 1%. The mean age of the patients generally treated with $^{131}$I for benign disease is rather high (58 years in present study). In Europe, $^{131}$I therapy is often not considered the first therapeutic option in thyrotoxicosis patients below the age of 40 years. In the ICRP-60 report [32], the cancer mortality after a single small dose of radiation for populations over 40 years at the time of exposure is calculated to be 2.5% per Sv. Using this value, a cancer mortality of 0.8% for patients treated with $^{131}$I can be deduced from the mean value of 0.33 Gy found for the ETBD in the present study. This estimate is comparable to the cancer mortality of 1% calculated above, but lower than the 1.6% calculated by Huysmans et al. [33] for patients treated with large doses of $^{131}$I for a multinodular goitre. This may explain why no significant increase
in the incidence of leukaemia or solid tumours has been reported in the literature [3, 6, 7, 34].

Conclusion

The cytogenetic results for the group of thyrotoxicosis patients in the present study support the contention that treatment with \(^{131}I\) that excludes younger (< 40 years) patients will result in a cancer mortality of less than 1%.

Acknowledgements

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References


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**PATIENT DOSIMETRY AFTER $^{131}$I-MIBG THERAPY FOR NEUROBLASTOMA AND CARCINOID TUMORS.**

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**Key words:**

Radionuclide therapy, $^{131}$I-MIBG, neuroblastoma, carcinoid tumors, dosimetry.
Patient dosimetry after $^{131}$I-MIBG therapy for neuroblastoma and carcinoid tumours

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Summary

Aim The aim of the study was to determine the equivalent total body dose (ETBD) using the cytokinesis-blocked micronucleus assay in 22 $^{131}$I-meta-iodobenzylguanidine ($^{131}$I-MIBG) therapies (18 neuroblastoma, mean 5097 MBq, SD 1591; and four carcinoid tumours, mean 7681 MBq, SD 487). The results are correlated with the total body radiation dose according to the Medical Internal Radiation Dosimetry (MIRD) formalism.

Methods For each patient, blood samples were taken immediately before and 1 week after $^{131}$I-MIBG therapy. The first blood sample was irradiated in vitro with $^{60}$Co γ-rays to determine the dose–response curve. Micronuclei were scored in 1000 binucleated cells. By using the dose–response curve the ETBD was derived from the increase in micronuclei after $^{131}$I-MIBG therapy (second blood sample). Based on three consecutive biplanar scans taken at 3, 6 and 9 days post-administration respectively, the total body dose following the MIRD formalism was calculated.

Results The micronucleus assay was evaluable in only 14 out of 22 $^{131}$I-MIBG therapies due to cell division inhibition caused by previous chemotherapy treatments and lymphocyte dilution due to blood transfusions given shortly after $^{131}$I-MIBG therapy. For these 14 therapies, the mean micronucleus yield after $^{131}$I-MIBG therapy was significantly increased ($P < 0.01$) with a mean of 92 (SD 77) for neuroblastoma patients and with a mean of 35 (SD 8) for carcinoid patients. The increase observed in the present study is greater than previously observed after $^{131}$I therapy and $^{89}$Sr therapy but much lower than after external beam radiotherapy. For all patients treated with multiple therapies, the initial increase in micronucleus yield had at least partially recovered by the time of the next therapy. This might be explained by an increased turnover of lymphocytes. A mean ETBD of 0.95 Gy (SD 0.55) for neuroblastoma patients and a mean of 0.46 Gy (SD 0.09) for carcinoid patients was calculated. A reasonable correlation ($R = 0.87$) between the ETBD and the MIRD dose was obtained. The slope value of 0.75 can be explained by the low dose rate effect.

Conclusions The observation in the present study of important inter-individual variability in the total body dose, with the possibility of high dose values, suggests the necessity of individual dosimetry when administering $^{131}$I-MIBG therapy, especially considering that generally more than one therapy is given to each patient. (© 2001 Lippincott Williams & Wilkins)

Keywords: patient dosimetry, $^{131}$I-MIBG therapy, neuroblastoma, carcinoid tumours.

Introduction

Since its first scintigraphic use, in 1981 [1], $^{131}$I-meta-iodobenzylguanidine ($^{131}$I-MIBG) has played an important role in the diagnosis and staging of neuro-endocrine tumours. With a cumulative sensitivity of 92% and specificity of 100% in 779 patients with neuroblastoma [2], $^{131}$I-MIBG scintigraphy has established itself as the most sensitive technique for detection, staging and follow-up of this disease. Moreover, reported results reveal that 70% of carcinoids in 275 patients concentrate this tracer [2]. Since 1984, $^{131}$I-MIBG has also been used therapeutically in neuroblastoma [3, 4].
experience in 276 children with neuroblastoma indicated an objective response rate of 35% [2, 5]. Most of these patients had progressive and intensely pretreated stage IV disease as they were only treated with 131I-MIBG after chemotherapy had failed. In addition, 131I-MIBG provided adequate palliation and improved the quality of life for many children. In 1991, results were available for 52 patients with metastatic carcinoid disease, revealing on the one hand an objective response of only 15% but on the other hand palliation, which may be very meaningful and long lasting, in 65% [2]. For both therapies, usually a fixed dose of 3700–7400 MBq of 131I-MIBG is infused intravenously over a 2–4 h period.

In general, 131I-MIBG therapy is well tolerated. Haematological side effects are usually limited to thrombocytopenia. However, the effect is much more pronounced when the 131I-MIBG therapy is given after pretreatment with chemotherapy. When bone marrow invasion is present, 131I-MIBG therapy can lead to severe bone marrow depression [3, 5–8].

As 131I-MIBG therapy is not exclusively used for palliation but can also have a curative effect, and as the therapy is usually repeated, the radiation dose to the patient should be determined. Although some dose estimation studies have been performed, [3, 7, 9, 10], cytogenetic evaluation of radiation induced cytogenetic damage to lymphocytes in vivo after therapy with 131I-MIBG has not yet been performed.

For other common radionuclide therapies, such as 131I therapy for thyroid disease and 89Sr therapy for pain palliation of bone metastases, examination of the radiation dose to lymphocytes has been performed using the cytokinesis blocked micronucleus assay [11–17]. The same procedure has also been used to study the radiation damage to lymphocytes after radiotherapy [18] and after fractionated partial body radiotherapy [19].

The purpose of the study was primarily an evaluation of the degree of cytological radiation induced damage to lymphocytes in vivo after 131I-MIBG therapy for neuroblastoma and carcinoid tumours using the cytokinesis-blocked micronucleus assay. Within this topic the effect of multiple 131I-MIBG therapies to the lymphocytes was also investigated. Secondly, the genetic damage to the lymphocytes was correlated with the total body dose calculated according to the Medical Internal Radiation Dosimetry (MIRD) formalism.

Patients and methods

Patient population

This study comprises a total of 22 131I-MIBG therapies carried out on 12 patients (eight females and four males). A group of 10 patients with a mean age of 8 years (range 2–32 years) received a total of 18 therapies with a mean activity of 4522 MBq (SD 1107 MBq) for neuroblastoma stage III or IV. The remaining two patients, aged 45 and 50 years, each received two therapies, with a mean of 7681 MBq (SD 487) 131I-MIBG for carcinoid tumours with multiple liver metastases.

Blood sample collection and irradiation

The first heparinized 5 ml blood sample was taken immediately before administration of the 131I-MIBG therapeutic dose. This blood sample was divided into three fractions. One fraction served as a non-irradiated control. The other two fractions were irradiated in vitro at 37°C with a dose of 0.5 Gy and 1.0 Gy 60Co γ-rays. A second heparinized blood sample of 5 ml was taken 7 days post-administration.

Micronucleus assay

Whole blood cultures were incubated at 37°C for 70 h in a 5% CO2 atmosphere. The culture medium consisted of RPMI 1640 with 2 mm L-glutamine and Hepes buffer (Gibco) supplemented with 15% fetal calf serum and antibiotics. Phytohaemaglutinin (PHAP, Difco) at a concentration of 40 μg·ml−1 was used to stimulate cell division. According to the method of Fenech and Morley [20], cytochalasin B (6 μg·ml−1 in DMSO, Sigma) was added 42 h after culture initiation in order to block cytokinesis. After an incubation period of 70 h, the cells were harvested, treated with a hypotonic solution of 0.075 M KCl, and fixed with a mixture of methanol–glacial acetic acid 8:1 following the protocol described by Vral et al. [21]. Slides were stained with Romanowsky–Giemsa and micronuclei were scored in 1000 binucleated cytokinesis-blocked cells under the light microscope with a magnification of 400 ×, based on the criteria summarized by Fenech [22].

Equivalent total body dose

The equivalent total body dose (ETBD) is the dose of ionizing radiation, which, if received homogeneously by the whole body, would produce the same yield of micronuclei, as the dose actually absorbed in the different organs and tissues.

For each patient group, the mean micronucleus yield, obtained after in vitro irradiation, was plotted against the 60Co dose and a linear-quadratic dose–response curve was derived by a least squares fit to the data. The linear-quadratic nature of the dose–response relationship for induction of micronuclei has been studied previously [23]. Based on this in vitro dose response, the ETBD was
Dosimetry after \(^{131}\text{I}\)-MIBG therapy for tumours

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derived from the increase in micronucleus yield in the blood sample of each patient 1 week after administration of the activity.

\(^{131}\text{I}\)-MIBG uptake and dose calculation according to the MIRD formalism

For each patient a set of three total-body 180° biplanar scans was made after therapy. All scans were made on an Elscint Helix double-head gamma camera fitted with high-energy parallel hole collimators. The first scan was made at day 3, the second scan at day 7 and the third scan at day 10 post-administration. A syringe containing a known activity of \(^{131}\text{I}\) in a polymethylmethacrylate (PMMA) syringe phantom (diameter 6 cm) was placed at the patient’s feet. By drawing regions of interest (ROIs) around the syringe, the total body and suitable background regions, the activity in each ROI could be determined by using the geometric mean of the total counts in the anterior and posterior scans after correction for the difference in thickness between phantom and patient.

The activity at the time of administration in each ROI was then plotted against time, and a bi-exponential function was fitted through the dataset. To allow a comparison between the ETBD derived from the cytokinesis blocked micronucleus assay and the total body dose calculated with the MIRD formalism, the cumulated activity until 168 h after administration was calculated by integrating the bi-exponential fit. The dose to the total body was then calculated using the standard MIRD formalism using weight adapted 5 (total body \(\rightarrow\) total body) values. These 5 values were obtained by a fit through the values of the different phantoms of various ages considered in the MIRDDOSE-3\(^{16}\) program (Oakridge associated Universities, 1994).

Statistical analysis

Statistical analysis was performed by means of Medcalc\(^{18}\). Data sets were first tested for normal distribution by means of a chi-squared test. Differences for the mean were evaluated by means of paired two-tailed Wilcoxon tests, where applicable. Correlations were investigated by means of the Spearman rank or Pearson correlation test. Error bars in the figures represent the standard deviations based on the Poisson distribution.

Results

An overview of the results obtained in the present study is given in Table 1. Because \(^{131}\text{I}\)-MIBG therapy for neuroblastoma is given as a second line treatment, many of our patients had received chemotherapy treatment shortly before the \(^{131}\text{I}\)-MIBG therapies. The effect of the chemotherapy is to render the lymphocytes less suitable for evaluation of cytotoxic damage by means of the cytokinesis blocked micronucleus assay because it inhibits cell division. Since the technique is based upon a baseline blood sample before therapy (divided into three fractions) and a blood sample at 7 days post-therapy, all blood samples, including the irradiated fractions, have to be evaluable (1000 binucleated lymphocytes have to be counted). As can be seen from Table 1, this was not the case in three of our patients (numbers 10, 11 and 12), so these data had to be excluded from the micronucleus yield and ETBD calculations in the article.

Even when we were able to count 1000 lymphocytes, we additionally found that a subset of patients had received transfusions (containing non-irradiated lymphocytes) before the second blood sample was taken. Thus, the micronucleus data of these patients (numbers 7, 8, 9 and 10) were useless for the determination of the ETBD. The ETBD results of the present study are therefore based on the first six patients (14 therapies) only.

As can be seen in Fig. 1, the micronucleus yield in all remaining patients was significantly \((P<0.01)\) increased after \(^{131}\text{I}\)-MIBG therapy. The mean increase was 92 micronuclei (SD 77) for neuroblastoma patients while it was significantly less \((P<0.001)\) with a mean of 35 micronuclei (SD 8) for carcinoid patients. The mean increase in micronucleus yield after \textit{in vitro} irradiation with 0.5 Gy and 1 Gy \(^{60}\text{Co}\) in this study was 40 micronuclei (SD 26) and 97 micronuclei (SD 30), respectively, for neuroblastoma patients, and 29 micronuclei (SD 11) and 66 micronuclei (SD 13), respectively, for carcinoid patients.

Five patients received multiple subsequent \(^{131}\text{I}\)-MIBG therapies. The micronucleus yields before and after each therapy are plotted against time in Fig. 2. As can be seen in Fig. 2, the increase in micronucleus yield 7 days after administration of the therapeutic activity has at least partially recovered by the time of the subsequent therapy. For all patients, the micronucleus yield rises again after the administration of the subsequent therapeutic amount of \(^{131}\text{I}\)-MIBG. The mean lymphocyte half-life that can be calculated from these results was 3.9 months (range 1.7–6.7 months).

From the increase in micronucleus yield after \(^{131}\text{I}\)-MIBG therapy the ETBD for each treatment was determined using the \textit{in vitro} dose–response curve. Within the different patient subgroups the highest ETBD was found for patients suffering from neuroblastoma (mean ETBD 0.96 Gy, SD 0.58), while it was significantly less \((P<0.01)\) for the patients suffering from carcinoid tumour (mean 0.46 Gy, SD 0.09). An ETBD value of more than 2 Gy (2.39 Gy) was obtained only for patient 1. As
Table 1. Overview of the demographic data and results

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* Numerical values (1–8) were used to identify patients, while a letter (a–e) was added to indicate different therapies for the same patient.
† Patient’s age at the time of the therapy.
‡ Activity administered activity to the patient.
§ Cumulated activity in the body until 168 h after administration of the activity.
¶ Time between last chemotherapy treatment and first treatment with 131I-meta-iodobenzylguanidine (131I-MIBG).
M, male; F, female; NB, neuroblastoma; CA, carcinoid tumour.
MN, micronucleus yield per 1000 binucleated cells; 0 Gy, before therapy; 0.5 Gy, after in vitro irradiation with 0.5 Gy 60Co γ-rays; 1 Gy, after in vitro irradiation with 1 Gy 60Co γ-rays; incr., increase in micronucleus yield 168 h after 131I-MIBG therapy.
ETBD, equivalent total body dose.
MIRD, total body dose as calculated by the Medical Internal Radiation Dosimetry (MIRD) formalism.

Fig. 1. Individual increase in micronucleus yield per 1000 binucleated cells 1 week after 131I-meta-iodobenzylguanidine (131I-MIBG) therapy. Error bars represent the standard deviations based on the Poisson distribution. (■), micronucleus yield before therapy; (□), micronucleus yield after therapy.

Fig. 2. Time plot of the micronucleus yield during multiple subsequent 131I-MIBG therapies in five patients.
can be seen from the total body scan presented in Fig. 3, this patient showed both extensive metastases and bone marrow invasion.

The mean cumulative activity to the total body calculated from the biplanar scans was 201 GBq h (SD 131) for neuroblastoma patients while it was significantly ($P < 0.001$) higher with a mean of 231 GBq h (SD 59) for carcinoid patients.

The mean total body dose as calculated by the MIRD formalism was 1.34 Gy (SD 0.66) for neuroblastoma patients while for carcinoid patients it was significantly ($P < 0.001$) lower with a mean of 0.46 Gy (SD 0.09).

As expected, no correlation was found between the ETBD and the administered activity. However, a reasonable correlation ($R = 0.87$) was obtained between the ETBD and the total body dose calculated by the MIRD formalism as shown in Fig. 4. The slope of the linear regression fit was 0.75.

Discussion

Since $^{131}$I-MIBG therapy is a second line treatment for neuroblastoma in Belgium, all of the included neuroblastoma patients received chemotherapy at a certain time before $^{131}$I-MIBG therapy. Previous chemotherapy can jeopardize the evaluability of the cytokinesis-blocked micronucleus assay. These problems are purely technical, because chemotherapy inhibits cell division when cells are stimulated by the phytohaemaglutinin that is added to the culture medium. For patients 10, 11 and 12, we were not able to induce 1000 cells in each fraction to divide, and therefore their data had to be excluded from calculation of the ETBD. As can be seen in Table 1, the time between the last chemotherapy treatment and the first $^{131}$I-MIBG treatment tended to be shorter (1–5 months) in these patients. The effect is individually dependent because patients 1 and 4 also had a rather short (2 to ‘several’ months) period of time between chemotherapy and $^{131}$I-MIBG therapy. Nevertheless, we were able to count 1000 lymphocytes in every blood sample.

Since every patient serves as his own personal control (blood sample before therapy), possible ‘cross talk’ between radiomimetic effects from chemotherapy and $^{131}$I-MIBG radiation did not present a problem in our study.

Additionally, a subset of patients (patients 7, 8, 9 and 10) received ‘whole blood’ transfusions. The effect of blood transfusions is not easy to calculate. The infusion of fresh lymphocytes dilutes the resident long-term irradiated lymphocytes. The lymphocytes for the blood transfusion are simply exposed to the $^{131}$I irradiation for a shorter period of time and, even more importantly, they
are exposed to a lower resident activity of $^{131}$I-MIBG because a large part of the unbound $^{131}$I-MIBG had already been excreted from the body. The effects of blood transfusion are obvious in patient 10 (Table 1). In this patient the number of micronuclei after treatment is actually significantly lower than before therapy in spite of the considerable total body dose calculated according to the MIRD formalism. To a lesser extent also patient 8 seems obviously affected because an unusually small increase in micronuclei is found after $^{131}$I-MIBG therapy. Although the effect is not directly observable for patients 7 and 9, the same mechanisms must be at work. We therefore decided to exclude also the data from these two patients from calculation of the ETBD to be sure of using only perfectly ‘clean’ data. Therefore, the ETBD results of the present study had to be based on the first six patients (14 therapies) only.

The mean increase in micronucleus yield for neuroblastoma patients (mean 92 micronuclei, SD 77) found in the present study is significantly higher ($P < 0.001$) than for carcinoid patients (mean 35 micronuclei, SD 8). When comparing the increase in micronucleus yield with other radionuclide treatments, the increase in micronucleus yield for neuroblastoma patients is higher than for patients treated with $^{131}$I therapy for thyroid disease (mean 32, SD 30 [17]; mean 21, SD 3 [15]; mean 9 [24]) or with $^{89}$Sr for palliation of painful bone metastases (mean 22, SD 6 [16]). On the other hand, the increase in micronucleus yield for carcinoid patients is within the same order of magnitude as for the other radionuclide therapies described above. However, the mean increase in micronuclei found in the present study is significantly lower than after external beam radiotherapy for carcinoma of the cervix (mean 298, SD 76) or Hodgkin’s disease (mean 640, SD 381) using the same methodology [18].

For most patients the initial micronucleus yield is already higher than expected for normal individuals of this age group [23]. This is probably due to the fact that most patients had previously received chemotherapy, because $^{131}$I-MIBG therapy is a second line treatment for neuroblastoma in Belgium.

For the first time the residual damage after multiple subsequent $^{131}$I-MIBG therapies was investigated in the present study. In all patients an initial large increase in micronucleus yield after administration of the $^{131}$I-MIBG therapy had at least partially recovered by the time of the subsequent $^{131}$I-MIBG therapy. A similar effect was reported by Watanabe et al. [16] by taking sequential blood samples up to 2 months after $^{89}$Sr therapy for painful bone metastases. Also Fenech et al. [19] reported an initial increase followed by slow decline (50% after 12 months, but with large inter-individual fluctuations) in micronucleus yield for patients treated with external partial body radiotherapy. On the other hand, in a case report with a long-term follow-up, Livingston et al. [11] reported only fluctuations in the micronucleus yield of a patient after $^{131}$I therapy for thyroid carcinoma but could not find a significant change in micronucleus yield up to 8 months after therapy.

The mean half-life of lymphocytes found in the present study (as derived from the reduction in micronucleus yield between subsequent $^{131}$I-MIBG therapies in the same patient) was 3.9 months (range 1.7–6.7 months). This result corresponds to the increased turnover of lymphocytes (micronucleus yields returning to pretreatment values within 4–6 months) found in children treated repeatedly for thyroid carcinoma, as reported by Streffer et al. [25]. From the analysis of the Goiânia accident, Ramalho et al. [26] concluded that the disappearance of unstable chromosome aberrations (such as micronuclei) is dose dependent. The mean lymphocyte half-life in their study was 5.3 months in people receiving up to 1 Gy while it was significantly less (3.7 months) in people receiving more than 1 Gy, a result very similar to the 3.9 months calculated in the present study.

The ETBD for neuroblastoma patients (mean 0.96 Gy, SD 0.58) was significantly higher than for carcinoid patients (mean 0.46 Gy, SD 0.09), although the administered activities were significantly higher in the latter patient group (4995 and 7681 MBq respectively). This is not surprising, taking into account the difference in body mass between the pediatric neuroblastoma patients and the adult carcinoid patients. Also the location of the activity within the body was very different for both patient groups: in the liver for carcinoid patients while for neuroblastoma patients the activity was localized in multiple sites more widely distributed throughout the body.

The mean ETBD of 0.96 Gy (SD 0.58) for neuroblastoma patients found in present study is significantly higher ($P = 0.0001$) than after $^{131}$I therapy for thyroid disease mean 0.4 Gy [17] (a result correlating well with a similar study carried out by Watanabe et al. [15], who found a mean of 0.33 Gy) or after $^{89}$Sr therapy (mean 0.5 Gy [16]). On the other hand, the mean ETBD of 0.46 Gy (SD 0.09) for carcinoid patients is within the same order of magnitude as for the other radionuclide therapies described above. Excluding patient 1 with a very high ETBD of 2.39 Gy, the ETBD values found in the present study are much lower than after external beam radiotherapeutic treatment for cervix carcinoma (mean 5.69 Gy, SD 1.40) or Hodgkin’s disease (mean 6.26 Gy, SD 1.28) [18].

For the patient group as a whole, a mean MIRD dose of 1.22 Gy (SD 0.57) was calculated. The MIRD dose was significantly ($P < 0.001$) higher for neuroblastoma patients (mean 1.34 Gy, SD 0.56 Gy) than for carcinoid patients (mean 0.46 Gy, SD 0.09). Within the neuroblastoma patient group, three patients (patients 1, 10 and 12)
received a total body dose of more than 2 Gy (2.26 Gy, 2.10 Gy and 2.59 Gy, respectively). As can be seen in Fig. 3 these patients presented with both extensive metastases and bone marrow invasion. According to the MIRD calculations, in our study seven additional therapies resulted in a total body radiation burden of more than 1 Gy. The observation in the present study of important inter-individual variability in the total body dose both according to the MIRD calculations and the ETBD, with the possibility of high dose values, suggests the necessity of individual dosimetry when administering $^{131}$I-MIBG therapy, especially considering that generally more than one therapy is given to each patient.

As observed in previous studies on patients treated with $^{131}$I for thyroid disease [17], no correlation was found between the administered activity and the ETBD, nor with the MIRD dose calculations. On the other hand, a reasonable correlation was found between the ETBD derived from biological dosimetry (where evaluable) and the total body dose according to the MIRD formalism based on biplanar scans ($R = 0.87$). The linear regression analysis depicted in Fig. 4, yields a slope value of 0.75. This value less than 1, reflects the low dose rate effect of the $^{131}$I irradiation in the body, allowing partial repair of the cellular damage, resulting in less genetic damage and an apparently lower radiation dose.

The fact that patient 1 seems to be such an isolated case in Fig. 4, is due to the blood transfusions and/or cytotoxic effects of previous chemotherapy treatments which has caused us to omit the data of patients 7A, 7B, 10A and 12, who also received high total body doses (1.89 Gy, 1.84 Gy, 2.10 Gy and 2.59 Gy, respectively) according to the MIRD calculations. When patient 1 is omitted from this figure, the correlation coefficient drops to 0.56 instead of 0.87. However, the slope value of the best fitting curve through the remaining data cloud (0.68 instead of 0.75) still supports the low dose rate effect and the ETBD is still generally lower than the MIRD value.

Since the recent developments within the neuroblastoma task group in Europe point to a combination of chemotherapy given at the same time as $^{131}$I-MIBG therapy, we have decided not to continue this type of cytogenetic study on patients treated with $^{131}$I-MIBG for neuroblastoma.

**Conclusion**

The observation in the present study of important inter-individual variability in the total body dose, with the possibility of high dose values, suggests the necessity of individual dosimetry when applying $^{131}$I-MIBG therapy, especially considering that, generally, more than one therapy is given to each patient.

**Acknowledgements**

Myriam Monsieurs is the recipient of the Mallinckrodt Benelux Award 1997 and the grant Bijzonder onderzoeksfonds 1998–1999. Hence, the financial support of Mallinckrodt and the University of Ghent is gratefully acknowledged. The data in this study could not have been collected without the help of Ms I. Meirlaen, who dealt with the cell cultures; Mr S. Vandeputte who assisted with the calculation of the bi-exponential fits; and Mr J.P. Van Haestel who prepared the standard syringes. The authors also wish to thank Dr G. Laureys for her help in gathering the data. Special thanks to Dr Y. Benoit and Dr C. Hoefnagel (Amsterdam).

**References**


TRANSLOCATION FREQUENCIES IN PATIENTS TREATED ONE YEAR EARLIER WITH RADIOACTIVE IODINE FOR THYROTOXICOSIS.

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Running title:

Translocations in Thyrotoxicosis patients.
Translocation frequencies measured in patients one year after radioactive iodine therapy for thyrotoxicosis

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Abstract.

Purpose: To investigate the incidence of translocations induced by iodine-131 therapy in thyrotoxicosis patients 1 year after the administration of the radiolabelled compound.

Materials and methods: Tricolour FISH with whole-chromosome specific probes for chromosomes 2, 4 and 8 was used for scoring translocations. From the genomic translocation frequencies, derived using the Lucas formula, equivalent whole-body doses were calculated, based on the in vitro 60Co γ-ray dose–response curve.

Results: A total of 101 translocations were observed in 4864 metaphases, 63% being of the two-way type. In the control group used for obtaining dose–response data, nine translocations were observed in 5278 metaphases, 55% being two-way translocations. No correlation was found between the observed frequency of translocations and administered radioactivity. Using the in vitro dose–response, an estimated average dose for the group of nine patients of 0.79±0.22 Gy was obtained. Compared with frequencies following the assumption that the involvement of a particular chromosome in a two-break exchange-type aberration is proportional to its DNA content, chromosome 4 was more frequently involved and chromosomes 2 and 8 less frequently involved in chromosomal rearrangements.

Conclusion: This study shows that 131I therapy for thyrotoxicosis patients induced translocations, especially in chromosome 4, which could be detected 1 year after the administration of the radiolabelled compound.

1. Introduction

Since its first use in 1942 (Hertz and Roberts 1942), the most important systemic treatment using ionizing radiation is radioiodine therapy for thyrotoxicosis and thyroid carcinoma. In Belgium about 1700 patients are treated every year (1500 for thyrotoxicosis, 200 for thyroid carcinoma). In the treatment strategy for differentiated thyroid carcinoma, the oral administration of 131I following surgical resection of the thyroid has been shown to improve prognosis (Mazzaferri et al. 1994). A standard activity of 3700–7400 MBq is usually administered. These high administered activities are necessary because only about 2% of the administered activity is retained within the thyroid remnant tissue. The rest is eliminated from the body within a few days after administration by urinary excretion.

For the treatment of thyrotoxicosis, the administered activities are lower (185–1110 MBq) because the hyperactive thyroid typically retains about 50–60% of the administered activity. This activity decreases in the thyroid with a mean effective half-life of about 4–5 days and again is excreted via the urine. Thyrotoxicosis patients are exposed to a lower initial activity but for a longer period as compared with thyroid carcinoma patients.

Large-scale studies (Edmonds and Smith 1986, Holm et al. 1991, Dottorini et al. 1995, Vathaire et al. 1997) with a long follow-up of patient populations treated with radio-iodine have shown that the risk for carcinogenic and genetic effects of 131I treatment is quite low. Review papers on this subject conclude that there is no epidemiological evidence for the induction of secondary neoplasms in spite of the high administered activities (Clarke 1991, Hall et al. 1992, Halnan 1992). However, some reluctance still exists to treat thyrotoxicosis patients <40 years of age with 131I, probably due to concern about the radiation burden and subsequent late effects. The radiation burden to the body is mainly due to iodine circulating in the bloodstream in addition to irradiation from the thyroid.

Cytogenetic effects in radio-iodine-treated patients have been reported. The majority of these studies used the micronucleus assay and were undertaken on thyroid carcinoma patients (Livingston et al. 1993, Catena et al. 1994, M’Kacher et al. 1996, Wuttke et al. 1996, Ramirez et al. 1997, Watanabe et al. 1998). Micronucleus studies on thyrotoxicosis patients were performed by Gutierrez et al. (1997) and Monsieurs et al. (1999). Ramirez et al. (1997) distinguished between the clastogenic and aneuploidogenic effects of the iodine therapy by means of fluorescence in situ hybridization (FISH) with a pancentromeric
probe. They confirmed the development of aneuploidy, thereby providing evidence for a potential increase in cancer risk in $^{131}$I-exposed populations. As far as stable chromosome aberrations are concerned, to the authors' knowledge only M'Kacher et al. (1998) have published data on the development of translocations after $^{131}$I therapy for thyroid carcinoma patients using FISH with a whole-chromosome-specific probe for chromosome 4. No studies seem to have been reported investigating the development of translocations after $^{131}$I-therapy for thyrotoxicosis patients.

2. Materials and methods

2.1. Study population

The study was carried out on nine patients with thyrotoxicosis (one male, eight female) with a mean age of 64 years treated with a mean activity of 711 MBq $^{131}$I given orally. Details on age, gender, clinical diagnosis as well as clinical data are summarized in table 1. Values of the maximum percent thyroid uptake and the effective half-life were deduced from the pretreatment uptake curve. All patients volunteered to give a blood sample when they reported for their first scheduled check-up at the endocrinology department 1 year after administration. All patients signed a written informed consent before inclusion in the study. The control population consisted of six healthy donors (three males, three females) aged between 24 and 58 years (mean 37 years).

2.2. Analysis of translocations

Whole-blood cultures were set up as follows: 500 µl whole blood was added to 5 ml MEM supplemented with 15% foetal calf serum, 2% phytohaemagglutinin, 1% penicillin–streptomycin, 1% L-glutamine (Life Technologies, IL, USA) and 4% BrdU (25% w/v in MEM) (Sigma Chemical Co., Belgium). The cultures were incubated for 52 h at 37°C including a 75 min colcemid (Life Technologies, IL, USA) treatment (0.06 µg ml$^{-1}$) before harvest. Subsequently the cells were treated with a hypotonic solution (0.075 M KCl) for 10 min and fixed three times with 3:1 methanol-acetic acid (Merck-Belgolabo, Belgium). The first mitosis was determined by harlequin staining.

FISH analysis of the chromosome aberrations was performed using a cocktail of chromosome-specific probes for chromosomes: WCP-2 spectrum green, WCP-2 spectrum orange, WCP-4 spectrum green and WCP-8 spectrum orange, used according to the manufacturer’s (Vysis, Downers, IL, USA) WCP chromosome painting system.

Each slide was treated with 100 µg ml$^{-1}$ RNase followed by pepsin digestion (0.005% solution, all Boehringer, Germany) before denaturation at 70°C in a mixture containing 70% formamide in a 2 × SSC buffer. The DNA mixture probe was also denatured at 72°C and 10 µl DNA probe was deposited per slide. Hybridization was performed overnight at 37°C in a humidified chamber. The slides were then washed three times at 45°C in a 50% formamide (Sigma, Belgium)/2 × SSC solution and once in 2 × SSC/0.1% NP-40. Finally DAPI I (10 µl per slide) was applied to the slides for chromosome counterstaining. The slides were stored at 4°C before observation under a Diaplan Leitz microscope, Germany 630 × magnification.

Metaphases were scored only if they appeared to be complete and all parts of the six painted chromosomes appeared somewhere in the cell. A bicoloured chromosome with one centromere was classified as a translocation. If both reciprocal counterparts of the translocation were present, the translocation was termed a two-way translocation (reciprocal complete). Therefore, the totals for translocations and two-way translocations were scored.

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<td>F</td>
<td>autonomous nodule</td>
<td>555</td>
<td>88</td>
<td>5</td>
</tr>
<tr>
<td>iod5</td>
<td>62</td>
<td>F</td>
<td>multinodular goiter</td>
<td>851</td>
<td>47</td>
<td>5</td>
</tr>
<tr>
<td>iod7</td>
<td>43</td>
<td>M</td>
<td>multinodular goiter</td>
<td>740</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>iod8</td>
<td>69</td>
<td>F</td>
<td>autonomous nodule</td>
<td>666</td>
<td>58</td>
<td>4</td>
</tr>
<tr>
<td>iod9</td>
<td>62</td>
<td>F</td>
<td>autonomous nodule</td>
<td>814</td>
<td>47</td>
<td>5</td>
</tr>
<tr>
<td>iod10</td>
<td>51</td>
<td>F</td>
<td>autonomous nodule</td>
<td>740</td>
<td>51</td>
<td>4</td>
</tr>
</tbody>
</table>
The frequencies of translocations for chromosomes 2, 4 and 8 were extrapolated to a frequency for the whole genome, \( F_p \), using the formula of Lucas et al. (1999)

\[
F_p = 2.05 \left[ f_{p2} (1 - f_{p2}) + f_{p4} (1 - f_{p4}) + f_{p8} (1 - f_{p8}) \right]
\]

\[
- f_{p2} f_{p4} - f_{p2} f_{p8} - f_{p4} f_{p8} \right] F_G
\]

where \( F_p \) is the frequency of translocations observed for the three chromosomes and \( f_{pX} \) is the length of each individual painted chromosome relative to the whole genome. For chromosomes 2, 4 and 8, \( f_{pX} \) of 0.0779, 0.0625 and 0.0481 respectively were taken from Morton (1991).

For the determination of the equivalent total-body dose from the observed \( F_G \), a calibration curve was used based on the translocation frequencies in \textit{in vitro} \(^{60}\)Co \( \gamma \)-ray irradiated blood samples of six donors published previously (Thierens et al. 1999)

\[
F_G = (0.050 \pm 0.013) D^2 + (0.031 \pm 0.004)
\]

\[
D + (0.002 \pm 0.007)
\]

where \( D \) is the dose (Gy). For the determination of the background translocation frequency for the six control donors, the number of cells scored was increased from 1747 to 5278 in order to improve the statistics.

3. Results

Translocation data for the thyrotoxicosis patients, around 1 year after administration of the radiolabeled compound, are summarized in table 2. A total of 101 translocations were observed in 4864 metaphases, 63% of these translocations being of the two-way type. In the control group nine translocations were observed in 5278 metaphases, 53% being two-way translocations. Applying the Mann–Whitney test the difference between the translocation frequencies in the control group and in the considered group of patients was statistically significant (\( p < 0.01 \)). There was no correlation between the observed frequency of translocations and the administered activity values.

The estimated doses for the individual patients derived from the \textit{in vitro} dose–response are also given in table 2. The quoted uncertainties are standard deviations (SD) derived from the uncertainties in the coefficients of the dose–response. For this group of patients an average estimated dose of 0.79 ± 0.22 Gy was obtained. The standard deviation was obtained by combination of the SD of the doses among the patients and the SD of the dose due to the uncertainties on the dose–response coefficients.

In table 3 the number of translocations per cell involving the chromosomes 2, 4 and 8 are given for the individual patients. In figure 1 the observed frequencies of the chromosomes 2, 4 and 8 are compared with the frequencies expected following the involvement of the different chromosomes in two-break exchange-type aberrations according to their DNA contents. Figure 1 shows that chromosome 4 was more frequently involved and that chromosomes 2 and 8 were less frequently involved in chromosomal rearrangements. Application of the \( \chi^2 \)-test shows that these differences from the expected values are statistically significant (\( p < 0.001 \)).

4. Discussion

The present study has shown that the frequency of translocations involving chromosomes 2, 4 and 8 was 12 times higher than in the control group (\( p < 0.01 \)). As the background translocation frequency in control individuals is known to follow a linear–quadratic age dependence (Lucas et al. 1999), the age-effect was investigated as a possible confounder in the present study because the iodine patient group was older than the control population (mean age 64 versus 37 years). Adopting the age-dependence from the thorough investigation by Lucas et al. (1999), one would expect a translocation frequency of 0.0028 and 0.0067 for control groups averaging 37 or 64 years of age. A correction of our control data (mean 0.0050) by a factor 2.4 for this age effect reduces the translocation frequency ratio between iodine patients and the control population to a factor five but does not change the statistical significance of the enhanced translocation frequency in the iodine treated patients (\( p < 0.01 \)).

The yield of two-way translocations is 63% of the total number of translocations in the patient group and 55% in the control group. These \textit{in vivo} data are in good agreement with those of Finnem et al. (1999) who reported that 60% of the translocations were of the two-way type after \(^{60}\)Co irradiation \textit{in vitro}. In their study of the persistence of translocations in the rhesus monkey, Lucas et al. (1996) demonstrated that the translocation frequencies had not changed significantly during almost three decades since exposure. The biodosimetry data of the victims of the Estonia accident showed a rapid decline in dicentric frequencies during the first year after exposure, while the translocation frequencies were only reduced by the elimination of co-existing unstable aberrations over 2 years (Lindholm et al. 1998a). Also the biodosimetry study of Snigiryova et al. (1997) of the Chernobyl clean-up workers supported the view that FISH chromosome painting is a sensitive method for quantifying radiation exposure retrospectively. All these data indicate that translocations are an efficient tool
Table 2. Translocation frequencies observed for the studied patient population and the derived dose estimates.

<table>
<thead>
<tr>
<th>Patient code</th>
<th>Cells scored</th>
<th>Number of translocations</th>
<th>Translocations per cell</th>
<th>Translocation frequency (Lucas)</th>
<th>Estimated dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Two-way type</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>iod1</td>
<td>559</td>
<td>8</td>
<td>14</td>
<td>0.025</td>
<td>0.073</td>
</tr>
<tr>
<td>iod2</td>
<td>523</td>
<td>8</td>
<td>11</td>
<td>0.021</td>
<td>0.061</td>
</tr>
<tr>
<td>iod3</td>
<td>501</td>
<td>6</td>
<td>6</td>
<td>0.012</td>
<td>0.035</td>
</tr>
<tr>
<td>iod4</td>
<td>532</td>
<td>4</td>
<td>7</td>
<td>0.013</td>
<td>0.038</td>
</tr>
<tr>
<td>iod5</td>
<td>520</td>
<td>6</td>
<td>8</td>
<td>0.015</td>
<td>0.045</td>
</tr>
<tr>
<td>iod7</td>
<td>538</td>
<td>7</td>
<td>12</td>
<td>0.021</td>
<td>0.061</td>
</tr>
<tr>
<td>iod8</td>
<td>520</td>
<td>7</td>
<td>14</td>
<td>0.027</td>
<td>0.079</td>
</tr>
<tr>
<td>iod9</td>
<td>543</td>
<td>13</td>
<td>19</td>
<td>0.035</td>
<td>0.102</td>
</tr>
<tr>
<td>iod10</td>
<td>608</td>
<td>5</td>
<td>10</td>
<td>0.016</td>
<td>0.046</td>
</tr>
<tr>
<td>Total</td>
<td>4884</td>
<td>64</td>
<td>101</td>
<td>0.021 ± 0.007</td>
<td>0.060 ± 0.022</td>
</tr>
<tr>
<td>Controls</td>
<td>5278</td>
<td>5</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Involvement of painted chromosomes in translocations.

<table>
<thead>
<tr>
<th>Patient code</th>
<th>Translocations per cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chromosome 2</td>
</tr>
<tr>
<td>iod1</td>
<td>0.0125</td>
</tr>
<tr>
<td>iod2</td>
<td>0.0115</td>
</tr>
<tr>
<td>iod3</td>
<td>0.0120</td>
</tr>
<tr>
<td>iod4</td>
<td>0.0113</td>
</tr>
<tr>
<td>iod5</td>
<td>0.0058</td>
</tr>
<tr>
<td>iod7</td>
<td>0.0089</td>
</tr>
<tr>
<td>iod8</td>
<td>0.0077</td>
</tr>
<tr>
<td>iod9</td>
<td>0.0203</td>
</tr>
<tr>
<td>iod10</td>
<td>0.0065</td>
</tr>
<tr>
<td>Mean</td>
<td>0.0107</td>
</tr>
</tbody>
</table>

to study the long-term DNA genotoxic effects of radio-iodine treatment on thyrotoxicosis patients. The stable properties of translocations explain the high frequency of aberrations in the present patient data.

The micronucleus assay can be useful to detect individual exposures to incorporated iodine within several days after the intake of the radiounclide (Wuttke et al. 1996). Micronucleus data from Monsieurs et al. (1999) on thyrotoxicosis patients treated with the same medical protocol as the patients of present study result in estimated doses ranging from 0.16 to 0.55 Gy with an average of 0.34 Gy, 1 week after administration. Nearly the same dose estimates, 0.32 and 0.33 Gy, were obtained with the micronucleus assay for thyroid cancer patients treated with radio-iodine by Monsieurs et al. (1999) and Watanabe et al. (1998) respectively. According to Baugnet-Mahieu et al. (1994), the increase in dicentrics induced by two doses of 1850 MBq of $^{131}$I in thyroid cancer patients was statistically significant but smaller than one would expect from the calculated whole-body dose. On the other hand, the dose to thyroid cancer patients estimated by chromosome 4 painting on day 4 after the administration of 3700 MBq of $^{131}$I was 0.52 Gy (M’Kacher et al. 1998). The dose estimates for thyrotoxicosis patients resulting from chromosome painting in present work (0.79 ± 0.22 Gy) are higher. The difference from the dose of 0.34 Gy obtained with the micronucleus assay on the same type of patient population by Monsieurs et al. (1999) can partly be explained by the difference in dose received after 1 week and after 1 year. On the other hand, Zanzonico (1997) showed that the administered activity of 1036 MBq of $^{131}$I, required for a standard 70 Gy absorbed dose to the thyroid for treatment of Graves’ disease, yielded a high blood
absorbed dose of 1.50 Gy due to the relatively long effective half-life of radio-iodine in the thyroid and high serum concentrations of long-lived protein-bound activity. This estimate is twice as high as our usual value but the administered activity in our study was only about 70%.

The present data show that in blood samples of thyrotoxicosis patients analysed 1 year after administration of $^{131}$I, chromosome 4 was more commonly involved in chromosomal rearrangements than expected according to a RCL proportional distribution, and chromosomes 2 and 8 were less involved.

Contradictory results on the involvement of target chromosomes in translocations analysed by painting techniques are reported in the literature. A number of studies on blood samples irradiated in vitro report deviations from a DNA-proportional distribution of chromosome aberrations. In Boel et al. (1997), aberrations involving chromosomes 1 and 4 were analysed by FISH with chromosome-specific DNA libraries after in vitro X-ray irradiation with a dose of 2 Gy. Whereas dicentric frequencies for chromosome 1 and 4 were close to those expected, frequencies of reciprocal translocations showed a clear overrepresentation of chromosome 4. This was supported by the data of Knehr et al. (1996), where other chromosomes with a high DNA content (chromosomes 1–3, 6 and 7) were less frequently involved in the formation of symmetrical translocations and dicentrics than expected according to their DNA contents. Also Stephan and Pressl (1997) found overrepresentation of chromosome 4 combined with underrepresentation of chromosome 2, not only in in vitro irradiated blood samples, but also in blood samples of radiation workers 11 years after an accidental exposure. Barquinero et al. (1998) showed that deviations from a DNA-proportional distribution become apparent for all aberration parameters analysed with the three nomenclature systems (PAINT, S&S and a conventional method). Chromosomes 2, 3 and 6 were less frequently involved and smaller chromosomes (15–22, with the exception of chromosome 19) were more frequently involved in aberration formations than expected. The tendency for short chromosomes to be more involved in exchange-type aberrations than long chromosomes could be related to their interphase territory surface (Cigarran et al. 1998).

Other studies of in vitro irradiated blood samples have shown no or a non-significant deviation from the predicted frequencies taking into account their DNA content (Natarajan et al. 1992, Tucker et al. 1993, Matsuoka et al. 1994, Gebhart et al. 1996). The yield of exchanges in chromosomes 1, 2 and 4 was equal to that expected from their DNA content in Luomahaara et al. (1999). In contrast, the breakpoint location of complete exchanges within these chromosomes was non-random. Chromosomes 1 and 4 contained more breaks in the central parts of the p and q arms, whereas breaks were observed more uniformly along chromosome 2. Also Lindholm et al. (1998b) observed that chromosome 4 took part in exchange-type aberrations as frequently as predicted.

Since translocations persist through cell division, their frequency among lymphocytes can be increased by clonal expansion (Lindholm et al. 1998a). In their study of the age-dependence of the translocation frequency, Lucas et al. (1999) found a high number of detectable clones involving the chromosomes 1 and 4 in the older subjects of their control population. The observation in the present study of a high number of translocations as well as overrepresentation translocations involving chromosome 4 suggest the need for a medical follow-up of thyrotoxicosis patients treated by radio-iodine. Structural anomaly of chromosome 4 and numerical alterations of certain autosomes may be associated with tumorigenic properties (Pathak et al. 1991). Translocations t(4;11) are regularly associated with a specific type of acute leukaemias and probably initiate the development of this disease (Kapelushnik et al. 1991, Palau et al. 1991, Gobbi et al. 1997, Reichel et al. 1998).

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**ADAPTIVE RESPONSE IN PATIENTS TREATED WITH $^{131}$I.**

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Adaptive Response in Patients Treated with $^{131}$I

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The aim of this study was to investigate whether an adaptive response (defined as the induction of radiation tolerance after a small dose of radiation) could be observed in peripheral blood lymphocytes of patients treated with $^{131}$I for thyroid disease.

**Methods:** For each patient, blood samples were taken immediately before and 1 wk after $^{131}$I administration. Each blood sample was divided into 3 fractions and the fractions were subsequently irradiated in vitro with 0, 0.5, and 1.0 Gy $^{60}$Co $\gamma$-rays. After blood culture for 70 h, cells were harvested and stained with Romanowsky-Giemsa and micronuclei were counted in 1000 binucleated cells. The increase in micronuclei by the in vitro irradiation of the blood samples taken before and after therapy was compared. In this setup, an adaptive response is represented by a significant decrease of the in vitro induced micronucleus yield after therapy compared with that before therapy. The iodine therapy can be considered as an in vivo adaptation dose, after which the subsequent in vitro irradiation acts as a challenge dose. To investigate the reproducibility of the method, 2 subsequent blood samples of healthy volunteers were taken 7 d apart. Irradiation and cell culture were performed as described.

**Results:** In 8 of 20 patients, a significant ($P = 0.0002$) decrease was found in the in vitro induced micronucleus yield in the blood sample taken 1 wk after $^{131}$I administration compared with that of the blood sample taken before therapy. No significant ($P > 0.1$) differences were observed between these 8 patients and the other patients when the number of micronuclei induced in vivo by the iodine treatment and the resulting equivalent total body dose were compared. None of the control subjects showed a significant change in micronucleus yield after in vitro irradiation between both blood samples taken 1 wk apart.

**Conclusion:** The iodine treatment can act as an in vivo adaptation dose and can induce an adaptive response that is observed by a decrease of the cytogenetic damage in peripheral blood lymphocytes after in vitro irradiation as a challenge dose. A large interindividual difference was observed.

**Key Words:** adaptive response; $^{131}$I therapy; thyrotoxicosis; thyroid carcinoma


Ever since its first therapeutic application in 1942 by Hertz and Roberts (1), $^{131}$I has played a major role in the treatment of thyrotoxic patients and patients suffering from differentiated thyroid carcinoma. The risk for late detrimental effects after $^{131}$I therapy was studied by several investigators (2–5) and was estimated to be $<1\%$ over a lifetime. Indeed, to our knowledge, no statistically significant increase in leukemia or solid tumors has been reported (2,3,6).

An additional explanation for the lack of epidemiologic evidence for late detrimental effects could be found in the existence of an in vivo adaptive response. This theory states that exposure to low levels of ionizing radiation (adaptation dose) can stimulate the DNA repair system in certain individuals, resulting in less genetic damage after subsequent high levels of ionizing radiation (challenge dose). This phenomenon has been termed “adaptive response” because it is similar to the induced repair described in *Escherichia coli* (7).

Much in vitro data confirm the existence of an adaptive response. Most of these studies consist of in vitro work on human cell cultures (8). In vitro pretreatment of lymphocytes with tritiated thymidine or with low doses of ionizing radiation makes these cells less susceptible to cytogenetic damage by subsequent high doses of ionizing radiation (8–16). Some evidence of an in vivo adaptive response exists for animals, usually mice (17–19).

The existence of an in vivo adaptive response in humans could explain why the incidence of cancer in some occupationally exposed populations is lower than expected, as suggested by the results of some epidemiologic studies recently reviewed by Pollycove (20) and Van Wijngaarden and Pauwels (21). However, only Barquinero et al. (22) presented experimental evidence for its existence in peripheral blood lymphocytes of occupationally exposed individuals. To our knowledge, no studies indicating the existence of an in vivo adaptive response after medical use of radiation have been published. Therefore, the aim of this study was to assess whether an adaptive response in vivo could be observed in peripheral blood lymphocytes of patients treated with $^{131}$I for thyroid disease.

**MATERIALS AND METHODS**

**Patients**

This study included 20 patients (5 men, 15 women; mean age, 57 y; range, 25–76 y) treated with $^{131}$I for thyroid disease. Seventeen of the patients were suffering from thyrotoxicosis and received a mean activity of 642 MBq (range, 259–1110 MBq). The 3 other patients were suffering from differentiated thyroid carcinoma and...
received 3700 MBq. As a control population, 7 healthy volunteers (1 man, 6 women; mean age, 39 y; range, 27–57 y) were also included.

All patients and volunteers gave their informed consent.

**Blood Sample Collection and Irradiation**

The first blood sample (heparinized) was taken immediately before administration of the 131I therapeutic activity. This blood sample was divided into 3 fractions. One fraction served as a nonirradiated control. The 2 other fractions were irradiated in vitro at 37°C with doses of 0.5 and 1.0 Gy 60Co γ-rays at a dose rate of 1.5 Gy/min. The second blood sample (heparinized) was taken 7 d after 131I administration. This blood sample was also divided into 3 fractions and subsequently irradiated following the same protocol as that used for the first blood sample.

**Micronucleus Assay**

Whole blood cultures were incubated at 37°C for 70 h in a 5% CO2 atmosphere. Culture medium consisted of RPMI medium with 2 mmol/L l-glutamine and N-[2-hydroxyethyl]piperazine-N’-[2-ethane sulfonic acid] buffer (GIBCO Laboratories, Grand Island, NY) supplemented with 15% fetal calf serum and antibiotics. Phytohemagglutinin (Difco, Detroit, MI) was used at a concentration of 40 µg/mL to stimulate cell division. According to the method of Fenech and Morley (23), cytochalasin B (3.5 µg/mL in dimethyl sulfoxide; Sigma Chemical Company, St. Louis, MO) was added 42 h after culture initiation to block cytokinesis. After an incubation period of 70 h, the cells were harvested, treated with a hypotonic solution of 0.075 mol/L KCl, and fixed with an 8:1 mixture of methanol:glacial acetic acid following the protocol of Vral et al. (24). Slides were stained with Romanowsky-Giemsa, and micronuclei were counted under a light microscope (magnification ×400) based on criteria summarized by Fenech (25).

**Equivalent Total Body Dose Calculated from Cytokinesis-Blocked Micronucleus Assay**

The equivalent total body dose (ETBD) is the 60Co dose that would produce the same yield of micronuclei as the in vivo 131I dose actually received. The micronucleus yield, obtained after in vitro irradiation, was plotted against the 60Co dose and an individual linear-quadratic dose–response curve was derived by a least-squares fit to the data. On the basis of this individual in vitro dose–response, the ETBD after 131I therapy was calculated from the number of micronuclei in the blood sample of the patient 1 wk after administration of the activity. For thyrotoxicosis patients, the ETBD was corrected for the dose (because of activity retained in the body after the second blood sample was taken) using the effective half-life determined from the pretherapy uptake curve.

**Adaptive Response**

To assess the existence of an adaptive response, the increase in micronucleus yield after in vitro irradiation of the blood samples taken before and after 131I therapy was compared. An adaptive response exists when the increase in micronucleus yield in vitro is significantly less in the blood sample taken after therapy than the increase in the blood sample taken before therapy.

**MIRD Total Body Dose**

For all thyrotoxicosis patients, the pretherapy uptake curve yielded both the maximal percentage uptake and the effective half-life of the 131I in the thyroid. Using this information, the total body dose for each patient, following the MIRD protocol, was calculated by applying the MIRDOS 3 code (Oak Ridge Associated Universities, Oak Ridge, TN) with the thyroid as the only source organ.

**Statistical Analysis**

Differences between the increase in micronuclei after in vitro irradiation were compared before and after therapy using 95% confidence limits and the Poisson distribution. Differences from the mean were assessed by 2-tailed unpaired Wilcoxon tests using Medcalc (Medcalc Software, Mariakerke, Belgium).

**RESULTS**

An overview of the results is given in Table 1.

The increase in micronuclei after in vitro irradiation (1.0 Gy 60Co γ-rays) of the blood sample taken before and 1 wk after 131I administration is shown in Figure 1. For the control subjects, the same variable determined for 2 subsequent weeks is presented. No significant differences (P > 0.1) were found between the increase in micronucleus yield after irradiation of the first and the second blood samples for the control subjects (Fig. 1). For the patient group as a whole, a significant decrease (P = 0.470) in micronucleus yield after in vitro irradiation with 1.0 Gy 60Co γ-rays was observed after therapy compared with the yield before therapy. However, this decrease was attributed solely to highly significant reduction (P = 0.0002) in the indicated patient subgroup, whereas no significant difference was observed in the other patients (P > 0.1). The results of the 0.5 Gy in vitro irradiation are comparable with the results of the 1.0-Gy samples, but the margin of error is larger. None of the patients showed a significant increase in micronucleus yield after irradiation in the second blood sample compared with the yield in the first blood sample.

The mean dose–response curves after in vitro irradiation with 60Co γ-rays before and after 131I therapy are shown in Figure 2. For the control subjects (Fig. 2A), the dose–response curves for the first and the second blood samples were not significantly different. The dose–response curves for the blood samples taken before and after therapy (Fig. 2B) also were not significantly different for the patient subgroup that did not show a significant difference in the in vitro induced micronucleus yield before and after therapy. For the other patients (Fig. 2C), the mean micronucleus increase after in vitro irradiation of the blood sample taken after therapy decreased significantly (P = 0.0002) compared with the blood sample taken before therapy. For in vitro irradiation with 0.5 Gy, mean values of 52 and 26 micronuclei were found before and after therapy, respectively, whereas mean values of 150 and 78 micronuclei before and after therapy, respectively, were found after in vitro irradiation with 1.0 Gy. When the dose–response curves from Figures 2B and C were compared with the dose–response curves of the control population (Fig. 2A), the curves in Figure 2B were similar whereas the curve before therapy (Fig. 2C) was higher and became normalized after therapy.

For 17 of 20 patients (81%), a statistically significant (P = 0.0164) increase in micronuclei was observed after therapy. The mean increase in micronuclei after 131I therapy
observed in this study was 23 micronuclei (range, 0–121 micronuclei). There were no significant differences in the mean increase in micronuclei after 131I therapy between thyrotoxicosis patients (mean, 23 micronuclei; range, 0–121 micronuclei) and thyroid carcinoma patients (mean, 29 micronuclei; range, 16–34 micronuclei). By fitting the micronucleus yield 1 wk after therapy to the dose–response curve after in vitro irradiation before therapy, the ETBD of each patient could be determined. The mean ETBD observed in this study was 0.37 Gy (range, 0.00–0.96 Gy). On the basis of these results, no significant difference in ETBD values could be observed between thyrotoxicosis patients and thyroid carcinoma patients. For the thyrotoxicosis patients, the MIRD total body dose was determined from the pretherapy uptake curve. These data are included in Table 1. A mean total body dose of 0.30 Gy (range, 0.14–0.55 Gy) was obtained, whereas the micronucleus assay yielded a comparable mean ETBD of 0.37 Gy (range, 0.00–0.96 Gy) for the thyrotoxicosis patient group.

The mean increase in micronucleus yield associated with 131I therapy seemed to be higher in the patient group that showed a significant difference in the micronucleus increase after in vitro irradiation before and after therapy (mean, 39 micronuclei; range, 6–121 micronuclei) than in the patient group that did not show this difference (mean, 12 micronuclei; range, 0–35 micronuclei). Also, the mean ETBD tended to be higher in the first patient subgroup: 0.45 Gy (range, 0.13–0.96 Gy) and 0.34 Gy (range, 0.00–0.70 Gy), respectively, using the micronucleus yields and 0.31 Gy (range, 0.19–0.54 Gy) and 0.28 Gy (range, 0.14–0.55 Gy), respectively, using the pretherapy uptake curve for thyrotoxicosis patients. However, the differences did not reach statistical significance ($P > 0.1$).

**DISCUSSION**

The results of this study show that exposure to low doses of ionizing radiation during medical treatment (adaptation dose) makes human peripheral blood lymphocytes less sensitive to subsequent exposures to 131I. This effect is known as the adaptive response and has been reported in various studies. The results of this study confirm the existence of an adaptive response in patients treated with 131I. The adaptive response is characterized by a decrease in the sensitivity of the cells to radiation, which can lead to a lower induction of micronuclei after 131I therapy compared to the pretreatment levels. This effect is significant in patients with thyrotoxicosis, where the mean increase in micronuclei after 131I therapy was lower than in patients with thyroid carcinoma.

**TABLE 1**

Overview of Results Obtained in Study

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Adm. activity (MBq)</th>
<th>MIRD (Gy)</th>
<th>ETBD (Gy)</th>
<th>Incr. MN therapy</th>
<th>Incr. MN before 0.5 Gy</th>
<th>Incr. MN before 1.0 Gy</th>
<th>Incr. MN after 0.5 Gy</th>
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susceptible to cytogenetic damage for subsequent in vitro irradiation at higher doses (challenge dose). The reproducibility of the data for the control population further shows that the observed differences cannot be attributed to cell culture or technical effects. Therefore, the observation can be interpreted as an adaptive response phenomenon. Barquinero et al. (22), using a similar experimental setup, reported the existence of an adaptive response in vivo after occupational exposure to ionizing radiation. In their study, a 2-Gy $^{60}$Co dose was used as the challenge dose. Cytogenetic damage was scored as dicentrics, acentrics, and chromosome breaks. The occupationally exposed individuals showed a significantly lower amount of chromosomal damage after in vitro irradiation than did the nonexposed individuals.

Determination of the mechanism behind the adaptive response is beyond the scope of this study. This mechanism has been studied in vitro by many investigators (10–14). The currently accepted model of the mechanism of adaptive response is the signaling loop model, first described by Weichselbaum et al. (26) in 1991. The assumption has been made that on treatment with a DNA-damaging agent, an alarm signal is generated in the nucleus. Activation of a set of genes follows, which leads to de novo protein synthesis. Some of these proteins are involved in repair of the damage inflicted by the challenge dose; hence, a lower biologic effect of the dose is observed than that in nonadapted cells.

However, instead of an increased DNA repair rate, the fidelity of repair seems to be changed, leading to a different proportion of damage seen at the chromosomal level. The lowered mutation frequency in adapted cells also points to this possibility (27). Thus, adaptive response may involve primarily a qualitative change in damage repair or processing (28). Only a few centigrays are needed to produce an adaptive response in human lymphocytes (29). In this study, the mean ETBD in the patient subgroup that showed an adaptive response was only 0.45 Gy.

The observation that only 8 of 20 patients showed an adaptive response after receiving $^{131}$I therapy clearly shows interindividual variability. This variability was also observed in the in vivo study by Barquinero et al. (22) and in previous in vitro studies (30–33). Both the pretherapy in vitro irradiation and the in vivo exposure by $^{131}$I therapy led to a somewhat higher increase in micronuclei in the patient group that showed an adaptive response than that in the other patient group. The in vitro dose–response curve for the patients showing an adaptive response seemed to normalize after $^{131}$I therapy (adaptation dose). Although the results did not reach statistical significance, the adaptive response in this study seems to be evident, especially in radiosensitive individuals.

For the 8 patients who showed an adaptive response, an in vivo exposure to ionizing radiation (challenge dose) after the $^{131}$I therapy (adaptation dose) would probably lead to less genetic damage. The duration of the adaptive response in

![FIGURE 1. Overview of increase in micronuclei after in vitro irradiation (1.0 Gy $^{60}$Co $\gamma$-rays) of blood samples taken before and after $^{131}$I therapy. For controls, 2 blood samples taken 1 wk apart were irradiated. Error bars represent 95% confidence limits. Increase in micronuclei before therapy (■), increase in micronuclei after therapy (□), and patients who show adaptive response (+) are indicated.](image-url)
The point of view of increasing numbers of investigators approach to evaluate the detrimental effects of low levels of ionizing radiation by itself is beneficial because the level of chromosomal damage is increased after the iodine treatment.

REFERENCES


CONCLUSION

These results show that, although the iodine treatment can act as an adaptation dose and can induce an in vivo adaptive response, interindividual variability exists. In the evaluation of the detrimental effects of exposure to radiation, some consideration should be given to the importance of biologic defense mechanisms. The results of this study do not suggest that exposure to ionizing radiation by itself is beneficial because the level of chromosomal damage is increased after the iodine treatment.

ACKNOWLEDGMENTS

This study was supported by the ADAC Advanced Clinical Research Program and the Mallinckrodt Benelux Award. The authors thank Isabelle Meirlaen, Marleen Vanderkerken, and Martine D’Halluin for their help in gathering the data and all patients and volunteers who donated blood samples.


Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

4.2.5. Limitations in the application of the in vitro micronucleus assay for biodosimetry of cancer patients treated with radionuclide therapies *Mutagenesis*. Accepted for revision, December 2002.

LIMITATIONS IN THE APPLICATION OF THE *IN VITRO* MICRONUCLEUS ASSAY FOR BIODOSIMETRY OF CANCER PATIENTS TREATED WITH RADIONUCLIDE THERAPIES.

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Abstract.

Applicability of the in vitro micronucleus (MN) assay was evaluated in 2 cancer patient groups receiving high activities of radiopharmaceuticals: 12 patients (22 therapies) treated with $^{131}$I-MIBG for neuroblastoma (NB; mean 4.5 GBq, SD: 1.1) or carcinoid tumors (CA; mean 7.7 GBq, SD: 0.5) and 15 patients (17 therapies) treated with $^{131}$I-lipiodol for hepatocellular carcinoma (HCC; mean 1.9 GBq, SD: 0.2).

Blood samples were taken immediately before and 1 week after administration of the radiopharmaceutical. For $^{131}$I-MIBG patients, the first blood sample was irradiated in vitro with $^{60}$Co γ-rays to determine the individual dose response curve. The equivalent total body dose (ETBD) was derived from the increase in MN yield after therapy. Based on consecutive bi-planar scans taken after therapy, the physical total body dose following the MIRD formalism was calculated for each therapy.

A significant correlation was found between the ETBD and the MIRD dose ($R = 0.87$). The ETBD was only 70% of the MIRD dose due to the differences in dose rate between the in vitro and in vivo exposure. The use of the standard MN dose response curve for healthy individuals in stead of the patient individual dose response curve gave the same overall results. The MN assay could be performed in 17 out of 22 $^{131}$I-MIBG therapies due to cell division inhibition caused by previous chemotherapy treatments and lymphocyte dilution caused by blood transfusions.

For HCC patients, we were able to stimulate lymphocytes in only 12 out of 17 blood samples. For these patients, there was no correlation ($p = 0.17$) between the MIRD dose and the ETBD based on the standard dose response curve. This is probably due to enhanced lymphocyte sequestration caused by hypersplenism.

Analysis of data for multiple therapies points to a shortened mean half-life of the lymphocytes ($T_{1/2} = 3.9$ months).

Introduction.

In Nuclear Medicine, target-finding molecules coupled to a radioisotope (radiopharmaceuticals) are injected into the patient to enable physiological imaging (diagnosis) or therapeutic effects (radionuclide therapy). For radionuclide therapy, high activities (several GBq) of radiopharmaceuticals are administered to the patient in order to have a significant therapeutic effect. Since 1942, the isotope most frequently used in nuclear medicine therapy is $^{131}$I. $^{131}$I emits both short (< 3mm) range β-rays, used to irradiate the tumour tissue, and long range γ-rays, used for patient scintigraphy. Its physical half-life of 8 days enables long term irradiation of the target tissue.

Although the injected radiopharmaceuticals mainly target the tissue under treatment, inevitably the rest of the body is also irradiated to some extent. This is partly due to the circulation of the radiopharmaceutical in the body before it is incorporated into the target tissue, or is excreted, and partly by the long-range γ-rays emitted from the radiopharmaceutical inside the target tissue. Since radionuclide therapies are often repeated several times for the same patient and can be considered as curative in the treatment of some tumours, it is important to determine the radiation dose to the patient as measure of the mutagenic effect of the therapies.

In the present study we included 27 patients given 39 radionuclide therapies with either $^{131}$I-MIBG (meta iodo benzyl guanidine) for neuroblastoma and carcinoid tumours or $^{131}$I-lipiodol for hepatocellular carcinoma.

Neuroblastoma, a slow growing tumour derived from the sympathetic nerve system is the fourth most common tumour in children. The treatment consists mainly of surgical dissection of the tumour, followed by several courses of chemotherapy. In Belgium, the $^{131}$I-MIBG is usually given to the patient as a palliative treatment in conjunction with or after chemotherapy. In 1991, the cumulative experience in children with neuroblastoma indicated an objective response rate of 35% (Hoefnagel CA, 1994). For metastatic carcinoid disease, in 1991, results were available for 52 patients, revealing on the one hand an objective response (improvement in disease status) of only 15% but on the other hand palliation (reduction of pain, patient resumes “normal” life), which may be very meaningful and long lasting, in 65% (Hoefnagel CA, 1994). For both types of malignancy, usually a fixed dose of 3700 to 7400 MBq of $^{131}$I-MIBG is infused intravenously over a 2h to 4h period.

Primary hepatocellular carcinoma (HCC) is one of the most common malignant tumours in the world. It is responsible for an estimated 1 million deaths annually. The tumour often presents late, which, with the underlying cirrhosis, makes surgery difficult or impossible in many patients (Novell and Hilson, 1994).
The survival time among patients with HCC is extremely short and may be as low as 1-2 months. Locoregional treatment of the liver is therefore used as a palliative or curative treatment. Lipiodol (or poppy seed oil) naturally contains up to 38% of iodine. Internal radiation therapy can be achieved, when some of the iodine present in the lipiodol is substituted by 131I. After intra-arterial injection into the hepatic artery, it is retained by HCC for periods ranging from several weeks to over a year, while it is cleared from the normal liver parenchyma within 7 days (Okuyasu et al., 1988, Ohishi et al., 1985).

The mutagenic effect of a certain treatment or drug can be determined by cyto genetic biodosimetry based on the in vitro cytokinesis blocked micronucleus assay (Ramalho et al., 1987; Thierens et al., 1995, Thierens et al., 1999). In previous papers, we have reported the results of studies on patient dosimetry in nuclear medicine with the cytokinesis-blocked micronucleus assay (Watanabe et al., 1998, Monsieures et al., 1999, Monsieures et al., 2001). In the present study, the following subjects were investigated:

1) The effect of the malignant disease status and previous treatments on the feasibility of cyto genetic biodosimetry using the micronucleus assay.
2) The comparison of the mean individual in vitro dose response relationship of the 131I-MIBG treated patient population to the standard dose response relationship determined for a control population.
3) The comparison between the equivalent total body dose (ETBD) determined by the micronucleus assay and the results of physical dosimetry with the MIRD formalism.
4) The micronucleus yield over time for patients undergoing several sequential radionuclide therapies.

Materials and methods.

Subject population.
This study comprises a total of 27 patients treated with either 131I-MIBG (for neuroblastoma and carcinoid tumours) or 131I-lipiodol (for hepatocellular carcinoma) at the Nuclear Medicine division of the University Hospital of Ghent during the period 1996 - 2001. All patients gave their written informed consent, prior to inclusion into the study. The group treated with 131I-MIBG consists of 12 patients (8 females and 4 males) who received a total of 22 therapies. Ten patients with a mean age of 8 years (range 2 - 32 years) received a total of 18 therapies with a mean activity of 4.52 GBq (SD: 1.11 GBq) for neuroblastoma stage III or IV. The 2 remaining patients, respectively 45 and 50 years old, each received 2 therapies with a mean of 7.68 GBq (SD: 0.49) 131I-MIBG for carcinoid tumors with multiple liver metastases.

A group of 15 adult patients (6 women and 9 men) with a mean age of 61 years receiving a total of 17 131I-lipiodol therapies for hepatocellular carcinoma were also included in the study. These patients received a mean activity of 1.88 GBq (SD: 0.20) of 131I-lipiodol administered intra-arterially into the liver artery by catheterisation. Only patient 1 received 3 consecutive therapies over a period of 8 months. The mean administered activity for this patient was 1.82 GBq.

Blood sample collection and in vitro irradiation.
The first heparinised 5 ml blood sample was taken immediately before administration of the therapeutic activity. For patients treated with 131I-MIBG, this blood sample was divided in three fractions. One fraction served as a non-irradiated control. The two other fractions were irradiated in vitro at 37°C with a dose of 0.5 Gy and 1.0 Gy 60Co γ-rays at a dose rate of 1 Gy/min. A second heparinised blood sample of 5 ml was taken 7 days post-administration.

Micronucleus assay.
Whole blood cultures were incubated at 37°C for 70 h in a 5% CO₂ atmosphere. Culture medium consisted of RPMI 1640 with 2 mM L-glutamine and Heps buffer (Gibco) supplemented with 15% fetal calf serum and antibiotics. 20 µl of a 1% phytohaemagglutinin solution (PHA-P; Difco) was used to stimulate cell division. According to the method of Fenech and Morley (1985), Cytochalasin B (final concentration 6 µg/ml; Sigma) was added 40 h after culture initiation in order to block cytokinesis. After an incubation period of 70 h, the cells were harvested, treated with a hypotonic solution of 0.075 M KCl, and fixed with a mixture of methanol-glacial acetic acid 8:1 following the protocol described by Vral et al. (1994). Slides were stained with Romanowsky-Giemsa and micronuclei were scored in 1000 binucleated cytokinesis-blocked cells under the light microscope with a magnification of 400×, based on the criteria summarized by Fenech M. (1993).

Equivalent total body dose.
The equivalent total body dose (ETBD) is the dose of ionizing radiation, which, if received
homogeneously by the whole body, would produce the same yield of micronuclei, as observed in the patients. The ETBD was derived from the increase in micronucleus yield in the blood sample of each patient, 1 week after administration of the activity, using the micronucleus dose response relationship of Thierens et al. (1999) determined in the laboratory. For the patients receiving $^{131}$I-lipiodol therapy, this value was then corrected for the $^{131}$I remaining in the body after the first week by multiplying with a factor of 1.71. This factor is based on the observed biological retention of the $^{131}$I in these patients: 5.23 days. For the patients receiving $^{131}$I-MIBG therapy, the ETBD was also calculated by fitting an individual linear-quadratic dose response curve through the obtained data points of the in vitro irradiated blood samples before therapy. For the patients receiving $^{131}$I-lipiodol therapy, an individual dose response curve could not be obtained. The initial low amount of lymphocytes present in the blood of these patients caused by hypersplenism did not allow to split-up the blood samples for in vitro irradiation.

**Total body scans.**

All patients had a set of 3 ($^{131}$I-MIBG) or 2 ($^{131}$I-lipiodol) $^{180}$ technetium planar total body scans taken up to 10 days ($^{131}$I-MIBG) or 14 days ($^{131}$I-lipiodol) after administration of the radiopharmaceutical. All scans were made on an Elscint Helix double head gamma camera fitted with high-energy parallel hole collimators. A syringe containing a known activity of $^{131}$I in a PMMA syringe phantom (diameter: 6 cm) was placed at the patient’s feet. The activity in the body was determined by comparing to the known activity in the syringe. The activity was then plotted versus time and a monoeponential function was fitted through the dataset. The data were inserted into the MIRODOSE3® (oak Ridge associated Universities) software program and the total body dose was calculated.

**Statistical analysis**

Statistical analysis was performed by means of Medcalc® and SPSS®. Differences for the mean were evaluated by Wilcoxon or paired Mann-Whitney tests, where applicable. Correlations were investigated by means of the Spearman's rank coefficient r. Error bars in the figures represent the standard deviations based on the Poisson distribution.

**Results**

All results have been summarized in table 1.

**Figure 1.**

![Graph](image)

The micronucleus yields for the patients before and after therapy are represented in Figure 1. For only 17 $^{131}$I-MIBG therapies out of 22, reliable results allowing the determination of the ETBD could be obtained with the cytokinesis blocked micronucleus assay. The mean increase in micronuclei after $^{131}$I-MIBG therapy was 88 (SD: 71) for these neuroblastoma patients while it was significantly less ($p < 0.001$) with a mean increase of 35 micronuclei (SD: 8) for carcinoid patients. The ETBD value, based on the standard in vitro dose response relationship of the laboratory (Thierens et al., 1999), obtained for the neuroblastoma patients (mean 0.90 Gy, SD: 0.51) was significantly ($p < 0.0001$) higher than for patients suffering from carcinoid tumours (mean: 0.34 Gy, SD: 0.08). The mean individual ETBD was determined based on the mean micronucleus dose response curve for this patient population using a linear-quadratic fit through the micronucleus yields obtained after in vitro irradiation of the first blood sample: $MN_{irr} = 32.9 D^2 + 62.7 D$ ($r = 0.31$) Where: $MN_{irr}$ is the micronucleus yield induced by the therapy and D is the in vitro $^{60}$Co dose. The mean ETBD values obtained with this curve (mean 0.93 Gy, SD: 0.47 for neuroblastoma patients and mean 0.45 Gy, SD: 0.09 for carcinoid patients) were not significantly different ($p > 0.20$) from the values obtained with the standard micronucleus dose response curve.

For patients treated with $^{131}$I-lipiodol, the cytokinesis blocked micronucleus assay was only feasible for 12 out of 17 therapies. The mean increase in micronucleus yield for patients treated with $^{131}$I-lipiodol at 7 days after therapy was 62 micronuclei (SD: 22).
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Pt: Patient number. The number points to the patient while the letter points to the therapy number. D: Diagnosis. (N: Neuroblastoma, C: Carcinoid tumour, H: Hepatocellular carcinoma). Y: Patient age (years). G: Patient gender (M: man, W: woman). A: Administered activity (GBq). MN bef: Micronucleus yield before therapy. MN 0.5: Micronucleus yield after in vitro irradiation with 0.5 Gy 60Co γ-rays. MN 1: Micronucleus yield after in vitro irradiation with 1 Gy 60Co γ-rays. MN aft: Micronucleus yield after therapy. MN inc: Micronucleus increase after therapy. ED LQ: Equivalent total body dose (Gy) using the general formula determined by Thierens et al., (1999). ED L: equivalent total body dose (Gy) using the linear component of the general formula determined by Thierens et al., (1999). ED ind: equivalent total body dose (Gy) using the individual dose response relationship. MIRD: Total body dose (Gy (N and C) or Sv (H)) according to the MIRDose-3.0 program. M: mean. SD: standard deviation.
For patients treated with $^{131}$I-lipiodol, a mean ETBD value of 1.10 Gy (SD: 0.42), calculated by means of the standard in vitro dose response relationship, was obtained after correction for the $^{131}$I-lipiodol remaining in the body after the first week post-administration.

Based on bi-planar images, the physical total body dose according to the MIRD formalism could be determined for each patient group and was highest for neuroblastoma patients (mean 1.34 Gy, SD: 0.56) compared to HCC patients treated with $^{131}$I-lipiodol (mean 0.97 Gy, SD 0.23), while it was significantly ($p < 0.05$) lower for carcinoid patients with a mean of 0.69 Gy (SD: 0.19) for carcinoid patients.

**Figure 2**

![Mean linear quadratic dose response relationship based on the general formula determined by Thierens et al (1999).](image)

When all patients included in the study are considered, figure 2 shows only a poor correlation between the physical MIRD dose and the ETBD derived from the standard micronucleus dose relationship ($R = 0.37$, $p = 0.055$). For the patient group treated with $^{131}$I-lipiodol for HCC, the ETBD values obtained with the micronucleus assay show no correlation with the physical dose ($r = -0.434$, $p = 0.170$). However, when the patients treated with $^{131}$I-MIBG are considered separately, a significant correlation is found ($r = 0.87$, $p = 0.000$). The full line in figure 2 is the result of the linear regression analysis through the $^{131}$I-MIBG data alone. As expected, the correlations did not change significantly when the mean individual dose response relationship was used in this patient group ($r = 0.78$, $p = 0.0006$). The slope value determined by regression analysis of the ETBD data versus the MIRD doses was 0.70.

**Figure 3**

![Overview of the micronucleus evolution over time following multiple therapies.](image)

For the patients treated with multiple therapies, the micronuclei yields before and after each subsequent therapy were plotted versus time in figure 3. The increase in micronucleus yield 7 days after administration of the therapeutic activity had at least partially recovered by the time of the subsequent therapy and rose again after the administration of this therapy. The mean lymphocyte half-life calculated from these results (as derived from the reduction in micronucleus yield between subsequent radionuclide therapies in the same patient) was 3.9 months (range: 1.7 – 6.7 months).

**Discussion**

Since $^{131}$I-MIBG therapy is a second line treatment for neuroblastoma in Belgium, all of the included neuroblastoma patients received already chemotherapy before the $^{131}$I-MIBG therapy. For all neuroblastoma patients, the initial micronucleus yield is already higher than expected for children (Thierens et al., 1995), which is probably due to the chemotherapy. Earlier chemotherapy can jeopardize the evaluable of the micronucleus assay due to cell division inhibition. This is clearly the case for patient 10 as we were not able to count one thousand binucleated cells in any blood sample either before or after the MIBG therapy. The same occurred in the in vitro irradiated 1 Gy and post-therapy blood samples of patient 9. For this patient the cumulative effect of both chemotherapy and radiation damage to the cell were responsible for the failure of the micronucleus assay. Additionally, a subset of neuroblastoma patients (patients 6 and 8) received "whole blood" transfusions before the second blood sample was taken. The infusion of fresh lymphocytes dilutes the resident long-term irradiated lymphocytes. This is illustrated by the data of patient 8 for whom the
micronucleus frequency was even significantly lower after therapy than before therapy (table 1).

In spite of these problems, for the remaining patients a significant correlation (shown in figure 2) was found between the ETBD, based on the standard micronucleus dose response relationship and the MIRD dose ($r = 0.87$). Within the range of micronucleus frequencies under consideration, the ETBD values derived from the mean in vitro dose response relationship: $MN_{av} = 32.9 \, D^2 + 62.7 \, D$ are not significantly different ($p > 0.20$) from those obtained from the standard dose response relationship: $MN_{av} = (19.5 \pm 0.5) \, D^2 + (81.1 \pm 0.3) \, D$ (Thierens et al, 1999). In the present study, the use of in vitro dose response relationship of the considered patients in stead of a standard curve had no major impact on the results.

On the average, the obtained ETBD values were 70% of the calculated MIRD values while using the standard curve. This can be attributed to the differences in dose rate between the acute in vitro irradiation for the determination of the dose response and the in vivo irradiation at low dose rate. It has been suggested that in this case it would be better to use only the linear component of the standard dose response (IAEA, 2001).

Applying this procedure to the MIBG data, the slope of the linear regression between the MIRD dose and the ETBD data is 0.92 which equals unity taking into account the uncertainty. Therefore, our results further support the procedure supported by the IAEA. For $^{131}$I-MIBG patients we can therefore conclude that biological dosimetry based on the micronucleus assay is feasible, provided it does not closely follow chemotherapy so the lymphocyte count is restored to normal values and the blood sample after therapy is taken before blood transfusions are given to the patient.

The reason why only 12 out of 17 $^{131}$I-lipiodol therapies could be evaluated by the micronucleus assay, is due to the low number of lymphocytes present in their peripheral blood and a reduction of their proliferation capacity. Here, the problem is a consequence of the hypersplenism occurring in many of these patients. According to Akimaru et al. (2001), splenic enlargement was found in 20% of their HCC patients, resulting in hypersplenism for many of them. The enlarged spleen together with reduced liver function (as a result of hepatocellular carcinoma) ensure an impaired detoxification of the body and a shortened half-life of all blood cells in the patient resulting in pancytopenia (Bain BJ., 1995). The radiation effect on these lymphocytes caused stimulation problems in the blood samples after treatment.

For the HCC patients, no correlation was found between the ETBD values and the MIRD doses. For 7 out of 11 patients the ETBD values were higher than the MIRD dose. Several studies point to an increased in vitro chromosomal radiosensitivity in cancer patients, especially in breast cancer patients (Darroudi et al., 1995, Scott et al., 1999, Terzoudi et al., 2000, Baria et al. 2001, Baria et al., 2002). The initial low amount of lymphocytes present in the blood of these patients due to hypersplenism, will not allow to split up the blood samples and determine the in vitro dose response. Further research on the biological radiosensitivity of HCC patients is necessary. Preliminary results on dicentrics scoring for this patient group in the laboratory (De Ruyck et al, 2002) do not point to an increased in vitro radiosensitivity in $^{131}$I-lipiodol treated patients. The lymphocytes in HCC patients clearly no longer show the normal in vivo behaviour of lymphocytes and are therefore not suitable for biological dosimetry purposes.

The residual damage after multiple subsequent $^{131}$I-MIBG and $^{131}$I-lipiodol therapies was investigated. As can be seen in figure 3, for all patients an initial large increase in micronucleus yield after administration of the therapy had at least partially recovered by the time of the subsequent therapy. A similar effect was reported by Watanabe et al. (1998) after $^{89}$Sr therapy for painful bone metastases and by Fenech et al. (1990) for patients treated with external partial body radiotherapy.

From figure 3 can be seen that after several subsequent therapies, the micronucleus yield before each therapy never reached the initial level again. Instead, it rose slowly over the course of subsequent therapies representing the residual genetic damage of the previous radionuclide therapies. The short mean half-life of 3.9 months of lymphocytes, found in the present study, is due to an increased turnover of lymphocytes. This result corresponds to micronucleus yields returning to pre-treatment values within 4 to 6 months, found in children treated repeatedly for thyroid carcinoma as reported by Streffer et al. (1998). From the analysis of the Goiânia accident, Ramalho et al. (1995) concluded that the disappearance of unstable chromosome aberrations (such as micronuclei) is dose
dependent. The mean lymphocyte half-life in their study was 5.3 months in people receiving up to 1 Gy while it was significantly less (3.7 months) in people receiving more than 1 Gy, a result very similar to the shortened lymphocyte half-life determined in present study.

Conclusion.

The present study shows that the results of cytogenetic biodosimetry of cancer patients based on the in vitro micronucleus assay have to be treated with caution. Not only the in vitro dose response may be different, but also hypersplenism and other confounding factors due to adjuvant therapy such as chemotherapy or blood transfusions have to be taken into account.

The analysis of the data for the multiple therapies points to a shortened mean half-life of the lymphocytes ($T_{1/2} = 3.9$ months).

Acknowledgments

The authors would like to thank all patients and their family for their kind cooperation. Special thanks to Dr. G. Laureys (Department of Pediatric Oncology, Ghent University Hospital) and Dr. R. Troisi (Department of Surgery, Ghent University Hospital) for their help with the clinical data and to Ms. I. Meirlaen (Department of Anatomy, Embryology, Histology and Medical Physics, University of Ghent) for her help with the cell cultures.

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Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

4.3. Determining the radiation burden to relatives of patients treated with $^{131}$I.


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REAL-LIFE RADIATION BURDEN TO RELATIVES OF PATIENTS TREATED WITH $^{131}$I: A STUDY IN 8 CENTRES IN FLANDERS (BELGIUM).

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Real-life radiation burden to relatives of patients treated with iodine-131: a study in eight centres in Flanders (Belgium)

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Abstract.

In view of the EURATOM 96/29 [1] regulations, a prospective multicentre study was performed to evaluate the present guidelines given to relatives of patients treated with iodine-131 for both thyroid carcinoma and thyrotoxicosis, based on the real-life radiation burden. This study comprised 166 measurements carried out on a group of 94 relatives of 65 patients. All relatives wore a thermoluminescent dosemeter (TLD) on the wrist for 7 days. Sixty-one relatives agreed to wear another TLD for an additional 7 days. TLD were placed on nine patients’ bedside tables. The eight participating centres were arbitrarily divided into three groups according to the period of time they advised their patients to sleep separately. Groups I, II and III respectively advised their patients to sleep separately for 0, 7–10 and 14–21 days. The median dose received by in-living relatives of thyroid carcinoma patients during the 14 days following hospital discharge was 281 µSv (doses to infinity not calculated); the median dose to infinity received by in-living relatives of ambulatory treated thyrotoxicosis patients was 596 µSv, as compared with 802 µSv for in-living relatives of hospitalised thyrotoxicosis patients. In general the children of patients received a significantly (*P<0.1) lower mean dose than their partners. For thyroid carcinoma patients, only two relatives out of 19 (10%) exceeded the EURATOM 96/29 limit of 1 mSv/year. For thyrotoxicosis patients, 28% of relatives exceeded the EURATOM 96/29 limit, but none of them were relatives of patients who followed guidelines for 21 days. The results of this study indicate that sleeping separately could be necessary in order to strictly abide by EURATOM 96/29. Therefore, the authors propose the implementation of a non-rigid dose constraint for people who “knowingly and willingly” help patients treated with 131I, while still following the ALARA principle.

Key words: Iodine-131 therapy – Thyroid carcinoma – Thyrotoxicosis – Guidelines


Introduction

Based on revised epidemiological data on the incidence of cancer and leukaemia in populations exposed to ionising radiation, mainly deriving from the lifespan study of Hiroshima and Nagasaki victims [2], EURATOM 96/29 [1] recommended that the limit for members of the public for exposure to ionising radiation be reduced from 5 mSv/year to 1 mSv/year [1]. When compared with the natural background radiation averaged over the world, of 2.4 mSv/year [3], the full extent of this reduction by a factor of 5 becomes clear.

It may prove difficult to ensure that the radiation burden to relatives of patients treated with iodine-131 for thyrotoxicosis or thyroid carcinoma complies with this new dose limit [4]. In Belgium about 1500 patients are treated with radioactive iodine every year [4]. The practical consequences of the EURATOM 96/29 regulations need to be investigated by studies measuring the real-life radiation burden to family members of 131I-treated patients [5]. However, because of logistic or
practical problems, most studies published so far have been based on dose rate measurements of $^{131}$I-treated patients upon leaving the hospital and extrapolations according to time spent at varying distances to the patient [5–13]. Though this technique allows estimation of doses received in varying circumstances, it has the major drawback of the use of occupancy models for the calculation of doses, which may be inaccurate [14]. Therefore, studies measuring the dose received by in-living relatives of the patient in real-life situations are a necessary complement to dose-rate studies [5, 9, 15].

Consequently, a number of studies have measured the radiation burden to family members using film badges, thermoluminescent dosemeters (TLDs) or digital dosemeters [16–25]. Most of these studies however, have been published as abstracts and report results with regard to relatives of small groups of patients (16–51 relatives) except for studies by Barrington et al. [19] and Mathieu et al. [25], which considered 92 and 74 relatives respectively). Furthermore, each individual study has used a separate set of guidelines. A multicentre study allows comparison of the radiation burden to relatives of groups of patients with different sets of guidelines, with data acquisition over a short period of time.

This paper reports the results of TLD measurements carried out in eight centres in Flanders (Belgium) over the period from 15 February to 15 November 1997. A total of 65 $^{131}$I-treated patients were included in this study and 94 of their relatives were monitored up to 14 days after the patient had returned home. Each participating centre advised patients of its own routine guidelines. The real-life radiation burden of the patient’s relatives, measured under different sets of guidelines, is compared with the EURATOM 96/29 dose limit.

Materials and methods.

Population. The study population comprised 65 patients referred by their endocrinologist to the nuclear medicine department of one of the eight participating centres for $^{131}$I therapy to treat differentiated thyroid carcinoma or thyrotoxicosis. A total of 166 measurements were carried out on a group of 94 relatives living at home with one of these patients. In addition, TLDs were placed on the bedside tables of nine patients to estimate the dose that their partners would have received during the night if they had been sleeping together.

A group of 13 patients with a mean age of 37 years (range: 17–58 years) were treated for differentiated thyroid carcinoma and received a median activity of 4121 MBq (range: 3700–5550 MBq). In this group 19 relatives were monitored comprising nine partners, five parents and five children with a mean age of 12 years (range: 6 months – 19 years).

A group of 52 patients with a mean age of 53 years (range: 25–89 years), suffering from thyrotoxicosis, received a median activity of $370$ MBq (range: 185–1665 MBq). Twenty-five patients suffered from Graves’ disease, 9 from an autonomous nodule and 18 from multinodular toxic goitre. Sixteen patients were hospitalised for a mean period of 3 days (range 2–5 days). All hospitalised patients were discharged with a dose rate at 1 m from the patient of less than 20 µSv/h. A total of 75 relatives were monitored, comprising 47 partners, 2 parents and 26 children with a mean age of 18 years (range: 3–26 years). All children living at home were included in the study even if their age exceeded the paediatric limit of 16 years.

Guidelines after therapy. In order to limit the radiation burden to the relatives of patients treated with $^{131}$I, the patient and his family were required to comply with radiation safety guidelines after the patient had returned home. In order to facilitate comparison between results, the guidelines of the eight participating centres were divided in three categories according to the duration for which each centre advised the patient to sleep separately (Table 1). The most severe regimen for thyrotoxicosis patients was applied in group III (14 to 21 days), followed by group II (7–10 days) and group I (no separate sleeping arrangements). For thyroid carcinoma patients, group I followed the regimen of longer hospitalisation (4 days) without separate sleeping arrangements after discharge while groups II and III were hospitalised for a shorter period (2–3 days) but advised to sleep separately for 7 days after discharge.

TLD measurements. The dose received by the patient’s relatives ($n=94$) was measured by TLDs (TLD 100). The TLDs were individually calibrated in the cesium-137 beam of the radiation protection department. Readings were performed by a Harshaw 953500 reader and each reading was corrected for background accumulation by co-reading non-irradiated controls. Under these conditions the standard deviation on the reading was less than 3%.

All relatives were asked to wear a TLD on the wrist continuously for a period of 7 days, starting from the day the patient returned home. Sixty-one family members agreed to wear another TLD on the wrist for an additional 7 days. For practical reasons (limited co-operation from patient and relatives), the longer observation period could not be asked of all patients. Relatives were given only one TLD per week on one wrist to enhance co-operation and especially because sequential data were preferred in this study.

In addition, TLD dosemeters were placed on the bedside tables of nine patients in order to measure the dose their partners would have received during the night if they had been sleeping together.

To validate guidelines, the data on doses received by the in-living relatives were separated for discussion according to the patient’s diagnosis (thyroid carcinoma or thyrotoxicosis), the treatment regimen (hospitalised or ambulatory) and the relative’s relationship to the patient (partner, child or parent).

Doses to infinity were calculated by correcting the measured doses for the remaining activity at the end of the measuring period. For this correction, an effective half-life of 5.1 days was used for thyrotoxicosis patients. This value was derived from the pre-therapy uptake curve of the patients from the University Hospital of Gent included in this study and concurs with values reported in the literature [26–28].

Statistical analysis. Statistical analysis was performed by Medcalc. Because data sets were not normally distributed, differences for the mean were investigated by means of paired or unpaired two-tailed Wilcoxon tests where applicable.
Results

Administered activity to the patient.

Evidently, the highest activities (median 4121 MBq, range 3700–5550 MBq) were administered to the 13 patients suffering from thyroid carcinoma. All participating centres administer a standard activity of 3700 MBq to patients suffering from non-metastatic differentiated thyroid carcinoma, except the Middelheim Hospital of Antwerpen (5550 MBq). In all centres, a standard activity of 5550 MBq is given when the thyroid carcinoma has metastasised (as shown on a pre-therapy total body scan) and when lung or bone metastases are absent.

For patients suffering from thyrotoxicosis, all participating centres except the University Hospital of Gent follow a standard activity protocol giving the higher activities to those patients suffering from an autonomous nodule or a multinodular goitre and the lower activities to those suffering from Graves’ disease. Except for one patient who received an activity of 888 MBq, the activity did not surpass 740 MBq.

In the University Hospital of Gent, an aimed dose-to-the-thyroid protocol is used, to give a dose of 70 Gy to patients suffering from Graves’ disease, 100 Gy to patients suffering from a multinodular goitre and 150 Gy to patients suffering from an autonomous nodule. The activity to be administered is calculated based on the formula given by Silver [29], including correction for thyroid mass, the maximum percentage of 131I-uptake and the effective half-life of 131I in the thyroid. This procedure occasionally leads to activities as high as 1110 MBq be-

---

Table 1. Guidelines given for patients treated with 131I in the participating centres, divided into three groups depending on the period of sleeping separately

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Group Ia</th>
<th>Group IIb</th>
<th>Group IIc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Text available for patient</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Avoid pregnancy</td>
<td>No info</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Hospitalisation time</td>
<td>4 days</td>
<td>2–3 days</td>
<td>2 days</td>
</tr>
<tr>
<td>Sleep separately</td>
<td>0 days</td>
<td>7 days</td>
<td>7 days</td>
</tr>
<tr>
<td>No children in the house</td>
<td>0 days</td>
<td>5 days</td>
<td>7 days</td>
</tr>
<tr>
<td>Keep distance from children/pregnant partner</td>
<td>A few days</td>
<td>7 days</td>
<td>7 days</td>
</tr>
<tr>
<td>Keep distance from adults</td>
<td>0 days</td>
<td>7 days</td>
<td>7 days</td>
</tr>
<tr>
<td>0 m</td>
<td>1–2 m</td>
<td>2–3 m</td>
<td></td>
</tr>
<tr>
<td>Don’t go to work</td>
<td>0 days</td>
<td>7 days</td>
<td>7 days</td>
</tr>
<tr>
<td>Mind personal hygiene</td>
<td>A few days</td>
<td>7 days</td>
<td>7 days</td>
</tr>
</tbody>
</table>

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a Middelheim Hospital Antwerpen
b University Hospital Gent, Maria Middelares Hospital Gent
c Onze Lieve Vrouw Hospital Aalst
d The upper row shows the period for which the guidelines should be followed; the lower row shows the distance advised to patients as safe
In one patient, suffering from a multinodular goitre, an exceptionally high activity of 1665 MBq was administered. In the present study, the median administered activity to patients suffering from thyrotoxicosis amounted to 370 MBq (range 185–1665 MBq). In this group, the highest activities were administered to 18 patients suffering from a multinodular toxic goitre, with a median of 566 MBq (range: 191–1665 MBq), followed by nine patients suffering from a toxic autonomous nodule, with a median activity of 500 MBq (range: 259–1158 MBq); 25 patients suffering from Graves’ disease received a median administered activity of only 264 MBq (range: 185–792 MBq). Table 2 gives an overview of the median (range) activities administered to the different patient groups classified according to the guideline category.

Dose to the relatives.

The data on the doses (median, range) received by the patients’ relatives obtained in the present study are also summarised in Table 2. Data are classified according to the guideline category. Figure 1 gives an overview of the doses received by the relatives during the first week, while Fig. 2 shows the difference in the median doses to the partners during the first versus the second week.

Thyroid carcinoma patients.

Considering all patients included in the study, the mean hospitalisation period was 3.4 days (range: 2–5 days). Patients from group I were given no guidelines after 4 days of hospitalisation. Patients from the other groups were hospitalised for a shorter period (2–3 days) and were advised to sleep separately for a period of 7 days and to limit close contact for the same period. Figure 1A illustrates the results in respect of the measured doses during the first week of observation. None of the family members exceeded the EURATOM 96/29 limit of 1 mSv during this week.

All groups stopped receiving guidelines during the second week of investigation. As can be seen in Fig. 2A, in spite of the fast wash out of the $^{131}$I from the patient’s body, the second week still contributes significantly to the total radiation burden to the patient’s relatives. The median dose received by the relatives of thyroid carcinoma patients during the 14 days following hospital dis-

### Table 2. Overview of the results of the study, according to the diagnosis, family relationships and guideline categories in respect of sleeping separately

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>One week</th>
<th>Two weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td>TCA Activity (MBq)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Partner (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Child (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Parent (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>TT ambulatory Activity (MBq)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Partner (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Child (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Parent (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>TT hospitalised Activity (MBq)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Partner (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Child (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Parent (µSv)</td>
<td>Median</td>
<td>Range</td>
</tr>
</tbody>
</table>

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charge was 281 µSv (range: 136–1263 µSv). Doses to infinity were not calculated as a mean effective half-life of 2.2 days [25] makes it improbable that the dose would rise significantly after the period under observation. Due to the low number of measurements in each group, statistical analysis of the results could not be performed.

Only 2 relatives out of 19 (10%) ended up exceeding the EURATOM 96/29 limit of 1 mSv during the period under investigation. These people were the mother and the little sister of young patients.

**Ambulatory treated thyrotoxicosis patients.**

As indicated above, patients from group I did not sleep separately after the administration of the activity. Patients of groups II and III were advised to sleep separately and to limit close contact with other people 7 and 14 days respectively.

An overview of the results obtained during the first week of observation is given in Fig. 1B. Only four relatives out of 50 (8%) exceeded the EURATOM 96/29 limit of 1 mSv during the first week of investigation. Two out of these four were partners of patients of group I, who did not sleep separately from the patient. The third was a partner of a patient of group II and the fourth, a 3-year-old child who was kept at home after the mother’s therapy because no other arrangements could be made.

Guidelines to patients of group II ceased to apply during the second week of observation, whereas those to patients of groups II and III remained unaltered (i.e. group I could sleep with their partners while group III could not).

In Fig. 2B, a statistically significant ($P<0.1$) reduction in the received dose can be observed in the relatives
of patients from group I, where the guidelines did not differ from the first week. An increase in the time spent close to the patient due to the removal of guidelines in group II is reflected in Fig. 2B by the significantly (P<0.1) higher dose received by the relatives during the second week. A slight but insignificant increase in dose was also observed in group III in spite of the longer duration of the guidelines.

Based on the data summarised in Table 2, the dose to infinity was calculated for each individual. Taking into account all relatives, the median dose to infinity amounted to 596 µSv (range: 162–2033) for a median administered activity of 333 MBq (range: 185–862 MBq). In general, patients’ children tended to receive a lower dose (median: 425 µSv; range: 0–3752 µSv) than their partners (median: 777 µSv, range: 0–5961 µSv), but the difference did not reach statistical significance. Relatives of group I patients tended to receive a higher dose to infinity (median: 1456 µSv; range: 538–5961 µSv) than relatives of patients of group II (median: 329 µSv; range: 0–2102 µSv) and group III (median: 885 µSv, range: 222–2145 µSv), but again the differences were not statistically significant.

Overall, the EURATOM 96/29 limit was violated for 13 out of 52 relatives (25%). More relatives of group I exceeded the EURATOM 96/29 limit (50%) than relatives of the other groups (21% in group II and 38% in group III). These results show that sleeping separately reduces the number of people who will violate the EURATOM 96/29 limit of 1 mSv/year.

**Hospitalised thyrotoxicosis patients.**

Patients were hospitalised for a mean period of 3 days (range: 2–5 days). All patients were advised to limit close contact with their relatives. As indicated above, patients of groups II and III were also advised to sleep separately from their partners for 7–10 and 21 days.

As can be seen from Table 2, patients of group II received a median activity of 1125 MBq (range: 777–1665 MBq), a value significantly higher (P<0.1) than the activity received by the other groups (median activity: 740 MBq, range 370–888 MBq).

An overview of the results of the TLD measurements obtained during the first week of observation is given in Fig. 1C. It should be noted that the guidelines issued to group II led to a median dose to relatives which was slightly lower than the median dose received by the relatives of group I patients, in spite of the higher activity administered to patients in the former group. During the first week, only 1 person out of 23 exceeded the EURATOM 96/29 limit of 1 mSv/year. This person received a dose of 1064 µSv and did not sleep separately from the patient.

During the second week of observation, guidelines to group II patients ceased to apply, while those to groups I and III remained unaltered (i.e. group I could sleep with their partners while group III could not). As can be seen in Figure 2C, a significant dose was received by the relatives during the second week of observation. For relatives of patients from groups I and III this dose was lower than that received during the first week. However, relatives of group II patients received a higher dose during the second week, reflecting an increase in the time spent at close proximity to the patient. The differences were statistically significant (P<0.1) in groups I and II.

Based on the data summarised in Table 2, the dose to infinity was calculated for each individual. Taking into account all relatives, the median dose to infinity amounted to 802 µSv (range: 7–3620 µSv) for a median administered activity of 759 MBq (range: 555–1665 MBq). The relatives of group I patients showed the highest dose (median: 894 µSv; range: 7–1495 µSv); the dose to relatives of group II patients was slightly lower (median: 819 µSv; range 639–2108) although these patients received a significantly (P<0.1) higher activity. Relatives of group III patients, who followed guidelines for 3 weeks, received the lowest dose to infinity (median: 325 µSv; range: 238–412). In general the patients’ children received a significantly (P<0.1) lower dose to infinity (median: 266 µSv; range: 132–3620 µSv) than did their partners (median: 812 µSv; range: 7–2108 µSv).

Overall the EURATOM 96/29 limit of 1 mSv/year was violated for 9 relatives out of 26 (35%). None of these were relatives of group III patients, who followed guidelines for 21 days.

**Bedside tables.**

TLDs were placed on the patient’s bedside tables of nine patients. The median dose measured by these TLDs was 1058 µSv, with a range of 0–2727 µSv. The wide range in the results probably derived not only from variation in the activity administered to the patient (median activity: 555 MBq; range: 222–3700 MBq) and the duration of hospitalisation (range: 0–5 days), but also from differences in the exact distance of the TLD from the patient.

**Discussion.**

**Thyroid carcinoma patients**

The data presented in our study confirm the results of other studies [7, 16, 24, 25] indicating that the doses received by relatives of thyroid carcinoma patients are generally lower than those doses received by relatives of thyrotoxicosis patients. This observation is due to the lower retention (thyroid remnant) and the faster wash-out of the 131I activity from the body of thyroid carcinoma patients in spite of the higher activity administered. The doses to the relatives of thyroid carcinoma patients measured in the present study (median 281 µSv) are somewhat higher than those presented by Mathieu et al. [24, 25] (median 170–240 µSv).
In the present study only two relatives out of 19 (10.5%) exceeded the EURATOM 96/29 limit of 1 mSv. Furthermore, these people represent exceptions as they were the sister of a patient aged 17 years, who slept in the same room as the patient, and the mother of a 26-year-old patient who did not follow the given guidelines.

On the basis of these results it therefore seems that (a) a longer hospitalisation period of 4 days without issuing guidelines to the patient and (b) or a shorter hospitalisation period of 2–3 days while recommending separate sleeping and limited close contact to other people for 7 days are equally effective in limiting the radiation burden to the 1 mSv limit. However, a longer hospital stay will increase the total cost of the treatment and limit the availability of the isolation room for patients treated with $^{131}$I. In our opinion, a hospitalisation period of 2–3 days, combined with guidelines effective for 7 days, will not place a high burden on the patient’s family life while reducing the dose to the relatives and limiting treatment cost. Problems can still occur following this procedure with young patients whose parents tend to be overcaring after the patient returns home. When this type of behaviour is to be expected, the patient should be kept in the hospital longer (e.g. 4 days instead of 2).

**Thyrotoxicosis patients**

In the present study, 25% of the relatives of ambulatory treated patients and 35% of the relatives of hospitalised patients exceeded the EURATOM 96/29 limit. These results are in good agreement with those obtained in the study by Mathieu et al. [25] where 33% of relatives exceeded the limit of 1 mSv/year. Concerning the different sets of guidelines, 24% (group III patients with only 14 days of guidelines), 28% (group II, 7–10 days of guidelines) and 38% (group I, no guidelines) of the relatives of thyrotoxicosis patients exceeded the EURATOM 96/29 limit in the present study. However, the limit was not violated when 21 days of guidelines were issued, as was the case for some patients of group III. Our results show that a period of sleeping separately and restricting close contact for 7 days is not sufficient. Implementation of a longer period of guidelines reduces both the median dose received by the family members and the number of people exceeding the EURATOM 96/29 limit.

The median doses to infinity received by family members of thyrotoxicosis patients presented in this paper (596 µSv for ambulatory treated patients and 802 µSv for hospitalised patients) are significantly lower than the doses calculated by Thomson et al. [20] (median to 1010 µSv for 200 MBq), O’Doherty et al. [5], (up to 12)400 µSv for 400 MBq) and Demir et al. [11] (up to 13)300 µSv for 370 MBq) because all of these authors presumed that no guidelines whatsoever were issued.

When our results are compared with those of studies in which guidelines were issued to patients, the dose to the partners (median 806 µSv, range 0–5961 µSv) is higher than the median doses of 407 µSv obtained in the study by Barrington et al. [18] and 444 µSv obtained in the study by Thompson et al. [21] after correcting for the difference in administered activity. In Barrington’s study, however, guidelines covered a considerably longer period (up to 25 days). On the other hand, somewhat higher dose values were found in the study by Mathieu et al. [25], who reported a median dose of 1070 µSv to the partner after 3 weeks of measurements when separate sleeping arrangements were adopted.

It should be noted that only 5 out of 26 included children exceeded the EURATOM 96/29 limit. Two of these were only 3 years old and were kept at home; the highest dose of 3752 µSv was received by a woman of 26 years old caring for her partially disabled mother. This corresponds with the study by Barrington et al. [19], in which only two children (aged 2 and 3 years) out of 64 received a dose of more than 1.5 mSv.

In the present study, as well as in others [5, 19, 24, 25], the children of thyrotoxic patients received a significantly lower dose than did the patients’ partners. The study carried out by Barrington et al. [18], on the other hand, concluded exactly the opposite, with a lower dose for partners (median: 220 µSv; SD: 120 µSv) and a higher dose for the children (median: 310 µSv; SD: 580 µSv) during a period from 3 to 6 weeks. However, in comparison with the present study Barrington et al. [17] included younger children (range: 0.5–17 years) who need more care and attention from the patient. In the present study, the mean age of the children was 18 years (range 3–26 years) since all in-living children of the patient were included, even when their age exceeded the paediatric limit of 16 years and also because the parents were advised to let children under 7 years of age stay at another location for about 5 days.

**Bedside tables**

The authors expected the TLDs placed on the bedside table of the patient to give an underestimation of the actual dose that would be received by the patient’s partner if they were sleeping together. However, when comparing the dose for bedside tables (median: 1058 µSv; range: 0–2727 µSv) to the dose for partners from group I after 2 weeks of observation (median: 782 µSv, range 6–5095 µSv), the results disagree with this assumption. The large range of values found in the present study can probably be explained by the inaccuracy of the distance between the patient and the TLD. These results indicate that in vivo measurements are more reliable than simply placing the TLD on a bedside table or calculating the dose to the partner.
Patients carried out by Thomson et al. [20, 21]: the highest concentration is in agreement with studies on thyrotoxicosis patients, with a median value of 1058 µSv, while only a median dose of 240 µSv (SD: 560 µSv) occurred during the day. O’Doherty et al. [5] even calculated that 92% of the total dose would occur during the night if the partner did not sleep separately from the patient.

For most of the participating centres, the duration of the guidelines is relatively short compared with the 7–19 nights of sleeping separately calculated as necessary by Thomson et al. [20, 21], the 2–15 nights calculated by Hilditch et al. [30], and the even longer period of 15–26 nights calculated by O’Doherty et al. [5]. In the present study, only a period of sleeping separately for 21 days, as was done for some of the relatives of group III patients, was successful in keeping the dose to the partner below the EURATOM 96/29 limit of 1 mSv/year. Therefore, the authors propose the implementation of a non-rigid dose constraint for people who “knowingly and willingly” help patients treated with 131I, while still following the ALARA principle. A period of sleeping separately and limiting close contact for 14 days is chosen as a compromise, between 7 days, which is usually too short, and 21 days, which may be unnecessary long, considering the social isolation of the patient and the radiation protection of the relatives.

Advising children under the age of 7 years to spend 5 days at family or friends leads to a significant dose reduction.

Conclusions

For patients suffering from thyroid carcinoma, the results of this multicentre study suggest that the patient should be hospitalised for 2 or 3 days with an additional 7 days of sleeping separately and avoidance of close contact to other people.

For thyrotoxicosis patients, up to 21 days of sleeping separately might be necessary in order to strictly adhere to the EURATOM 96/29 limit of 1 mSv/year. Therefore, the authors propose the implementation of a non-rigid dose constraint for people who “knowingly and willingly” help patients treated with 131I, while still following the ALARA principle. A period of sleeping separately and limiting close contact for 14 days is chosen as a compromise, between 7 days, which is usually too short, and 21 days, which may be unnecessary long, considering the social isolation of the patient and the radiation protection of the relatives.

Advising children under the age of 7 years to spend 5 days at family or friends leads to a significant dose reduction.

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The investigators dedicate this study to Dr. K. Schelstraete, previous head of the Division of Nuclear Medicine (University Hospital, Gent), whose work in nuclear endocrinology inspired us all.
References


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5. Discussion and Conclusions
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

In this work, eight questions regarding patient dosimetry and radiation protection issues in radionuclide therapy using $^{131}$I have been addressed. The results of this work will be discussed briefly and conclusions drawn for each separate question. Also possible future research or extended research going on in our laboratory is addressed to.

5.1. Can the patient dose after radionuclide therapy be determined before administration of the therapeutic activity?

Although previously published studies (Fielding et al., 1991; Tristam et al, 1996) also compare pre-and post-therapy dosimetry for patients treated with $^{131}$I-MIBG, our study is the first in which a series of total body scintigrapies are compared before ($^{123}$I-MIBG) and after ($^{131}$I-MIBG) therapy in the same circumstances, thereby combining “the best of both worlds”.

The combination of the pre-therapeutical and post-therapeutical data sets can be represented by a bi-exponential curve through the combined data cloud. An example of one of these bi-exponential fits is shown in the figure below.

![Figure 5.1](image_url)
Our results show that the $^{131}$I-MIBG therapy dose can be predicted from a single set of $^{123}$I-MIBG dosimetric scans for all following $^{131}$I-MIBG therapies, taking into account a correction factor of 1.20 ($R = 0.85$). Moreover, $^{123}$I-MIBG pre-therapy scans do not need to be repeated before each therapy except when the biodistribution of $^{131}$I-MIBG is expected to change rapidly. This is the case especially in patients where bone marrow invasion is present. In view of the encouraging results of this study, dosimetric pre-therapeutic $^{123}$I-MIBG scanning is now routinely carried out before administration of $^{131}$I-MIBG therapy in the Ghent University Hospital.

We will try to extend our study into tumor and organ dosimetry, by scanning on another camera (the GE-IRIX system) that allows dual isotope scanning, and scatter correction using triple energy windows around the 364 keV photo peak of $^{131}$I. Results for $^{131}$I-MIBG therapy are not yet available since the number of patients presenting for $^{131}$I-MIBG therapy has fallen over the last year. The same protocol is however applied to patients undergoing $^{131}$I-lipiodol therapy.

5.2. What are the differences for the absorbed dose to organs and the effective dose to the patient between calculations by means of the Monte Carlo code MCNP® and the MIRDOSE® program?

In this study the absorbed dose to the organs and the effective dose to the patient was determined by 2 different methods for HCC patients receiving $^{131}$I-lipiodol therapies.

In general it should be stated that MCNP results are more accurate than MIRDOSE results. This is due to the inclusion of patient specific modelling of the liver and of the tumour within the liver in the MCNP program. Additionally, by including the tumour into the geometry, extra S-factors (e.g. $S_{\text{Liver} \rightarrow \text{Tumour}}$, $S_{\text{Tumour} \rightarrow \text{Liver}}$, $S_{\text{Lungs} \rightarrow \text{Tumour}}$,...) could be calculated by the MCNP program, which is impossible with MIRDOSE. Finally, in our MCNP calculations, the contribution of the electron-dose deposited outside the tumour was also included. However, due to the medium energy of the $\beta$ rays of $^{131}$I, the contribution of the additional S values to the dose is less important, and all other organs were not modelled patient specifically. Therefore, the mean absorbed dose for most organs was comparable between the MCNP calculations and MIRDOSE. Overall, a good correlation ($R = 0.93$) was obtained between the effective dose calculated by Monte Carlo simulation techniques (mean 2.01 Sv)
and the effective dose calculated by MIRDOSE (mean 2.05 Sv). Such would not be the case however, when high-energy beta emitters (such as $^{188}$Re) were considered. In fact, the only organ where the differences in absorbed dose were significant was the tumour. The absorbed dose to the tumour was systematically higher calculated by MIRDOSE than by MCNP. The difference is due to the linear interpolation that is necessary between the tabulated discrete sphere sizes (and corresponding S-factors) tabulated in the “node module” of MIRDOSE. The difference is particularly large (mean 15%) for the smaller tumours (< 3 cm).

In our study, uptake measurements were carried out using bi-planar scans. The scans were not corrected for scatter, and the attenuation correction was performed homogeneously for the whole abdominal region.

Nowadays, oncological scans in the nuclear medicine department of the Ghent University Hospital, are performed on the GE-IRIX gamma camera system. This system is capable of dual isotope scanning using either a flood sheet filled with $^{57}$Co or $^{99m}$Tc placed underneath the patient, or the “Beacon” moving line source. The IRIX system is also capable of using triple energy windows, allowing for correction of scatter. All these methods are currently being investigated to correct for scatter and inhomogeneous attenuation and should improve the determination of the correct activity inside the organs of interest.

In order to use correct volumes and anatomical localisation of the organs into completely patient specific phantoms, fusion between SPECT and CT or MRI images can now be performed and will hopefully lead to the determination of patient specific S-factors. However, the use of SPECT imaging is not evident in patients treated with $^{131}$I, since the radiopharmaceutical is highly concentrated in the tumour(s) inside the liver. It is therefore not evident to obtain images rendering sufficient quality in order to enable the performance of dosimetry. HCC patients are recently also treated with $^{188}$Re-lipiodol where SPECT scanning should be easier due to the lower energy of the $\gamma$-rays.

In our study, we found a significant $^{131}$I uptake in the thyroid of patients treated with $^{131}$I-lipiodol. This was never described by the early authors (Raoul et al., 1988; Madsen et al., 1988; Nakajo et al., 1988) and in fact, the guidelines of the European Association of Nuclear Medicine (EANM, 2000) do not recommend any special precautions. The reason for this iodine uptake in the thyroid remains unclear since non-ionic contrast media injected during the arterioscopic procedure contain free inorganic iodide and the amount of stable iodide injected should saturate the thyroid iodine uptake mechanism. Of course, other mechanisms, such as the existing slight iodine deficiency in Belgium, may also play a role.
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We also calculated a significantly lower mean absorbed dose to the thyroid of 7.2 Gy for patients who received thyroid blocking compared to the other patients (13.8 Gy). Since our patient group is relatively small to compare 2 treatment schedules, a larger (68 therapies) randomised prospective study (Bacher et al., 2002) was undertaken. The results of that study confirm the halving of the absorbed dose to the thyroid when thyroid blocking is administered. Since thyroid blocking is well tolerated and $^{131}$I-lipiodol treatment is usually repeated so the thyroid will be irradiated several times, we now systematically give KI to all these patients.

5.3 How do the results of a biological dosimetry method such as the *in vitro* micronucleus assay compare to a physical dosimetry method based on bi-planar scans?

For patients treated with $^{131}$I-MIBG and patients treated with $^{131}$I-lipiodol, the ETBD calculated by means of the in-vitro micronucleus assay were compared to the total body doses calculated by means of MIRDOSE based on bi-planar scans.

For patients treated with $^{131}$I-MIBG, the mean individual dose response curve is given in figure 5.2.

![Graph showing mean individual dose response curve for patients treated with $^{131}$I-MIBG.](attachment:mean-individual-dose-response-curve.png)

*Fig. 5.2: Mean individual dose response curve for patients treated with $^{131}$I-MIBG.*
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After exclusion of $^{131}$I-MIBG treated patients having lymphocyte division problems due to chemotherapy and/or lymphocyte dilution caused by whole blood transfusions, a significant correlation was found between the ETBD, based on the in-vitro micronucleus assay and the MIRD dose ($r = 0.87$).

On the average, the obtained ETBD values were 70% of the calculated MIRD values. This can be attributed to the differences in dose rate between the acute in vitro irradiation for the determination of the dose response and the in vivo irradiation at low dose rate, which allows a longer time for repair of DNA damage. It has been suggested that in this case it would be better to use only the linear component of the standard dose response (IAEA, 2001). Applying this procedure to the MIBG data, the slope of the linear regression between the MIRD dose and the ETBD data is 0.92, which equals unity taking into account the uncertainty. Therefore, our results further support the procedure proposed by the IAEA.

In order to take the low dose rate effect into account, experiments using low dose rate irradiation are planned. For $^{188}$Re, the low dose rate can be mimicked by long-term irradiation of the lymphocytes in a water bath at 37°C in a low dose rate $^{60}$Co beam. For $^{131}$I however, the duration of irradiation would be too long using this methodology. We therefore have to add $^{131}$I into the cell culture medium, In this way the cells can be exposed for a longer period of time, after which, the $^{131}$I is washed from the medium. In this way, we hope to determine individual dose response curves at low dose rate for each patient.

For the HCC patients treated with $^{131}$I-lipiodol, no correlation was found between the ETBD values and the MIRD doses. For 7 out of 11 patients the ETBD values were higher than the MIRD dose. The lymphocytes in HCC patients clearly no longer show the normal in vivo behaviour of lymphocytes and are therefore not suitable for biological dosimetry purposes.

In order to avoid the problem with cellular division of the lymphocytes after mitogen stimulation, the “premature chromosome condensation” or PCC method was tried out. The addition of Calyculin A to the culture medium condenses the chromosomes in interphase, allowing scoring of chromosome aberrations in interphase. This was compared to the normal scoring of dicentrics. As it turned out, the PCC technique can be used for $^{131}$I-lipiodol patients, but the results present no improvement on the results of dicentrics scoring (De Ruyck et al., 2002).
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Since the ETBD doses in the HCC patients treated with $^{131}$I-lipiodol patients were higher than the physical dosimetry results, the question of whether or not these patients could be radiosensitive was raised. For a number of cancer patient groups, an enhanced radiosensitivity was found (Darroudi et al., 1995; Scott et al., 1999; Terzoudi et al., 2000; Baria et al. 2001; Baeyens et al., 2002). In order to get an answer for this question, individual dose response curves were determined for these patients using dicentrics scoring. The individual dose response curves included 5 dose points and compared to those of normal healthy volunteers (De Ruyck K., unpublished results). In fact, the dose response curves of the HCC patients were slightly, but not significantly, elevated in comparison to the healthy volunteers, as shown in figure 5.3. It was therefore concluded that HCC patients do not show an increased radiosensitivity compared to healthy volunteers (De Ruyck K., unpublished results).

![Graph](image)

**Fig. 5.3.:** Comparison of dose response curves of HCC patients compared to healthy volunteers.
5.4. What is the effect of multiple radionuclide therapies on the micronucleus yield?

The micronucleus yield after multiple subsequent $^{131}$I-MIBG and $^{131}$I-lipiodol therapies was investigated.

For all patients an initial large increase in micronucleus yield after administration of the therapy had at least partially recovered by the time of the subsequent therapy. A similar effect was reported by Watanabe et al. (1998) after $^{89}$Sr therapy for painful bone metastases and by Fenech et al. (1990) for patients treated with external partial body radiotherapy.

The short mean half-life of 3.9 months of lymphocytes, found in the present study, is due to an increased turnover of lymphocytes. This result can be compared to micronucleus yields returning to pre-treatment values within 4 to 6 months, found in children treated repeatedly for thyroid carcinoma as reported by Streffer et al. (1998). From the analysis of the Goiânia accident, Ramalho et al. (1995) concluded that the disappearance of unstable chromosome aberrations (such as micronuclei) is dose dependent. The mean lymphocyte half-life in their study was 5.3 months in people receiving up to 1 Gy while it was significantly less (3.7 months) in people receiving more than 1 Gy, a result very similar to the shortened lymphocyte half-life determined in the present study.

5.5. What is the residual damage after radionuclide therapy one year after treatment?

In the present study the FISH method was used to explore the potential DNA damage induced by radioiodine therapy in hyperthyroidism patients one year after treatment by scoring the translocations involving chromosomes 2, 4 and 8.

The present study has shown that the frequency of translocations involving chromosomes 2, 4 and 8 was 5 times higher than in an age-matched control population. The stable properties of translocations explain the high frequency of aberrations found in the present patient data.

Micronucleus data on hyperthyroidism patients treated with the same medical protocol as the patients of this study result in estimated doses ranging from 0.16 Gy to 0.55 Gy with an average of 0.34 Gy, 1 week after administration of the $^{131}$I. The dose estimates resulting from chromosome painting are higher (mean 0.79 Gy ± 0.22 Gy). The difference in dose can partly be explained by the difference in the dose received after 1 week and 1 year. Zanonico (1997) showed that the standard administered activity of 1036 MBq of $^{131}$I, required for a standard 70 Gy absorbed dose to the thyroid for treatment of Graves’ disease, yielded a high
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blood absorbed dose of 1.50 Gy due to the relatively long effective half-life of $^{131}$I in the thyroid and high serum concentrations of long-lived protein-bound activity. This estimate is twice as high as our value but the administered activity in their study was higher: 130% of the administered activity in our study.

The observation of a high number of translocations as well as an over-representation of translocations involving chromosome 4 in present study suggests the need for medical follow-up of these patients. Chromosome 4 translocations t(4,11) are regularly associated with a specific type of acute leukaemia and probably initiate the development of this disease (Kapelushnik et al., 1991; Palau et al., 1991). However, after over 40 years of treating patients with $^{131}$I no epidemiological evidence on secondary carcinomas has been found (Clarke S.1991; Hall P. et al. 1992; Halnan K. E.1992).

The final conclusion, how far an increase in chromosomal translocation frequency reflects an increased risk for cancer at the individual level, is not solved at the moment.

5.6. Can $^{131}$I treatment be considered as an in vivo conditioning dose leading to an in vivo adaptive response?

The existence of an in vivo adaptive response was investigated in a population of $^{131}$I treated hyperthyroidism patients by comparing the micronucleus yield after in vitro irradiation (conditioning dose) of blood samples taken from these patients before and after $^{131}$I therapy (adaptation dose). The definition of an adaptive response is that the biologic effect inflicted by a high dose of a mutagen is less when the organism has been exposed to a chronic small dose of a mutagen beforehand, than when the high dose is given without previous exposure. In our study, an adaptive response exists when the number of micronuclei induced after in vitro irradiation before $^{131}$I therapy is significantly higher than the increase in micronuclei after the same in vitro irradiation after $^{131}$I therapy as is shown in figure 5.4.
In the present study, an adaptive response could be visualized in 8 out of 20 individuals. These results are the first demonstration that exposure to low doses of ionising radiation during medical treatment (conditioning dose) makes human peripheral blood lymphocytes less susceptible to cytogenetic damage for subsequent in vitro irradiation at higher doses (challenge dose). They show that the iodine treatment can act as a conditioning dose and can induce an in vivo adaptive response, but that an inter-individual variability exists. The reproducibility of the data for the control population further shows that the observed differences cannot be attributed to cell culture or technical effects. Therefore, the observation can be interpreted as an adaptive response phenomenon. Recently, our group has also reported the existence of an in vivo adaptive response for temporary nuclear workers exposed to low dose rate irradiation for a short period of time (Thierens et al., 2002).

Investigation for the mechanism behind the adaptive response is beyond the scope of this study. Adaptive response may primarily involve a qualitative change in damage repair or processing (Joiner, 1994). Only a few cGy are needed to produce an adaptive response in human lymphocytes (Wolff, 1992). Also in present study, the mean ETBD in the patient subgroup showing an adaptive response was only 45 cGy, so selective “killing” of more radiosensitive sub-populations of lymphocytes is highly unlikely.
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Adaptive response phenomena have been studied primarily on human lymphocyte cultures, but also on other cell cultures such as mouse bone marrow cells, mouse spermatocytes, mouse embryonic cells as well as mouse and human fibroblasts. It has also been described in different cancer cell lines (UNSCEAR 1994), but the existence of an adaptive response on thyroid cancer cell lines has not been reported yet.

The observation that only 8 out of 20 patients showed an adaptive response after receiving $^{131}$I therapy, clearly demonstrates the inter-individual variability. Both the pre-therapy in vitro irradiation and the in vivo exposure by the $^{131}$I therapy lead to a somewhat higher increase in micronuclei in the patient group showing an adaptive response compared to the other patient group. The in vitro dose response curve for the patients showing an adaptive response seems to normalize after $^{131}$I therapy (adaptation dose). Although the results did not reach statistical significance, it therefore seems that the adaptive response in present study is seen especially in radiosensitive individuals.

For the 8 patients showing an adaptive response, an in vivo exposure to ionising radiation (challenge dose) following the $^{131}$I therapy (adaptation dose) would very probably lead to less genetic damage. Therefore, in the evaluation of the detrimental effects of exposure to radiation, some consideration should be given to the importance of biological defence mechanisms.

**5.7. Are there specific problems for biodosimetry of cancer patients?**

In a healthy population, the mutagenic potential of a certain treatment or drug can be determined by cytogenetic techniques, such as the in vitro cytokinesis-blocked micronucleus assay (Ramalho et al., 1995; Thierens et al., 1995; Thierens et al., 1999). The success of the micronucleus assay in genetic toxicology depends mainly on normal peripheral lymphocyte kinetics and their intact cellular division mechanisms. As can be seen from the rather low success rate in our study of patients treated with $^{131}$I-MIBG or $^{131}$I-liodol, this may not always be the case for a cancer patient population.

Since $^{131}$I-MIBG therapy is a second line treatment for neuroblastoma in Belgium, all of the included neuroblastoma patients received chemotherapy before the $^{131}$I-MIBG therapy. Earlier chemotherapy can jeopardize the evaluability of the micronucleus assay due to cell division inhibition. As a result, we were not able to count 1000 binucleated cells in some blood samples.
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Additionally, a subset of neuroblastoma patients received "whole blood" transfusions before the second blood sample was taken. The infusion of fresh lymphocytes dilutes the resident long-term irradiated lymphocytes. This is illustrated in some patients by an unusually low increase or even a significant reduction in micronucleus yield after therapy. In spite of these problems, a significant correlation (shown in figure 2) was found between the ETBD, based on the standard micronucleus dose response relationship and the MIRD dose ($r = 0.87$). In the present study, the use of in vitro dose response relationship of the considered patients instead of a standard curve had no major impact on the results.

For $^{131}$I-MIBG patients we can therefore conclude that biological dosimetry based on the micronucleus assay is feasible, provided it does not follow too closely after chemotherapy so the lymphocyte count is restored to normal values and the blood sample after therapy is taken before blood transfusions are given to the patient.

For the patients treated with $^{131}$I-lipiodol, only 12 out of 17 $^{131}$I-lipiodol therapies could be evaluated by the micronucleus assay, due to the low number of lymphocytes present in their peripheral blood and a reduction of their proliferation capacity. Here, the problem is a consequence of the hypersplenism occurring in many of these patients. The radiation effect on these lymphocytes caused stimulation problems in the blood samples after treatment. For the HCC patients, no correlation was found between the ETBD values and the MIRD doses. For 7 out of 11 patients the ETBD values were higher than the MIRD doses. Several studies point to an increased in vitro chromosomal radiosensitivity in cancer patients, especially in breast cancer patients (Darroudi et al., 1995; Scott et al., 1999; Terzoudi et al., 2000; Baria et al. 2001; Baeyens et al., 2002). We could not study this effect in HCC patients because the initial low amount of lymphocytes present in the blood of these patients due to hypersplenism, did not allow splitting up the blood samples and determining the in vitro dose response. Further research on the biological radiosensitivity of HCC patients is necessary.

Preliminary results on dicitronics scoring for this patient group in the laboratory (De Ruyck et al., 2002) do not point to an increased in vitro radiosensitivity in $^{131}$I-lipiodol treated patients (fig 5.4.). Also, external physiological factors such as diet, pharmaceuticals or hormone levels can influence the number of chromosome aberrations (Robert et al., 1997; Greenrodt et al., 2001). The lymphocytes in HCC patients clearly no longer show the normal in vivo behaviour of lymphocytes and are therefore not suitable for biological dosimetry purposes using the in vitro micronucleus assay.

The present study shows that the results of cytogenetic biodosimetry of cancer patients based on the in vitro micronucleus assay have to be treated with caution. Not only the in vitro dose response may be different, but also hypersplenism and other confounding factors due
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to adjuvant therapy such as chemotherapy or blood transfusions have to be taken into account.

5.8. What is the radiation burden of relatives of patients treated with $^{131}$I for thyroid diseases when implementing different sets of guidelines?

In the present work, relatives of patients receiving $^{131}$I therapy for hyperthyroidism or thyroid carcinoma were monitored during 2 weeks after the patient returned home. A multicentre approach was favoured to obtain results with several different regimens of routine radiation protection guidelines.

The data presented in this study confirm the results of other studies (Harbert and Wells, 1974; Culver and Dworkin, 1992; Mathieu et al., 1997) observing that the doses received by relatives of thyroid carcinoma patients are generally lower than the doses received by relatives of hyperthyroidism patients. This observation is due to the lower retention (thyroid remnant) and the faster wash out of the $^{131}$I activity from the body of thyroid carcinoma patients in spite of the higher administered activity: only 2 out of 19 relatives of thyroid carcinoma patients exceeded the EURATOM-29 (1996) limit of 1 mSv. It seems therefore, that based on these results both the method of a longer hospitalisation period of 4 days without issuing guidelines to the patient, or a shorter hospitalisation period of 2 to 3 days, while recommending separate sleeping and limiting close contact to other people for 7 days, are equally sufficient in limiting the radiation burden to the 1 mSv limit. However, a longer hospital stay of the patient will increase the total cost of the treatment and limit the availability of the isolation room for patients treated with $^{131}$I.

For hyperthyroidism patients, in the present study, 25% of the relatives of ambulatory treated patients and 35% of the relatives of hospitalised patients exceeded the EURATOM-29 (1996) limit. Concerning the different sets of guidelines, our results show that a period of sleeping separately and restricting close contact for 7 days is not sufficient. Implementation of a longer period of guidelines reduces both the median dose received by the family members and the number of people exceeding the EURATOM-29 (1996) limit.

In the present study, as well as in other studies (O’Doherty et al., 1993; Barrington et al., 1997; Mathieu et al., 1996; Mathieu et al., 1997), the children of hyperthyroid patients received a significantly lower dose than the patient’s partners did. It should be noted that only 5 out of 26 of the children included in the study exceeded the EURATOM-29 (1996) limit.
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This is probably partly due to the mean age of the children in our study: 18 years (range 3 to 26 years) since all in-living children of the patient were included, even when their age exceeded the paediatric limit of 16 years and also because the parents were advised to let children under 7 years of age stay at another location for about 5 days.

We have also studied the opposite relationship: dose received by the parents for $^{131}\text{I}$-MIBG therapy of the child. The results were quite different from $^{131}\text{I}$ therapy. The doses were much higher than for $^{131}\text{I}$ therapy, because children are not self-sufficient and need to be helped by the parents. The doses to the relatives were usually higher when the administered or retained activity was higher, when the child was younger and when parents were given less information about the guidelines to apply. It was further observed that the dose for the patient’s mother (mean 595 µSv, range: 72-2272) was usually higher than for the father (mean: 262 µSv, range: 44-814).

Recently the question has been raised whether or not family members should be considered as “members of the public” or rather as “people knowingly and willingly helping” in the care of their relatives. For the latter category, maybe less stringent dose limits could be applied. Since long hospital stays would increase the cost for radionuclide therapies considerably and longer periods of applying guidelines would isolate the patient even further, we adhere to the judgement of the Belgian High Counsel of Medicine, to consider relatives of patients treated with radionuclides not as member of the public, but instruct them with useful guidelines to reduce their dose within the context of ALARA.

As far as the dose to the nurses in the isolation ward is concerned, their mean effective dose amounts to 240 µSv a year (SD: 70 µSv). (Kolindou et al., 2002). When considering that these nurses took care of 168 patients during 631 days and that these patients were treated with various kinds of radionuclide therapies (65 with $^{131}\text{I}$ for thyroid diseases, 64 with $^{131}\text{I}$-lipiodol for HCC, and 39 with $^{131}\text{I}$-MIBG for neuroblastoma), these results show that radionuclide therapy by means of $^{131}\text{I}$ is safe for both occupationally exposed personnel as well as members of the public. For comparison, the nurses taking care of the 14000 diagnostic procedures, receive a mean yearly dose of 2.56 mSv a year (SD: 1.46) (Kolindou et al., 2002). This value is ten times higher than the dose received by the nurses in the isolation ward.

The problem of $^{131}\text{I}$ contamination to relatives of patients treated with $^{131}\text{I}$ has not been taken into account here. Recently however, the contamination problem has been addressed by several authors (Lassmann et al., 1998). The mean dose to the thyroid for relatives from the

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Incorporation of $^{131}$I was measured to be 0.2 mSv, with a maximum of 2 mSv for children and 0.4 mSv for adults. This corresponds to an effective dose of 0.01 mSv. As this dose is small compared to the dose received by external radiation, it does not necessitate a longer hospitalisation for the patients.

For patients suffering from thyroid carcinoma, the results of this multicentre study suggest to implement hospitalisation of the patient for 2 or 3 days and an additional 7 days of sleeping separately and avoiding close contact to other people as principal guidelines. For hyperthyroidism patients, up to 21 days of sleeping separately could be necessary in order to strictly abide by the EURATOM-29 (1996) limit of 1 mSv/y Therefore, the authors propose the implication of a non-rigid dose constraint for people who “knowingly and willingly” help patients treated with $^{131}$I, while still following the ALARA principle. A period of sleeping separately and limiting close contact of 14 days is chosen as a compromise, between 7 days which is usually too short and 21 days which may be unnecessary long, considering the social isolation of the patient and the radiation protection of the relatives. Advising children under the age of 7 to spend 5 days at family or friends leads to a significant dose reduction.

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5.9. General conclusions.

Several important conclusions regarding radionuclide therapy using $^{131}$I-labeled radiopharmaceuticals can be drawn from the present work:

For patients treated with radionuclide therapies, both the biological dosimetry results as the physical dosimetry results point to relatively high absorbed organ doses and high effective doses. Since these therapies are often repeated and since some therapies can be curative, the need for individual dosimetry in these patient groups is obvious.

For patients treated with $^{131}$I-MIBG it is feasible to calculate the dose to the patient after $^{131}$I-MIBG therapy from a single set of $^{123}$I-MIBG pre-therapeutic scans taking into account a factor of 1.20.

For $^{131}$I-MIBG patients there is a good correlation ($r=0.87$) between the total body dose obtained with biological and physical dosimetry methods. However, due to the difference in between the acute in vitro irradiation of the blood samples and the long term in vivo irradiation allowing more time for repair of genetic damage, it is better to use only the linear component of the in vitro dose response.

For patients treated with $^{131}$I-lipiodol, Monte Carlo simulation by MCNP, taking into account the patient's specific anatomy is preferable to MIRDOSE calculations especially to assess the absorbed dose to the tumour.

For patients treated with $^{131}$I for hyperthyroidism and thyroid carcinoma, the lack of evidence for development of secondary neoplasms after $^{131}$I-therapy may be explained by the existence of an in vivo adaptive response. Therefore, at least some consideration should be given to the importance of biological defense mechanisms in risk assessments after low doses of ionising radiation.

The results of cytogenetic dosimetry of cancer patients, based on the in vitro micronucleus assay, have to be treated with caution. For $^{131}$I-MIBG patients biological dosimetry is feasible, provided it does not closely follow chemotherapy so the lymphocyte counts are restored to normal values and the blood sample after therapy is taken before blood transfusions are given to the patient. For $^{131}$I-lipiodol patients however, due to the existing hypersplenism, the lymphocytes no longer show the normal in vivo behaviour and may therefore lead to erroneous results in biological dosimetry.
In order to restrict the dose to relatives of patient treated with $^{131}$I to acceptable levels, we propose to combine restrictive guidelines (especially separate sleeping arrangements), for a period of 14 days for hyperthyroidism patients and of 7 days for thyroid carcinoma patients, with a short hospitalisation stay of 2 to 3 days. In this way therapies can be kept cost effective without socially isolating the patient.
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References to chapter 5.


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Summary.

Introduction.
In Nuclear Medicine, for radionuclide therapy, high activities (several GBq) of $^{131}$I-labelled radiopharmaceuticals are administered to the patient in order to have a significant therapeutic effect. Although the injected radiopharmaceuticals mainly target the tissue under treatment, inevitably the rest of the body is also irradiated to some extent. Since radionuclide therapies are often repeated, can be considered as curative in the treatment of some tumours and is also applied for treatment of benign diseases like hyperthyroidism, it is important to determine the radiation dose to the patient as measure of the mutagenic effect of the therapies and to determine the risk for development of fatal cancers.

A second problem caused by the radiopharmaceutical inside the patient, is the radiation hazard they pose for their relatives. EURATOM-29 (1996) has recommended reducing the limit for members of the public for exposure to ionising radiation to 1 mSv/y. It is therefore necessary to determine what safety measures have to be taken to ensure that the dose to the relatives does not exceed this dose limit.

In this work the patient dose and the dose to the relatives has been determined for different radionuclide therapies using $^{131}$I-labeled radiopharmaceuticals: $^{131}$I for thyroid diseases, $^{131}$I-MIBG for neuroendocrine tumours and $^{131}$I-lipiodol for treatment of HCC. Both physical and biological dosimetry methods have been used.

Aim of the study.
In this work, an answer to the following eight questions was sought:

1. Can the whole body dose for the patient from radionuclide therapy be predicted before administration of the therapeutic activity?
2. What are the differences for the absorbed dose to the organs and the effective dose to the patient between calculations by means of the Monte Carlo code MCNP® and the MIRDOSE® program?
3. How do the results of a biological dosimetry method such as the in vitro micronucleus assay compare to a physical dosimetry method based on bi-planar scans?
4. What is the effect of multiple radionuclide therapies on the micronucleus yield?
5. What is the residual damage after radionuclide therapy one year after treatment?
6. Can $^{131}$I treatment be considered as an in vivo conditioning dose leading to an in vivo adaptive response?
7. Are there specific problems for biodosimetry of cancer patients?
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8. What is the radiation burden to relatives of patients treated with $^{131}$I for thyroid diseases when implementing different sets of guidelines?

**Materials and methods.**

Physical dosimetry methods in nuclear medicine make use of the MIRD (Medical Internal Radiation Dosimetry) formalism:

$$D_T = \sum_s \tilde{A}_s \cdot S_{T\rightarrow S}$$

Where: $D_T$ = Absorbed dose to target organ T

$\tilde{A}_s$ = Cumulated activity in the considered source organ S

$S$ = The organ specific S factor:

The cumulated activity values are determined by means of a set of biplanar scans (including a syringe containing a known activity of $^{131}$I) taken at various intervals after administration of the radiopharmaceutical. ROI’s were drawn over the relevant structures. Attenuation correction factors were calculated based on phantom experiments. The Cumulated activity was determined by time-integrating the activity values in each ROI to infinity.

The absorbed dose to the organs and the effective dose to the patient were calculated with the MIRDOS-3® standard software program, providing standard S factors for phantoms, sex and age matched to the patient. For HCC patients treated with $^{131}$I-lipiodol, liver and tumour volume and position, determined by CT or MRI, were introduced in a standard Bodybuilder® phantom. Patient specific S factors were then calculated using the Monte Carlo simulation program MCNP-4B®.

For $^{131}$I-MIBG patients, a set of pre-therapeutic $^{123}$I-MIBG scans was taken only once before administration of the first $^{131}$I-MIBG therapy. The total body dose predicted by the $^{123}$I-MIBG scans was compared to a bi-exponential fit through the combination of the pre-therapeutic $^{123}$I-MIBG and the post therapeutic $^{131}$I-MIBG data.

The total body dose to the patient was also determined by a biological dosimetry method: the *in vitro* micronucleus assay. For each patient, a first blood sample was taken before therapy and a second one 7 days later. For patients treated with $^{131}$I and $^{131}$I-MIBG, the first blood sample was irradiated *in vitro* with $^{60}$Co $\gamma$-rays to determine the individual dose response curve. For some $^{131}$I patients, also the second blood sample was irradiated *in vitro*, and the *in vitro* increase in micronuclei before and after therapy was compared. In this set-up, an adaptive response is represented by a significant decrease of the *in vitro* induced micronucleus yield after therapy as compared to before therapy.

From the increase in micronucleus yield between the first and the second blood sample, the equivalent total body dose (ETBD) was calculated using either the individual dose response or the dose response of a control population as determined by Thierens et al (1999). The ETBD was compared to the total body dose calculated by means of MIRDOS for $^{131}$I-MIBG.
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and $^{131}$I-lipiodol patients. For $^{131}$I-lipiodol patients the ETBD was also compared to MCNP results.

In order to study the residual damage after $^{131}$I therapy for thyroid diseases one year after administration of the activity, the incidence of translocations (stable chromosome aberrations) was scored by tricolour fluorescence in-situ hybridisation (FISH) for chromosomes 2, 4 and 8. From the genomic translocation frequencies, derived using Lucas formula (1999), whole body doses were calculated based on the in vitro dose response.

In order to determine the real-life radiation burden to relatives, a multicenter study was set up. Wearing a TLD dosimeter on the wrist for 7 days monitored a total of 94 relatives of 65 patients, treated with 131I for thyroid diseases. 61 relatives agreed to wear another TLD for an additional 7 days. The 8 participating centres were divided in 3 groups according to the period of time they advised their patients to sleep separately. Group I, II and III respectively advised their patients to sleep separately for 0, 7 to 10 and 14 to 21 days. The median dose to infinity received by the relatives for the three different sets of guidelines was calculated and compared to the EURATOM-26 dose limit.

Results and discussion.

1. There has been a lot of discussion in the literature as to whether or not the kinetics of a tracer amount of $^{123}$I-MIBG and a therapeutic amount of $^{131}$I-MIBG are the same. However, we found a significant correlation between pre-therapy total body dose and the total body dose based on a bi-exponential fit through a combination of the data ($R = 0.85$) when all following therapies of the patients are considered (correction factor = 1.20). Our results show that it is acceptable to benefit from the better count statistics and the better image resolution of $^{123}$I to calculate the total body dose pre-therapy, taking into account a factor of 1.20.

2. For $^{131}$I-lipiodol patients, the MIRDose results for the mean absorbed dose to the tumour (mean 144 Gy, SD: 68) are systematically higher than the MCNP values (mean 129.5 Gy, SD: 58.2), which are more reliable. The difference is due to the linear interpolation that is necessary between the tabulated discrete sphere sizes (and corresponding S-factors) tabulated in the “nodule module” of MIRDose. The difference is particularly large (mean 15%) for the smaller tumours (< 3 cm).

For all other organs and for the calculation of the effective dose, a good correlation ($R = 0.93$) was obtained between MCNP and MIRDose results.

3. After exclusion of patients having lymphocyte division problems due to chemotherapy and/or lymphocyte dilution caused by whole blood transfusions, a significant correlation was found between the ETBD and the MIRD dose ($r = 0.87$) for patients treated with $^{131}$I-MIBG. On the average, the obtained ETBD values were 70% of the calculated MIRD values. This can be attributed to the differences in dose rate between the acute in vitro irradiation for the
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determination of the dose response and the in vivo irradiation at low dose rate, which allows a longer time for repair of DNA damage.

4. For all $^{131}$I-MIBG and $^{131}$I-lipiodol patients receiving multiple therapies, an initial large increase in micronucleus yield after administration of the radionuclide therapy had at least partly recovered by the time of the subsequent therapy. The analysis of these data point to a shortened mean half-life of the lymphocytes ($T_{1/2} = 3.9$ months). These results are similar to the results calculated by Ramalho et al. (1995) concluding that the disappearance of micronuclei is dose dependent and equals 3.7 months in people receiving more than 1 Gy.

5. The frequency of translocations for patients treated with $^{131}$I for thyroid diseases was 5 times higher than in an age-matched control population. Micronucleus data on these patients result in estimated doses ranging from 0.16 Gy to 0.55 Gy with an average of 0.34 Gy, 1 week after administration of the $^{131}$I. The dose estimates resulting from chromosome painting are higher (mean 0.79 Gy ± 0.22 Gy). The difference in dose can partly be explained by the difference in the dose received after 1 week and 1 year. The observation of a high number of translocations as well as an overrepresentation of translocation involving chromosome 4 in present study suggests the need for medical follow-up of these patients.

6. For 8 out of 20 patients treated with $^{131}$I, the in vitro increase in micronucleus yield was higher before than after therapy. These results are the first demonstration that exposure to low doses of ionising radiation during medical treatment (conditioning dose) makes human peripheral blood lymphocytes less susceptible to cytogenetic damage for subsequent in vitro irradiation at higher doses (challenge dose). Although the results did not reach statistical significance, it seems that the adaptive response in present study is seen especially in radiosensitive individuals. Today, although we know that radiation can be harmful, a fact based scientific approach to evaluate the detrimental effects of low levels of radiation should be adopted. While making such a risk assessment, at least some consideration should be given to the importance of biological defense mechanisms that could be stimulated by low levels of radiation. However, the results presented here do not mean that exposure to low levels of ionizing radiation by itself is beneficial, since higher levels of chromosome aberrations are found in exposed populations compared to non-exposed populations.

7. The success of the micronucleus assay in genetic toxicology depends mainly on normal peripheral lymphocyte counts and their intact cellular division mechanisms. As can be seen from the rather low success rate in our study of patients treated with $^{131}$I-MIBG or $^{131}$I-lipiodol, this may not always be the case for a cancer patient population.

For $^{131}$I-MIBG patients, biological dosimetry based on the micronucleus assay is feasible, provided it does not follow too closely after chemotherapy so the lymphocyte count is restored to normal values and the blood sample after therapy is taken before blood transfusions are given to the patient. A significant correlation (shown in figure 2) was found.
between the ETBD and the MIRD dose \((r = 0.87)\). The use of *in vitro* dose response relationship of the considered patients instead of a standard curve had no major impact on the results.

For the patients treated with \(^{131}\)I-lipiodol, the low number of lymphocytes present in their peripheral blood and a reduction of their proliferation capacity caused stimulation problems in the blood samples after treatment. Here, the problem is a consequence of the hypersplenism occurring in many of these patients. No correlation was found between the ETBD values and the MIRD doses. The lymphocytes in HCC patients clearly no longer show the normal *in vivo* behaviour of lymphocytes and are therefore not suitable for biological dosimetry purposes.

8. The real-life radiation burden for relatives of patients treated with \(^{131}\)I for thyroid diseases was determined. For thyroid carcinoma patients both the method of a longer hospitalisation period of 4 days without issuing guidelines to the patient, or a shorter hospitalisation period of 2 to 3 days, while recommending separate sleeping and limiting close contact to other people for 7 days, are equally sufficient in limiting the radiation burden to the 1 mSv limit. However, a longer hospital stay of the patient will increase the total cost of the treatment and limit the availability of the isolation room for patients treated with \(^{131}\)I. For hyperthyroid patients, 25 % of the relatives of ambulatory treated patients and 35 % of the relatives of hospitalised patients exceeded the EURATOM-29 (1996) limit. However, the limit was never violated when 21 days of guidelines were issued. Therefore, the authors propose the implication of a non-rigid dose constraint for people who “knowingly and willingly” help patients treated with \(^{131}\)I, while still following the ALARA principle. A period of sleeping separately and limiting close contact of 14 days is chosen as a compromise, between 7 days which is usually too short and 21 days which seems unnecessary long, considering the social isolation of the patient.

References to the summary.


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7. Samenvatting.
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**Samenvatting.**

**Inleiding.**
In de nucleaire geneeskunde worden voor radionuclidentherapie hoge activiteiten (verschillende GBq) van $^{131}$I gemerkte radiofarmaca aan de patiënt toegediend om een therapeutisch effect te bekomen. Hoewel deze radiofarmaca voornamelijk in het doelwit orgaan terechtkomen, wordt onvermijdelijk ook de rest van het lichaam in zekere mate bestraald. Omdat radionuclidentherapieën vaak herhaald worden, als curatief beschouwd kunnen worden in de behandeling van sommige tumoren en ook ingezet worden voor de behandeling van geneeslijke aandoeningen (hyperthyreoïdie), is het belangrijk de dosis voor de patiënt te berekenen als maat voor het mutageen effect van de behandeling en voor de berekening van het risico op ontwikkeling van fatale secundaire maligniteiten.

Een tweede probleem dat ontstaat door de toegediende radiofarmaca, is het stralingsrisico dat de patiënten vormen voor hun familieleden. Volgens richtlijnen van EURATOM (EURATOM-26, 1996) dient de dosis voor personen van het publiek beneden 1 mSv per jaar te blijven. Maatregelen die de dosis voor de familieleden hiertoe verlagen moeten dus uitgewerkt worden.

In dit werk worden de dosis voor de patiënt en zijn familieleden bepaald voor verschillende radionuclidentherapieën die gebruik maken van $^{131}$I-gemerkte radiofarmaca: $^{131}$I voor de behandeling van schildklieraffiniteiten, $^{131}$I-MIBG voor de behandeling van neuronendocriene tumoren en $^{131}$I-lipiodol voor de behandeling van leverkanker. Er wordt gebruik gemaakt van zowel fysische als biologische dosimetrische technieken.

**Doel van de studie:**
In dit werk werd een antwoord gezocht op de volgende 8 vragen:

1. Kan de patiëntdosis bij radionuclidentherapie voorspeld worden?
2. Wat zijn de verschillen voor de geabsorbeerde dosis in de organen en de effectieve dosis tussen dosimetrische berekeningen met MCNP® en MIRDSE®?
3. Wat is de correlatie tussen biologische dosimetre met de in vitro micronucleus test en fysische dosimetre gebaseerd op bi-planaire scans?
4. Wat is het effect van herhaaldelijke therapieën op het aantal micronuclei?
5. In hoeverre zijn de stralingseffecten van $^{131}$I therapie nog aanwezig 1 jaar na de toediening?
6. Kan $^{131}$I therapie beschouwd worden als een in vivo conditioneringsdosis die aanleiding geeft tot een in vivo adaptieve respons?
7. Zijn er specifieke problemen bij biologische dosimetre van kanker patiënten?
8. Wat is de stralingsdosis opgelopen door familieleden van schildklierpatiënten behandeld met $^{131}$I wanneer verschillende sets van leefregels gehanteerd worden?

**Materiaal en methoden.**

Fysische dosimetrie methoden binnen de nucleaire geneeskunde maken gebruik van het MIRD (medical internal radiation dosimetry) formalisme:

$$D_T = \sum_s \tilde{A}_s \cdot S_{(T_{\text{e}}-S)}$$

Met: $D_T =$ Geabsorbeerde dosis in het doelwit orgaan: $T$

$\tilde{A}_s =$ Gecumuleerde activiteit in het bronorgaan: $S$

$S_{(T_{\text{e}}-S)} =$ De orgaan specifieke S factor:

De gecumuleerde activiteit wordt bepaald aan de hand van een set bi-planaire scintigrafische scans, genomen op verschillende tijdstippen na toediening van het radiofarmacon. ROI’s (regions of interest) worden getrokken rond de relevante orgaan structuren. Attenuatie correctie factors worden bepaald uit fantoom metingen. De gecumuleerde activiteit wordt berekend door de activiteit in de ROI’s te integreren.

In dit werk wordt de geabsorbeerde dosis in elk orgaan en de effectieve dosis voor de patiënt berekend via het programma MIRDOSE-3, waarbij gebruik wordt gemaakt van standaard S factoren voor fantomen die qua geslacht en leeftijd overeenkomen met de patiënt. Voor de $^{131}$I-lipiodol patiënten werden de positie en het volume van de tumor en de lever, bepaald via CT of MRI, in een standaard “Bodybuilder” fantoom ingebracht. Via Monte Carlo simulaties met het MCNP programma konden dan patiënt specifieke S factoren berekend worden.

Voor $^{131}$I-MIBG patiënten werd één set van $^{123}$I-MIBG scans genomen voor een reeks $^{131}$I-MIBG therapieën. De dosis van de therapie, berekend uit $^{123}$I-MIBG scans werd vergeleken met de dosis berekend uit een bi-exponentiële fit door de combinatie van $^{123}$I-MIBG en $^{131}$I-MIBG data.

De dosis voor de patiënt werd ook berekend via biologische dosimetrie met de *in vitro* micronucleus test. Bij elke patiënt werd een bloedstaal afgenomen voor therapie en een tweede 7 dagen na therapie. Voor $^{131}$I en $^{131}$I-MIBG patiënten werd het eerste bloedstaal *in vitro* bestraald met $^{60}$Co om de individuele dosis repons relatie te bepalen. Voor sommige $^{131}$I patiënten werd dit ook gedaan bij het tweede bloedstaal en de toename in micronuclei na *in vitro* bestraling voor en na therapie werd vergeleken. Een adaptieve respons geeft in het staal na therapie een significante verlaging in de vorming van micronuclei in vergelijking met voor therapie.

De toename in micronuclei na radionuclide-therapie in vergelijking tot voor therapie, geeft de equivalent lichaamsdosis (ETBD) bepaald via de individuele dosis respons relatie of de dosis respons relatie van een controle populatie (Thierens et al., 1999). De ETBD werd vergeleken met de dosis berekend door MIRDOSE voor de $^{131}$I-MIBG en $^{131}$I-lipiodol.
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patiënten. Voor $^{131}$I-lipiodol patiënten werd de ETBD ook vergeleken met de dosis berekend via MCNP.

Om de stralingseffecten nog overblijvend 1 jaar na de radionuclidetherapie te bepalen, werd de incidentie van stabiele chromosoom aberraties (translocaties) gemeten door driekleuren fluorescentie in-situ hybridisatie (FISH) op chromosoom 2, 4 en 8. Uit de frequenties van de translocaties die op deze manier verkregen werden kon de lichaamsdosis bepaald worden via de formule van Lucas (1999) na het bepalen van de in vitro dose respons relatie.

Om de reële stralingbelasting van familieleden van $^{131}$I patiënten te bepalen werd een multicenter studie opgezet. De 8 deelnemende centra werden opgesplitst in 3 groepen afhankelijk van de tijd die zij adviseerden aan de familieleden om apart van de patiënt te slapen. Groep I, II en III adviseerden respectievelijk 2, 7 tot 10 en 14 tot 21 dagen. In totaal werd de stralingbelasting van 94 familieleden van 65 patiënten gemeten via thermoluminescente dosimeters (TLD’s) die gedurende 7 dagen aan de pols gedragen werden. 61 familieleden stemden toe om een tweede TLD te dragen voor de volgende 7 dagen. De geïntegreerde dosis voor de familieleden in de drie groepen werd vergeleken.

Resultaten en discussie.

1. In de literatuur bestaat onenigheid over het al dan niet overeenkomen van de kinetiek van een $^{123}$I-MIBG speuractiviteit en een $^{131}$I-MIBG therapeutische activiteit. In ons werk werd echter een goede correlatie ($r = 0.85$) gevonden tussen de dosis voorspeld op basis van de pretherapeutische $^{123}$I-MIBG scans en de dosis berekend via een bi-exponentiële fit door de combinatie van $^{123}$I-MIBG en $^{131}$I-MIBG data, zelfs wanneer alle volgende therapieën in beschouwing werden genomen (correctie factor $= 1.20$). Onze resultaten tonen aan dat het aanvaardbaar is gebruik te maken van de betere beeldresolutie en telstatistiek van $^{123}$I om de dosis bij $^{131}$I-MIBG therapie te voorspellen, wanneer met een factor van 1.20 wordt rekening gehouden.

2. Bij $^{131}$I-lipiodol patiënten werd de geabsorbeerde dosis in de tumor systematisch overschat door MIRDOSE (gemiddeld 144 Gy, SD: 68) in vergelijking met het meer betrouwbare MCNP programma (gemiddeld 130 Gy, SD: 58). Het verschil is te wijten aan de lineaire interpolatie die in MIRDOSE nodig is tussen de getabuleerde diameters (en corresponderende S-factoren) in de “nodule module” voor de tumorbron. Het verschil is vooral belangrijk (15%) voor kleinere tumoren ($< 3$ cm). Voor de geabsorbeerde dosis van andere organen en voor de effectieve dosis werd een goede correlatie ($r = 0.93$) bekomen tussen MCNP en MIRDOSE.

3. Een goede correlatie werd vastgesteld ($r = 0.87$) tussen de ETBD berekend met de micronucleus testen en de MIRD dosis van $^{131}$I-MIBG patiënten, na uitsluiting van patiënten waarbij problemen met de lymfocytaire celdeling werden vastgesteld, veroorzaakt door
vroegere chemotherapie en/of waarbij de bestraalde lymfocyten gemengd werden met onbestraalde door toediening van bloedtransfusie. Gemiddeld was de ETBD slechts 70% van de MIRD dosis. Dit verschil is te wijten aan de verschillen in dosistempo tussen de acute in vitro bestraling voor het bepalen van de dosis respons relatie en de in vivo bestraling met laag dosistempo, die meer tijd laat voor DNA herstel.

4. Voor al de $^{131}$I-MIBG en $^{131}$I-lipiodol patiënten die herhaaldelijke therapieën kregen toegediend, was de initiële stijging in micronuclei na therapie gedeeltelijk genormaliseerd bij aanvang van de volgende therapie. Deze data wijzen op een verkort halfleven van de lymfocyten (3.9 maanden). Dit is in overeenstemming met de resultaten van Ramalho et al. (1995): de snelheid waarmee de micronuclei verdwijnen is dosis afhankelijk en voor dosissen groter dan 1 Gy gelijk aan 3.7 maanden.

5. De translocatie frequentie bij $^{131}$I patiënten was 5 keer hoger dan in een controle populatie. Micronucleus data geven een dosis van gemiddeld 0.34 Gy, 1 week na toediening van het $^{131}$I. De dosis schatting via FISH is hoger: $0.79 \pm 0.22$ Gy. Het verschil in dosis kan gedeeltelijk verklaard worden door het verschil in dosis tussen 1 week en 1 jaar. De hoge translocatie frequentie en de overmatig voorkomen van chromosoom 4 translocaties nopen tot zorgvuldige medische opvolging van deze patiënten.

6. Bij 8 van de 20 onderzochte patiënten die behandeld werden met $^{131}$I voor schildklieraandoeningen, werd bij in vitro bestraling van de bloedstalen na therapie een beduidend lagere toename in micronuclei gevonden dan voor therapie. Deze resultaten tonen aan dat blootstelling aan een lage stralingsdosis voor een medische behandeling (conditioning dose) humane perifere lymfocyten minder gevoelig maakt aan de cyogenetische schade veroorzaakt door daaropvolgende in vitro bestraling met een hoge dosis (challenge dose). Hoewel de resultaten niet statistisch significant waren, lijkt het erop dat de adaptieve respons vooral bij stralingsgevoelige individuen kon worden vastgesteld. Ons inziens dient men rekening te houden met dit fenomeen bij de evaluatie van de risico’s verbonden aan blootstelling aan straling.

7. Het welslagen van de micronucleus test in genetische toxicologie hangt grotendeels af van het intact blijven van de celdeelingsmechanismen. Zoals blijkt uit de nogal beperkte slaagkans ervan bij onze patiënten, is dit niet altijd het geval voor kanker patiënten.

Voor $^{131}$I-MIBG patiënten, is biologische dosimetry via de micronucleus test mogelijk, wanneer de radionuclidetherapie niet direct volgt op de chemotherapie. Bovendien moet het bloedstaal na therapie genomen worden voordat men bloedtransfusies toedient. Wij vonden een significante correlatie tussen de ETBD en de MIRD dosis ($r = 0.87$). Het gebruik van een individueel bepaalde dosis respons relatie in plaats van de standaard dosis respons relatie voor gezonde vrijwilligers had geen invloed op deze resultaten.
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Voor patiënten behandeld met $^{131}$I-lipiodol werden problemen met de stimulatie tot celdeling vastgesteld in bloedstalen genomen na therapie. Deze worden veroorzaakt door het lage aantal lymfocyten dat deze patiënten nog bezitten en een vermindering van hun proliferatie capaciteit. Deze problemen zijn het gevolg van het hypersplenisme dat bij een aantal van deze patiënten voorkomt. Er werd geen correlatie gevonden tussen de ETBD en de MIRD dosis. Deze lymfocyten vertonen duidelijk niet langer het normale in vivo gedrag en zijn daarom niet geschikt voor biologische dosimetrie met de in vitro micronucleus test.

8. Voor schildklier carcinoom patiënten blijken de methoden van een lange hospitalisatieduur (4d) en een korte hospitalisatieduur (2d), waarbij gedurende 1 week leefregels aan de patiënten worden opgelegd, beide even effectief in het reduceren van de dosis voor de familieleden tot 1 mSv. Een langere hospitalisatieduur laat de kostprijs voor de therapie echter gevoelig stijgen en beperkt de beschikbaarheid van isolatiekamers.

Voor familieleden van hyperthyreoidie patiënten bleek de dosis voor 25% van de familieleden van ambulante patiënten en 35% van de familieleden van gehospitaliseerde patiënten hoger dan de dosislimiet van 1 mSv, behalve wanneer de gedurende 21 dagen leefregels werden opgelegd. Wij stellen dan ook voor om voor familieleden van $^{131}$I patiënten, een soepelere dosisbeperking op te leggen terwijl het ALARA principe toch nog gevolgd wordt. Een periode van leefregels gedurende 14 dagen wordt voorgesteld als compromis tussen 7 dagen, die duidelijk te kort zijn en 21 dagen die de patiënt sociaal isoleren.

Literatuurlijst.


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Myriam Monsieurs

8. Addenda.
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Curriculum Vitae of the applicant.

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*Business:*  
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Histology and Medical Physics  
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Dorpsstraat 21  
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Belgium  

Date of birth: 5th February 1971, Tongeren, (Belgium).  
Nationality: Belgian

**Diplomas:**

Limburg University Center (LUC).

1992:  

University of Gent (RUG).

1994:

Thesis: laboratory for Microbiology, University of Gent.  
Promotor: Prof. K. Kersters.  
Title: Taxonomische studie van enkele klinische flavobacteria en “Bordetella hinzii”.  
(Taxonomical study of some clinical flavobacteria and “Bordetella hinzii”).

1995:

*Highschool teacher degree, Chemistry, September 1995, distinction.

1996:

*Biomedical and Clinical Engineering, Option Radiation Physics, July 1996, great distinction.  
Thesis: Division of Nuclear medicine, University Hospital of Gent.  
Promotor: Prof. H. Thierens.  
Title: Aanbevelingen tot regelgeving i.v.m. $^{131}$I therapie voor schildklieraandoeningen op basis van praktijkgegevens uit het UZ Gent.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

(Recommendations for regulation concerning $^{131}$I therapy for thyroid disease based on practical data from the UH Gent).

2003:
* January 1997 – May 2003: PhD. in Medical Sciences:
  Thesis: Department for Anatomy, Embryology, Histology and Medical Physics..
  Promotor: Prof. H. Thierens. Co-promotor: Prof. R.A. Dierckx, MD
  Title: Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

Jobs:

2000-2001:
* from 1st February 2000 untill 30th September 2001: Chemist at the Division of Nuclear Medicine, University Hospital of Ghent, Ghent, Belgium.

From 2001:
* Since 1st October 2001: Health Physicist at the Department of Health Physics at the University of Ghent, Ghent, Belgium.

General Information.

Languages:
Dutch: mother tongue
English, French, German: fluently
Spanish, Turkish: notions

Programming:
Fortran 77

Software:
Microsoft Windows®, Mackintosh®, Hermes®, MIRDOSE 3®, Matlab®, SPSS®

Hobby’s:
Scubadiving (2* CMAS, member of “Sepia” club, Ghent, Belgium).
Dog training (member of “Kwispel” club, Beervelde, Belgium)
Travelling, Swimming, Hiking, Off road, Reading, Cinema...
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

**Publications.**

**International Publications.**

1995:

1997:


1999:

2000:


2001:


2002:
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.


**National Publications.**

**1999:**


**Book chapters.**

**1999:**

Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

**International Communications.**

**1994:**


**1996:**


**1998:**


Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.


1999:


2000:


Curriculum vitae of the applicant. 8. 7
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.


2001:


2002:


Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.


2003:


**National Communications.**

1998:


2000:


2001:


Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.


**Theses.**

**1994:**

1. “Taxonomische studie van enkele klinische flavobacteria en “Bordetella hinzii”.
Scriptie voorgelegd tot het behalen van de graad van licentiaat in de Biotechnologie”.
Promotor: K. Kersters.

**1996:**

2. “Aanbevelingen tot regelgeving i.v.m. 131-I therapie voor schildklieraandoeningen op basis van praktijkgegevens uit het UZ Gent.
Scriptie ingediend tot het behalen van de graad van gediplomeerde in de gespecialiseerde studie van de biomedische en klinische ingenieurstechnieken, optie stralingsfysica”.
Promotor: H. Thierens.

**Peer reviewed grants.**

**1996:**

1. **Adac Advanced Clinical Research Grant.**
**Company:** Adac.
**Subject:** “Optimisation of $^{131}$I-therapy to patient and environment” (Optimalisatie van de $^{131}$I therapie naar patiënt en omgeving). Multicenter study (1/2/1997-1/2/1998).

**1998:**

2. **Bijzonder Onderzoeksfonds (BOF).**
**University:** Ghent University.

**Awards.**

**1997:**

1. **Mallinckrodt Benelux Award 1997.**
**Company:** Tyco-Mallickrodt.
**Subject:** Project: “Cytogenetic studies of patients undergoing $^{131}$I therapy for malignant and benign thyroid disease and $^{131}$I-MIBG therapy for neuroblastoma”.
Patient dosimetry and radiation protection issues for radionuclide therapy using $^{131}$I.

2000:
2. **Alavi-Mandell prize 2000.**
   - **Journal:** The Journal of Nuclear Medicine.
   - **Subject:** Article: “Adaptive response in patients treated with $^{131}$I”. JNM 2000, 41; 17-22.

2001:
3. **Mutagenesis Poster Award 2001.**
   - **Journal:** Mutagenesis.

**Memberships.**

**Commissions.**

International:
- EANM: Taskgroup on Dosimetry (vice chairman).
- SIOP taskgroup on Neuroblastoma.

National:
- BGNG: (Belgisch Genootschap voor Nucleaire Geneeskunde): Taskgroup Radiation Protection.

**Associations.**

International:
- EANM (European Association of Nuclear Medicine).

National:
- BGNG (Belgisch Genootschap voor Nucleaire Geneeskunde).
- BVZF (Belgische Vereniging voor Ziekenhuis Fysici).
- BVS (Belgische Vereniging voor Stralingshygiëne).
- BNS (Belgian Nuclear Society).