FACULTY OF MEDICINE AND HEALTH SCIENCES

Extending the scope of radioiodine therapy with multi-modality therapy, pre-medication and quality of life

Boudewijn Brans

Thesis submitted in fulfilment of the requirements for the degree of doctor in medical sciences

2003

Promotor:
Prof Dr R.A. Dierckx
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All studies of this thesis except chapter 4 were carried out at the department of Nuclear Medicine of the University Hospital Ghent, Belgium.
The study in chapter 4 was performed in collaboration with the University Hospital Utrecht, Netherlands.

Financial support for the publication of this thesis was kindly provided by K.S. Biomedix and Schering S.A.
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ISBN 90-805957-5-6

Vakgroep Radiotherapie en Kerngeneeskunde  
De Pintelaan 185  
B-9000 Gent  
België / Belgium
Ter nagedachtenis aan

Roelof Veldman

(1909-1999)
“We cannot heal the wounds we do not feel”

S.R. Smalley
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In 1942, two groups reported the successful treatment of hyperthyroidism by radioiodine. However, in 1940 Hamilton and colleagues had concluded from contact radioautographs that “the failure of cancerous thyroid tissue to acquire appreciable quantities of radioiodine suggested the impracticality of therapeutic application of this radioelement in malignancies of the thyroid”. Nevertheless, it was a patient by the name of Mr B.B., with an unusual combination of features, and the talents of his physician, Dr Samuel M. Seidlin, chief of Endocrinology at Montefiore Hospital in New York, U.S.A. who prompted the first use of $^{131}$I in oncology. This is their story.

Seidlin was asked to examine Mr B.B., which presented with classical symptoms of hyperthyroidism following a complete thyroidectomy for “malignant adenoma” 20 years before, along with severe back pain caused by a pulsating tumour removed at Th12 and proven to be a metastatic thyroid adenocarcinoma. Because he anticipated functionality of the metastases which had to imply radioiodine uptake and a possible therapeutic effect, he persuaded the cyclotron people to produce a minute amount of $^{131}$I (a mixture of $^{130}$I and $^{131}$I) to use as a tracer dose, costing him $1500 off his research fund, a formidable amount of money in those days.

In March 1943, B.B. received his tracer dose and with a hand-held Geiger counter (long before the Anger gamma-camera was used) the localisation of radioiodine in the body was mapped. The patient asked for “the machine” to be placed on the right parietal part of his head, where he stated there was “a pain which was not a headache!” On this memorable occasion, in which the positive localisation of all known lesions plus two previously unsuspected ones, but no uptake in the neck was revealed, the attending pathologist of the hospital, Dr Marine stated that he had “seen many metastases under the microscope, but this was the first time he heard a metastasis talk!”

After this, therapeutic amounts of radioactive iodine were administered orally between May and October 1943. In April 1944 and March 1945 additional $^1$I was administered to B.B. In 1949, Seidlin and his group reported that “the patient, who six years ago was bedridden and required opiates, was now moving about freely and had no pain. Roentgenologically, no new metastases had appeared, the pulmonary metastases had completely disappeared and the osseous ‘shadows’ had shown neither increase nor decrease in size”. External measurements with the Geiger counter, which initially showed high readings, showed no uptake in the last year (..). In May 1949, an excised skull metastasis was found to be extensive necrotic with no evidence of viable tumour tissue.

Mr B.B. became a celebrity and visitors streamed from all over the world to Montefiori Hospital to see him and his physician. Life magazine wrote in an article devoted on him: “… tumours were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine” One must not forget that in those days metastatic cancer was considered 100% fatal on a very short term. His constantly improving condition made him even believe that a misdiagnosis must have been made, as illustrated in a conversation when Seidlin said: “Is that all the gratitude you show, after all, I cured you from cancer?” on which patient B.B. replied: "Dr Seidlin, you are supposed to be a smart man; if I had cancer five years ago, you know I’d be dead now!”

FOREWORD
In 1952, nine years after the institution of radioiodine therapy, Mr B.B. died, revealing widespread undifferentiated anaplastic type of thyroid tumour. Although Geiger counts detected no uptake of radioiodine (anymore), radioautographs remained positive.

Subsequently, dr Seidlin and his team established the cornerstones of thyroid cancer therapy, i.e. thyroid gland ablation after thyroidectomy (“to eliminate competition for the administered radioiodine”) and also that stimulation of tumour uptake could be accomplished in some cases by thyrotropic hormone (TSH) injection.

The story of Dr Seidlin and Mr B.B. illustrates that, rather than deliberately pursuing a completely new substance, great inventions are sometimes made by using an existing substance to a new direction. We hope that this story may serve as a small source of inspiration to investigators in radionuclide therapy.

INTRODUCTION

The origin of radioiodine therapy

Iodine is derived from the Greek ‘iodes’, meaning ‘violet-coloured’ and refers to its colour when vaporised. Courtois thus discovered its stable form, iodine-127, in 1811, when he used sulphuric acid in an attempt to remove sulphur from seaweed.

In 1896, Henri Antoine Becquerel discovered a material energy emanating from natural uranium, which resembled the year earlier discovered Roentgen- or x-rays, and was named “radioactivité” by his student Marie Curie, née Sklodowska. Together with her husband Pierre Curie, these three pioneers made numerous discoveries of the characteristics of natural occurring radioisotopes, powerful inventions that would change the world and made her famous by achieving an unprecedented two Nobel prizes.¹

Georg de Hevesy demonstrated from 1924 that radionuclides behaved chemically and biologically precisely as their corresponding stable elements did, so that radioisotopes constituted valuable “radioactive indicators” or tracers ², a concept recognising him as the “father of the tracer” and consequently nuclear medicine. This instigated the development of numerous diagnostic procedures using radioisotopes.

The discovery of the cyclotron by Lawrence in 1932 allowed the production of higher quantities of purer radioisotopes, among which ^{131}\text{I}, leading the way for therapeutic applications. Livingood and Seaborg ³ discovered radioactive iodine in 1938. In early days, this was ^{128}\text{I}, a beta- and gamma-emitter with a half life of 25 minutes, ^{130}\text{I} as a beta– and gamma-emitter with a half-life of 12.36 hours, and ^{131}\text{I} with a half-life of 8.02 days. No less than 33 radioactive isotopes of iodine have been described to date. Currently, 3 remain used in medicine, i.e. ^{123}\text{I} for in-vivo, ^{125}\text{I} for in-vitro diagnostic procedures, and ^{131}\text{I} for therapeutic purposes.

In 1938 Hertz, Roberts and Evans demonstrated uptake of radioiodine by the thyroid gland, using about 1/20 of a microcurie ^{128}\text{I}, with a half live of 25 minutes!⁴ This cleared the way for the diagnostic in-vivo as well as in-vitro procedures, which proved fundamental in the understanding of thyroid physiology. The same Evans operated the first medically dedicated cyclotron in 1938 at MIT, U.S.A., which supplied the mixture of the 12-hr half-life ^{130}\text{I} and 8-day half-life ^{131}\text{I}, also described as \*I.⁵ This allowed the therapeutic use of radioiodine a fact that was claimed by two independent groups in 1942 for the clinical indication of hyperthyroidism.⁶,⁷

During the war, all means were redirected towards the production of the atomic bomb and little medical progress through radioisotopes was made. From 1946, pure ^{131}\text{I}, besides other isotopes, would become available by the support of the U.S. Atomic Energy Agency funding, marking the beginning of “atomic medicine”, later renamed “nuclear medicine”, and facilitating its rapid expansion.
Radionuclide therapy applications today

Radionuclide therapy, therapy with radioisotopes or “metabolic radiotherapy” may be defined as a radiation therapy that uses local, loco-regional or general administered open (i.e. unsealed) “radionuclides” or radioisotopes that may be conjugated with a targeting pharmacon to achieve a selective and internal irradiation of a particular target tissue.

The radioisotopes presently used in routine practice all derive their therapeutic effect from the emission of beta radiation. In table 1, the current most often studied radioisotopes for therapeutic applications are listed. The targeting pharmacon that may be used encompass a wide variety of molecules of very diverse nature, such as colloids, monoclonal antibodies, peptides and oligonucleotides. In fact, any substance that can be radiolabeled and accumulates to a sufficient degree in pathological target tissue (tumoural, or non-tumoural such as in hyperthyroidism) rather than in normal, non-targeted tissues may be considered. The whole of radioisotope and pharmacon molecule is commonly called “radiopharmacon”.

The unique feature of radionuclide therapy, as compared to other cancer treatments, is the ability to selectively target tumours in the whole of the body and by a protracted low dose-rate radiation. This makes radionuclide therapy unique and incomparable to the local and high dose-rate of external radiotherapy. Loco-regional application such as intra-arterial $^{131}$I-Lipiodol makes it possible to achieve higher radiation doses, but limits its application to loco-regional disease.

The variable emission energy, weight and charge of the particle makes that every isotope has an optimal tumour diameter in which ideally the whole of emitted energy is absorbed and thus the highest possible radiation dose is achieved. For example, for $^{131}$I this is theoretically 2.6-5.0 mm and for $^{90}$Y 28-42 mm in human tissue. Another physical parameter of paramount importance is the physical half-life of the radioisotope. The radioactive decay and thus radiation is ideally situated entirely in the target tissue and not outside, especially not in sensitive normal tissues. In practice, the power of the pharmacon to selectively concentrate itself in or around a target cell depends on a large number of factors: tumour perfusion, diffusion speed, number and distribution of target binding sites, catabolism of the pharmacon and/or binding site, whole-body biodistribution of the radiopharmacon, etc (collectively giving the effective half-life). The variability of these factors will anyhow result in a heterogeneous distribution of the radiopharmacon compared between patients, between tumours and even within tumours in the same patient (figure 1). This compromises the complete sterilisation of tumours in the whole of the body, in the same way as other substances such as chemotherapy. However, with radionuclide therapy this is to a certain degree compensated by the so-called “cross-fire” effect (figure 1), whereby cells that do not have a direct interaction with the radiopharmacon can still suffer a fatally cytotoxic radiation dose from a nearby-situated radioactive complex within the range of the emitted radiation.
Table 1. Radioisotopes for therapeutic applications

<table>
<thead>
<tr>
<th>Category</th>
<th>Isotope</th>
<th>$T \frac{1}{2}$ (days)</th>
<th>$E$ average (keV)</th>
<th>Maximum range (mm)</th>
<th>Imaging</th>
</tr>
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<tbody>
<tr>
<td>Long range beta-emitters</td>
<td>Y(Yttrium)-90</td>
<td>2.67</td>
<td>940</td>
<td>12,0</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Re(Rhenium)-188</td>
<td>0,71</td>
<td>778</td>
<td>11,0</td>
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<tr>
<td></td>
<td>Ho(Holmium)-166</td>
<td>1,1</td>
<td>667</td>
<td>10,0</td>
<td>Yes</td>
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<tr>
<td>Middle range beta-emitters</td>
<td>I(Iodium)-131</td>
<td>8,02</td>
<td>183</td>
<td>2,0</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Re(Rhenium)-186</td>
<td>3,78</td>
<td>340</td>
<td>5,0</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Sm(Samarium)-153</td>
<td>1,95</td>
<td>269</td>
<td>3,1</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Cu(Cupper)-57</td>
<td>2,6</td>
<td>192</td>
<td>1,8</td>
<td>Yes</td>
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<tr>
<td>Short range beta emitters</td>
<td>Lu(Lutecium)-177</td>
<td>6,71</td>
<td>148</td>
<td>1,5</td>
<td>Yes</td>
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<tr>
<td>Alpha emitters</td>
<td>As(Astatine)-211</td>
<td>0,30</td>
<td>5800</td>
<td>&lt;0,1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Bi(Bismuth)-213</td>
<td>0,04</td>
<td>5870</td>
<td>&lt;0,1</td>
<td>Yes</td>
</tr>
<tr>
<td>Auger emitters</td>
<td>I(Iodium)-125</td>
<td>59,4</td>
<td>&lt;26</td>
<td>&lt;0,02</td>
<td>No</td>
</tr>
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</table>


Figure 1. Illustration of the crossfire effect.
The cell at the lower left has no specific binding but receives two hits. The cell in the middle has three binded radiopharmaceuticals that hit two neighbouring cells too. In this case, the maximum range of the beta particle is about two times the diameter of the tumour cell.
Aim and development of this thesis

$^{131}$I, $^{131}$I-mIBG and $^{131}$I-Lipiodol are, together with bone metastases therapy agents ($^{89}$Sr, $^{186}$Re-HEDP and $^{153}$Sm-EDTMP) and $^{32}$P for haematological malignancies, considered the “established” radionuclide therapies today (see: www.eanm.org). The key reason for these relatively simple molecules to be so successful may be presumed to be that their tumoural percentage of uptake is enough to reach a cytotoxic radiation dose, with a cell kill exceeding the tumour proliferation rate. Other agents such as antibodies or peptides, although they may target more specific tumour properties, have to date been unable to meet their exciting prospects, besides being much more costly.

Faced with more aggressive tumour with higher proliferation rate it may be stated that it is difficult for any radionuclide therapy, or any oncological therapy for that matter, to achieve a meaningful tumour response with an acceptable level of toxicity. On top of this, radioprotection rules limit the activity administered in many instances to below the maximum tolerated dose commonly used in oncology.

It is therefore pivotal for the further development of radionuclide therapy to extend its scope to combination treatments. Such treatments aim to increase tumour response and/or decrease normal organ toxicity:

- Multi-modality therapy with surgery, chemotherapy, radiotherapy
- Stimulators of uptake: cytokines, hormones, vaso-active substances,...
- Radiosensitising agents: cisplatin,...
- Radiobiology manipulation: fractionation, cell cycle kinetics,...
- Gene-therapy: upregulation of the sodium/iodide symporter,…
- Pre-targeting systems (in conjunction with antibodies).
- Compartmental delivery systems: loco-regional, intrathecal, intratumoural,..
- Use of different or a combination of radionuclides / radiopharmaceuticals.
- Radioprotective agents such as KI, amifostine, growth factors,..
- Psychological support

The aim of this thesis was the exploration of some of these concepts to the optimisation of established clinical radiiodine therapy.

As early as 1949-50 $^{131}$I was used for thyroid carcinoma cases in the University Hospital Ghent. Although very successful in many, but not all patients, it was remarkable that this treatment had not changed in all these years. Was this therapy therefore in its form already optimal?

In 1995-96 the first child with neuroblastoma was treated with $^{131}$I-mIBG therapy. Although used in very late stage cases, a very meaningful palliative response was reached in many. Here the same question was raised, and maybe more deliberately because of the involvement of children: how can we optimise this therapy further, in order to achieve this or even better result in more patients?

Although $^{131}$I-Lipiodol was therapeutically used in Ghent as early as 1964 for lymphatic metastases, it had never been used for hepatocellular carcinoma. The first publication of this thesis (paper I) was on its neo-adjuvant use before liver transplantation, an original indication conceived after the first case that was done in 1999. This therapy proved very promising and effective, and no side effects occurred. One of the conclusions was therefore that the administered dose of $^{131}$I-Lipiodol could (and should) be increased. However, for the patients this would mean longer admittance-isolation periods. We therefore started an evaluation of the psychological condition of the patients admitted to the
radiotherapy-isolation facility, whether patients could be expected to cope with this and how otherwise. This evaluation was continued along the whole period of this thesis and will appear as its last publication in time (paper 8). At the same time we evaluated the other possibility, using the same dose in a more selective catheterisation and targeting procedure (paper 3).

On the other hand, the majority of patients presented for palliative $^{131}$I-Lipiodol therapy. For this, we found the literature data on tumour response and survival not promising. We therefore explored the use of a radiosensitiser, i.e. cisplatin, straight from the start (paper 2) to increase the effectiveness of the therapy. However, in this setting we did find side effects and some of these were serious. As the life expectancy of these patients was anyhow very limited, and admittance in isolation was at least one week every three months with an invasive procedure on top of this, a need came to evaluate the impact of these therapeutic efforts on the subjective well being of the patient. It was a very logical step to use the standardised EORTC quality of life questionnaire in radionuclide therapy too (paper 7).

During this time it became clear that hypothyroidism is the most frequently observed side effect in radioiodine therapy in general. In other studies, we have therefore evaluated means to decrease side effects on the thyroid, such as hypothyroidism in $^{131}$I therapy (paper 4), and the thyroidal uptake of unbound radioiodine in $^{131}$I-mIBG therapy (paper 5) and $^{131}$I-Lipiodol (paper 6).

Personally, I think that any therapy in oncology should be evaluated by the collective impact of survival, side effects, quality of life and the money this has to cost. This thesis is an attempted contribution to extend the scope of the established radioiodine therapies, i.e. $^{131}$I, $^{131}$I–mIBG and $^{131}$I-Lipiodol, towards this.
Physical characteristics and radiobiology of $^{131}$I

As all experiments were done with Iodine-131 ($^{131}$I), its physical characteristics are mentioned here in more detail. $^{131}$I (iodine), formed by neutron bombardment of $^{131}$Te (tellurium), decays to stable $^{133}$Xe (non) by beta emission with an average energy of 183 keV and a maximum beta energy of 807 keV. Gamma emissions suitable for imaging range from 80 to 637 keV, most abundantly 364 keV (83%). The physical half-life to decay is 8.02 days.\(^{10}\)

The biological effect of ionising radiation on cellular organisms results from chemical changes induced in biomolecules. The energy transfer of beta particles brings about ionisation or excitation that alters their structure and function. Indirect actions are the result of radiation interaction producing free radicals (most importantly $\text{O}_2^*$ and $\text{OH}^*$) that in turn can react with critical biomolecules. Some molecules, such as membrane constituents, organelles or enzymes require a (very) high radiation dose to be ‘critical’, i.e. that their dysfunction causes cell death, because they are present in many copies in that cell. DNA in the cell nucleus is present in limited copies while its function is principal to overall cell function. Therefore, irreversible damage to the DNA is regarded as the critical target of radionuclide therapy.\(^{11}\)

$^{131}$I-Lipiodol therapy for hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is worldwide one of the most prevalent cancers due to the worldwide hepatitis virus dissemination. Liver transplantation is the best option for curative therapy but limited to the number of donors. Resection is only possible with limited size and enough functional liver reserve. Thus more than 80% are only eligible for palliative therapy. While systemic chemotherapy is not effective and external radiotherapy will cause too much liver damage, a wide range of percutaneous and intra-arterial therapy forms have been developed.\(^{12}\)

Lipiodol is a mixture of fatty acid ethylesters derived from natural occurring poppy seed oil. As it contains 37% iodine by itself, radiiodine labelling is easily performed by exchange reaction, creating the highly stable $^{131}$I-Lipiodol with high specific activity. $^{131}$I-Lipiodol can be administered in the hepatic artery or its branches according to the distribution of the visible tumours and was first reported in 1986.\(^{13}\) After injection, $^{131}$I-Lipiodol is ‘sucked into’ the tumours by the strong hypervascularity, trapped in the tortuous vessels around the tumour and then partly diffuses into the tumour by virtue of the increased capillary permeability. While the activity in the normal liver is subsequently washed out, this is hampered in the tumours by the absence of Kupffer cells and biliary system, building an uptake ratio of 2.3 to 12 to normal liver. Excretion is predominately renal (30-50% within 7 days). Faecal excretion is low (3% in 5 days). Some activity is retained in the lungs, thyroid and, depending on the collateral circulation, stomach and intestines.

As hepatocellular carcinoma is principally a multifocal disease, it may be one of the major advantages of $^{131}$I-Lipiodol to selectively target all tumours in one session, also the occult. From this principle, interesting results have recently been reported in the use of $^{131}$I-Lipiodol after resection (adjuvant setting).\(^{14}\) In paper 1, we report the first results of its effectiveness in a neo-adjuvant setting, before liver transplantation.

The chemotherapeuticum cisplatin presumably creates cross-bridges between base pairs in the chromosomes, thereby inhibiting DNA repair after sublethal radiation damage. This increases the degree of lethal DNA radiation damage. Cisplatin has been used with success for different indications with external radiotherapy, producing “synergistic” tumour response, i.e. more than the sum of both modalities, without supra-additive toxicity. Paper 2 describes the use of cisplatin as radiosensitiser to enhance the radiation effect of $^{131}$I-Lipiodol therapy.
As an interventional radiology procedure, different modalities have been employed but never compared. In paper 3, selective and hyperselective administration approaches are compared in terms of tumour $^{131}$I-Lipiodol uptake and response.

**Thyroid function and pre-medication**

**Recombinant humane TSH (rhTSH) for $^{131}$I in thyroid carcinoma**

As stated in the foreword, the use of $^{131}$I for differentiated thyroid carcinoma has had a long tradition and has virtually been unchanged over the decades. It is one of the cornerstones of primary therapy: total thyroidectomy followed by a radioiodine ‘ablation’ dose and chronic suppressive thyroxin therapy. Thyroid cancer has a low prevalence as well as a low mortality, with a 10-year survival of more than 85%. Available studies are generally on limited numbers and follow-up, and particularly with very different methodology. A meta-analysis producing reliable results on the impact of therapies, particularly radioiodine therapy, is therefore still difficult. The optimal activity of $^{131}$I remains controversial. This is further hampered by the difficulty of clinical dosimetry, with potentially large calculation errors, making it difficult to establish a dose-response relationship. After oral administration, $^{131}$I is rapidly absorbed from the upper gastrointestinal tract, about 90% in 60 minutes and enters the bloodstream. There it is removed by the thyroid, in normal circumstances about 20% in its first pass, and the kidneys with urinary secretion varying to 37-75%. Faecal excretion is low, 10%. Small amounts of iodine are also found in the salivary glands, gastric mucosa, breast milk, placenta and choroid plexus. Sweat excretion is almost negligible.

First choice treatment of metastatic disease is currently repeated administration of $^{131}$I, possibly in combination with surgery and/or external radiotherapy. One problem is that as the metastatic process continues, progressively lower $^{131}$I uptake is generally observed as the consequence of tumoural cell de-differentiation and selection of intrinsic radioiodine-negative cell lines surviving radioiodine therapy. The effectiveness of radioiodine therapy could be improved by adding drugs that 1) increase radioiodine uptake by the tumour, 2) alter tumour metabolism so that iodine is retained longer, or 3) enhance the radiation damage. Another problem is that $^{131}$I treatment requires withdrawal of thyroid hormone (i.e. levothyroxine or L-T4) suppression therapy for 4–6 weeks to raise the endogenous thyroid stimulating hormone (TSH) level and thereby selective radioiodine uptake by neoplastic cells. However, withdrawal of L-T4 induces symptoms of hypothyroidism causing major disruption of the patient’s family, social and work life, increases the risk of cardiac complications, may increase the risk of thyroid cancer growth and is potentially a lethal factor in patients with a poor physical condition, such as elderly patients with widespread metastatic thyroid carcinoma. In paper 4, we report on the use of exogenous recombinant human TSH (rhTSH) as a newly available pharmacological method that may increase radioiodine without inducing hypothyroidism.

**Potassium iodide (KI) for $^{131}$I-mIBG therapy and $^{131}$I-Lipiodol therapy**

High uptake of unbound radioiodine produced at manufacturing, and/or by radiolysis and/or metabolisation occurs in the thyroid if this is not blocked by “cold” iodine premedication, such as potassiumiodide or perchlorate. Hypothyroidism may be the most frequent late organ side effect of $^{131}$I-mIBG therapy.

The most direct effect of a high dose cold iodine is the Wolff-Chaikoff effect by blocking of the organic binding of iodine to thyreoglobuline, measured by a decrease of the
percentage of thyroidal uptake of anorganic (radio)iodine. This effect disappears after a few days by the resulting decrease of intracellular iodine concentration. When cold iodine is chronically administered such as in the thyroid protection schemes in radionuclide therapy, the amount of radioiodine uptake can increase again because the preferential re-utilisation of iodine from the thyroid is abolished. The effectiveness of thyroid protection by cold iodine has been studied in relation to the two established non-thyroidal radio-iodine therapies, i.e. \(^{131}\text{I}\)-mIBG therapy which is administered generally, in high activities and as a molecule with a low shelf-life (paper 5), and \(^{131}\text{I}\)-Lipiodol which is administered locally, in a lower dose and as a very stable molecule with a long shelf-life (paper 6).

\(^{131}\text{I}\)-mIBG therapy for neuroendocrine tumours

\(^{131}\text{I}\)-mIBG or \textit{meta-iodobenzylguanidine} is a synthetic radioiodinated aromatic analogue of norepinephrine.\(^{17}\) It is thought to have a similar uptake and storage mechanism to that of norepinephrine and therefore has a strong affinity for adrenal medulla and adrenergic nerve tissue. Tumours derived from the neural crest and capable of production and storage of catecholamines may also concentrate mIBG. This is especially true for pheochromocytoma/paraganglioma and neuroblastoma, and to a lesser extent carcinoid tumours and medullary thyroid carcinoma. For example, the high specificity (100% in 400 cumulative patients) and sensitivity (94%) have made mIBG the gold standard of diagnostic tools for the detection, staging and the evaluation of therapeutic response in patients with neuroblastoma.\(^{18}\) For imaging purposes, mIBG labelled with \(^{123}\text{I}\) provides certain advantages over \(^{131}\text{I}\). \(^{123}\text{I}\) decays without beta emission and has a short half-life of 13.3 hours which reduces the radiation burden, while its 159 keV gamma radiation is a more suitable energy for scintillation cameras and provides a high flux per Gy of absorbed dose. For therapy, \(^{131}\text{I}\) is the agent used today, usually in a fixed dose or a dose per kg body weight or body surface. More sophisticated tumour/organ dosimetry could optimise individual patient dose and is the subject of intense research, but has not reached any clinical applications to date. Effectiveness of \(^{131}\text{I}\)-mIBG therapy has been shown for end–staged palliative therapy, adjuvant treatment to chemotherapy in mIBG-positive lesions, and neo-adjuvant stage III neuroblastoma cases before curative resection. Although malignant disseminated pheochromocytoma is a rare disease, neuroblastoma is the most common solid tumour in children under 5 years.\(^{19,20}\) Therefore this has been the most important indication for \(^{131}\text{I}\)-mIBG therapy in the University Hospital Ghent. Figure 2 illustrates two examples of treated patients, one malignant thoracic pheochromocytoma (left) and one skeletal disseminated neuroblastoma (right).

Following intravenous injection, mIBG has a rapid initial urinary clearance, after which the mIBG plasma curve becomes flat. Up to 55% of the injected dose of mIBG is excreted unmetabolized in the urine during the first 24 hours and up to 90% by the fifth day. Appreciable organ uptake occurs in the salivary glands, heart, liver and urinary bladder, and to a lesser extent in the cerebellum, spleen, gut, kidneys, adrenals and lungs.
Quality of life

In the last chapter the subjectivity of the patient, as opposed to the objectivity of tumour response and toxicity, is placed centrally. If we foresee to employ radionuclide therapy for more aggressive tumours too, and (multimodality) therapy intensifies, we have to accept more side effects along the way. Quality of life will then be affected accordingly. Parameters that measure the subjective experience of the patients towards her/his disease and treatment will anyhow become more and more important in the evaluation of oncology treatment justification in general. For radionuclide therapy this may be particularly so since the good tolerance has generally been proposed as a major advantage. Measurements of the patient subjectivity will also be able to more fully appreciate the impact of each modality in a combination therapy. In paper 6, we validate measurements of stress and quality of life as endpoints for evaluating the effectiveness of $^{131}$I therapy.
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Section I:

Multi-modality $^{131}$I-Lipiodol therapy
Paper 1:

Neo-adjuvant $^{131}$I-Lipiodol therapy
THE ANTI-TUMOURAL ACTIVITY OF NEO-ADJUVANT INTRA-ARTERIAL ¹³¹I-LIPIODOL TREATMENT FOR HEPATOCELLULAR CARCINOMA: A PILOT STUDY

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Cancer Biotherapy & Radiopharmaceuticals 2001; 16: 333-8

Purpose. The high recurrence rate after curative resection has stimulated the development of adjuvant treatment modalities, such as local embolisation. This study was set up to investigate the anti-tumoural potential of neo-adjuvant ¹³¹I-Lipiodol administration before liver transplantation.

Methods and materials. In this preliminary, prospective study we treated 10 consecutive HCC patients by intra-arterial injection of ¹³¹I-Lipiodol into the hepatic artery followed by liver transplantation within 1-9 months (mean 3.4). After hepatic catheterisation, 1332-2146 MBq (mean 1887 MBq) or 36-58 mCi (mean 51 mCi) was instilled as selective as possible, depending on the distribution of the tumours: selectively in the hepatic artery propria (n=4), hyperselectively in the right and/or left hepatic artery (n=3) or superselectively in segmental arteries (n=3).

Results. Anti-tumoural activity was regarded as obvious with 1) a strong decrease of alfa-fetoprotein (AFP), comparing the highest recorded value before and after ¹³¹I-Lipiodol and/or 2) a downstaging in TNM classification on the post-therapy MRI as compared to the pre-therapy MRI and/or 3) tumours with >50% necrosis on histo-pathology of the explanted liver, without previous cheomo-embolization. Either of these criteria were met by 5/10 (50%) of patients. A 4) downstaging in pTNM classification on histo-pathology compared to the TNM classification of the MRI and/or a 5) tumour necrosis of only 10-50% were regarded as possibly tumour-related but were not accepted as a single criteria of anti-tumoural activity. This was seen in 3/10 (30%) of patients. Clinical side-effects of the ¹³¹I-Lipiodol therapy were generally mild with a temperature rise in two cases, nausea without vomiting in another two and upper back pain in one patient. In one patient progressive liver failure developed one week after ¹³¹I-Lipiodol therapy necessitating premature liver transplantation after 4 weeks.

Conclusion. With the use of stringent anti-tumoural criteria, this study shows evidence of an anti-tumoural effect in 50% of patients. Our data support the evaluation on larger patient numbers to confirm the promising anti-tumoural activity of ¹³¹I-Lipiodol in HCC patients candidated for liver transplantation.
INTRODUCTION

Hepatocellular carcinoma (HCC) is increasing worldwide and represents the eight place in worldwide cancer incidence [1]. Cure can only be achieved by the use of surgery, i.e. segmental resection or liver transplantation.

Neo-adjuvant hepatic artery chemo-embolisation (TACE) has been popularised by Bismuth [2] and has been widely used, also in our institution [3]. Using a non-selective arterial instillation, $^{131}$I-Lipiodol has been found to be equally effective in tumour control but far better tolerated than the classical chemo-embolisation by cisplatinum, Lipiodol and gelatin-sponge fragments in a group of inoperable, palliative patients [4]. The use of $^{131}$I-Lipiodol in a neo-adjuvant setting has not been reported so far.

This study was set up to investigate the anti-tumoural potential of neo-adjuvant $^{131}$I-Lipiodol administration before liver-transplantation, as a pilot study and pre-requisite to a possible follow-up study which could establish the eventual clinical relevance of neo-adjuvant $^{131}$I-Lipiodol in terms of recurrence rates and long term survival.

MATERIALS AND METHODS

Patient eligibility

In this preliminary, prospective study we treated 10 consecutive patients with HCC by intra-arterial injection of $^{131}$I-Lipiodol into the hepatic artery (between June 1999 and October 2000). All patients underwent liver transplantation within 1.0-9.0 months (mean 3.4 months). Ethics committee approval for this study was obtained with inclusion of informed written consent (protocol 99/208). Preoperative biopsy diagnosis was omitted to avoid tumour dissemination [5]. HCC was diagnosed by Magnetic Resonance Imaging (MRI) findings highly suspect for HCC (hyperintensity on T2 images, gadolinium enhancement on MRI, morphology) in conjunction with liver cirrhosis and a rising alpha-fetoprotein. Tumour localization on MRI was correlated with characteristics on hepatic angiography at $^{131}$I-Lipiodol therapy (hypervascular blush, tortuous vessels) and Lipiodol retention on Computerized Tomography (CT) 2 weeks post-therapy (focal dense and homogeneous contrast). Lipiodol-CT is usually performed after 4 weeks but with $^{131}$I-Lipiodol 2 weeks was necessary because of the smaller quantity of Lipiodol that is used compared to “cold” applications. In one patient (#4), CT of the liver with intravenous contrast enhancement was used instead of MRI.

Radioisotope therapy protocol

The $^{131}$I labeled Lipiodol used in this study (Lipiocis®, CIS bio international, France) has a specific activity of 854-870 MBq/g (23-23.5 mCi/g) and radioactive concentration of 1.11 GBq/ml (30 mCi/ml). After hepatic catheterisation, 1332-2146 MBq (mean 1887 MBq) or 36-58 mCi (mean 51 mCi) in a total volume of 2-4 ml was instilled through the catheter in place as selective as possible. This depended on the distribution of the tumours: selectively in the hepatic artery propria (n=4), hyperselectively in the right and/or left hepatic artery (n=3) or superselectively in segmental arteries (n=3). Four of ten patients (patients 2, 5, 8 and 9) had previously been treated by chemo-embolization with cisplatinum and Lipiodol 7, 12, 12 and 3 months respectively.

Liver transplant procedure

Transplant criteria were defined as HCC complicating cirrhosis, allowing a maximum of 1 lesion less than 5 cm in diameter or 3 lesions less than 3 cm in diameter as assessed with MRI pre-$^{131}$I-Lipiodol [6]. For radioprotection precautions to the operating theatre personnel, patients were principally not transplantable for 6 weeks following $^{131}$I-Lipiodol instillation. This was met in all patients except one (#4), who required transplantation after 4 weeks because of progressive liver failure. Patients received principally one $^{131}$I-Lipiodol treatment. The mean interval between $^{131}$I-Lipiodol and transplantation was 3.4 months. In one patient (#1), a second treatment was performed 4 months after the first with a resulting total transplant interval of 9 months.

Evaluation of endpoints

Total hepatectomy specimens were transsected in 1 cm thick slices and examined by a specialized senior pathologist. Macroscopically, sampling from the explanted liver was focused on nodules corresponding to a tumour localization on MRI and, routinely of larger sized regenerative nodules in the other segments. Histopathological diagnosis of HCC was made on the basis of cellular and architectural atypia comprising of broadened trabeculae consisting of 3 or more liver cells with varying degree of nucleus atypia. Additional reticulin and immuno-staining with von Willebrand factor (F8) and CD34 were also carried out. Number of tumours, their anatomical location, size, percent necrosis (>90%, 60-90% or 10-50%) and presence or absence of
microvascular invasion was noted. Additional tissue characteristics such as hyperplasia, dysplasia, tumour, necrosis or fibrosis were noted.

Anti-tumoural activity was regarded as obvious with 1) a strong decrease of alfa-fetoprotein (AFP), comparing the highest recorded value before and after \(^{131}\)I-Lipiodol and/or 2) a downstaging in TNM classification \(^7\) on the post-therapy MRI as compared to the pre-therapy MRI and/or 3) tumours with \(>50\%\) necrosis on histo-pathology of the explanted liver, without previous chemo-embolization. A 4) downstaging in pTNM classification on histo-pathology compared to the TNM classification of the MRI and/or a 5) tumour necrosis of only \(10-50\%\) were regarded as possibly tumour related but were not accepted as a single criteria of anti-tumoural activity.

RESULTS

General patient characteristics

Table 1 summarises the baseline characteristics of the patients. Most of the patients (7/10) had an associated chronic viral hepatitis, in 4 cases hepatitis C, in 2 cases hepatitis B and of combined aetiology in 1 case. In 6/10 patients, disease was limited to a clinical OKUDA stage I. \([8]\) The mean number of tumour was 2.5 (range n=1.0-3.0) and the mean maximum diameter of 1.4 cm (range 0.5-3.0 cm). Patients were transplanted after a mean interval of 3.4 months (range 1.0-9.0 months) following \(^{131}\)I-Lipiodol.

<table>
<thead>
<tr>
<th>Table 1. General patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Sex M/F</td>
</tr>
<tr>
<td>Etiology liver cirrhosis</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Viral</td>
</tr>
<tr>
<td>Alcohol+viral</td>
</tr>
<tr>
<td>OKUDA classification</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>Alpha fetoprotein (ng/ml)</td>
</tr>
<tr>
<td>Tumours (MRI) (*)</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Size (cm)</td>
</tr>
<tr>
<td>Location: R/L/R+L lobe</td>
</tr>
</tbody>
</table>

(*) Values in mean +/- 1 standard deviation; 
R=right, L=left
In table 2, radiological diagnostic parameters are collected. In all patients the diagnosis of HCC was positively made by all three modalities. However, complete agreement in number of lesions between MRI, CT Lipiodol and angiography was only seen in 4/10 or 40% of patients; between MRI and angiography or MRI and CT Lipiodol this was 6/10 or 60%.

**Table 2.**

Correlative findings on radiology diagnosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>MRI a</th>
<th>Angiography b</th>
<th>LipiodolCT c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 / 1.3</td>
<td>1 / 2</td>
<td>2 / 2</td>
</tr>
<tr>
<td>2</td>
<td>3 / 2.1</td>
<td>2 / 3</td>
<td>3 / 3</td>
</tr>
<tr>
<td>3</td>
<td>2 / 2.3</td>
<td>2 / 2</td>
<td>1 / 2</td>
</tr>
<tr>
<td>4</td>
<td>3 / 2.7</td>
<td>2 / 3</td>
<td>3 / 3</td>
</tr>
<tr>
<td>5</td>
<td>3 / 1.2</td>
<td>3 / 3</td>
<td>3 / 3</td>
</tr>
<tr>
<td>6</td>
<td>3 / 2.0</td>
<td>1 / 3</td>
<td>2 / 3</td>
</tr>
<tr>
<td>7</td>
<td>3 / 1.5</td>
<td>3 / 3</td>
<td>3 / 3</td>
</tr>
<tr>
<td>8</td>
<td>3 / 2.8</td>
<td>3 / 3</td>
<td>2 / 3</td>
</tr>
<tr>
<td>9</td>
<td>2 / 3.0</td>
<td>2 / 2</td>
<td>2 / 2</td>
</tr>
<tr>
<td>10</td>
<td>1 / 0.5</td>
<td>1 / 1</td>
<td>1 / 1</td>
</tr>
</tbody>
</table>

**Table 2 Notes:**
- a MRI before 131I-Lipiodol treatment; number of lesions/diameter of largest lesion in cm
- b Angiography at 131I-Lipiodol treatment; number of hyperemic blushes in corresponding MRI lesions
- c Lipiodol CT after 131I-Lipiodol treatment; number of focal Lipiodol spots in corresponding MRI lesions

**Treatment Response**

In table 3, evolutions of AFP and MRI before and after 131I-Lipiodol treatment as well as final histological diagnosis as criteria of anti-tumoural activity are listed.

**Table 3.**

Correlative findings on anti-tumoural activity

<table>
<thead>
<tr>
<th>Patient</th>
<th>AFP pre/post a</th>
<th>MRI pre b</th>
<th>MRI post c</th>
<th>Histology d</th>
<th>Antitumoural activity e</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27.1 / 14.9</td>
<td>2 / 1.3</td>
<td>0 / 0</td>
<td>T2N0M0</td>
<td>MRI</td>
</tr>
<tr>
<td>2</td>
<td>42.7 / 19.9</td>
<td>3 / 2.1</td>
<td>2 / 2.0</td>
<td>T2N0M0</td>
<td>MRI</td>
</tr>
<tr>
<td>3</td>
<td>3.3 / 3.7</td>
<td>2 / 2.3</td>
<td>2 / 3.5</td>
<td>T3N0M0</td>
<td>Histology</td>
</tr>
<tr>
<td>4</td>
<td>17.7 / 11.9</td>
<td>3 / 2.7</td>
<td>1 / &lt;90</td>
<td>T4N0M0</td>
<td>Histology</td>
</tr>
<tr>
<td>5</td>
<td>1849 / 20.2</td>
<td>3 / 1.2</td>
<td>3 / 10-50</td>
<td>T4N0M0</td>
<td>AFP</td>
</tr>
<tr>
<td>6</td>
<td>2.5 / 3.4</td>
<td>3 / 2.0</td>
<td>1 / 10-50</td>
<td>T1N0M0</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>7</td>
<td>450 / 756</td>
<td>3 / 1.5</td>
<td>1 / 10-50</td>
<td>T4N0M0</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>8</td>
<td>4.6 / 4.4</td>
<td>3 / 2.8</td>
<td>2 / 10-50</td>
<td>T4N0M0</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>9</td>
<td>82.0 / 86.5</td>
<td>2 / 3.0</td>
<td>M / 10-50</td>
<td>T4N0M0</td>
<td>No Evidence</td>
</tr>
<tr>
<td>10</td>
<td>102 / 120</td>
<td>1 / 0.5</td>
<td>ND</td>
<td>NET / pT0N0M0</td>
<td>No Evidence</td>
</tr>
</tbody>
</table>

**Table 3 Notes:**
- a Alpha-fetoprotein (AFP) before 131I-Lipiodol (“pre”) / after 131I-Lipiodol, before transplantation (“post”); highest values recorded, in ng/ml (normal values < 20 ng/ml)
- b MRI before 131I-Lipiodol; c MRI after 131I-Lipiodol, before liver transplantation; number of lesions / diameter of largest lesion in cm / clinical TNM classification; ND=not done
- d Histological findings on explanted liver; number of lesions / degree of necrosis / pathology TNM classification; NET=no evidence of tumour; M=multi-focal tumour spread
- e Anti-tumoural activity as evidenced by AFP, MRI or histology
Five of ten patients (#1-5) showed an anti-tumoural activity: Patient #1 was the only patient treated twice. In this patient both contrast and Lipiodol positive HCC lesions disappeared on the Lipiodol-CT after the second treatment. At histology, no tumours were found. Patient #2 showed downstaging on MRI post-therapy (from T4 to T2) and histology (from T2 to T1). Patient #3 had 2 tumours which, by conventional radiological response criteria, would be referred to as progressive disease but showed both more than >90% necrosis on histology without previous chemoembolization. Patient #4 showed three lesions with 60-90% necrosis without previous chemoembolization. No follow-up MRI was available due to the urgent nature of the transplant procedure. Patient #5 showed a strong decrease in AFP from 1849 before $^{131}$I-Lipiodol to 20.2 ng/ml after 8 weeks, one week before transplantation, as well as moderate necrosis although no change on MRI staging. In three other patients, #6-8, a moderate degree of tumour necrosis was seen on histology but MRI did not change. The anti-tumoural effect in these patients remains uncertain because no other confirmatory anti-tumoural criteria were present, especially no change in tumour stage assessed by pre/post treatment MRI. The observed moderate necrosis in these tumours could have been spontaneous, as we observed in an earlier study in 4/14 (29%) of cases pre-transplant without neo-adjuvant treatment [3]. In two patients, no evidence of an anti-tumour effect could be demonstrated. In patient #9, diffuse microscopic disease was found on pathology which was not detected before $^{131}$I-Lipiodol. In patient #10, a MRI, angiography and CT-Lipiodol positive tumour of 0.5 cm could not be found in the explanted liver. Because cirrhosis, but no area of necrosis or scarring was neither found in this area, a false-positive result could not be ruled out.

Side-effects

Clinical side-effects of the $^{131}$I-Lipiodol therapy were a temperature rise in two cases, nausea without vomiting in another two and upper back pain in one patient. All of these could be treated with first-line analgetics and anti-emetics. Biochemically, we saw an increase in liver enzymes (bilirubin, ALT, AST) in 6 patients. These were slight in 4 patients; more than a doubling of value was seen in 2 cases. As for major events, progressive liver failure developed in one patient, from one week after $^{131}$I-Lipiodol therapy, necessitating premature liver transplantation after 4 weeks.

DISCUSSION

The high recurrence rate of HCC of up to 65% in post-liver transplant patients has prompted strict transplantation criteria including only limited disease as well as the use of multi-modality approaches, especially loco-regional neo-adjuvant procedures [9,10]. In classical neo-adjuvant trans-arterial chemoembolisation, a decrease in incidence of local recurrences and disease-free has been documented, but its beneficial effect on final long-term survival has not been consistently demonstrated [11]. Trans-arterial loco-regional $^{131}$I-Lipiodol therapy has been found to substantially reduce recurrence rates and increase disease-free survival in an adjuvant setting after partial hepatectomy [12], but this is different from the pre-transplant setting, for which no data presently exist. However, loco-regional trans-catheter treatment with $^{131}$I-Lipiodol is an attractive modality for this indication too because of its good tolerability and capacity to treat the whole liver in view of the multi-focal, partially sub-clinical nature of HCC.

The unique feature of a neo-adjuvant treatment group such as in this study is the opportunity to directly evaluate the effect of $^{131}$I-Lipiodol by histology. We observed several histo-pathological features of HCC treated with $^{131}$I-Lipiodol such as apoptosis, necrosis, chromosome rarifications and loss of cell contacts. In view of the fact that there are no data on
any specific histological effects of $^{131}$I-Lipiodol, we chose only to accept a 60-100% tumour necrosis as a histological anti-tumoural activity criterion. If any spontaneous tumour necrosis would occur in these small tumours, we presumed that it would probably not exceed 50% in these small tumours. Indeed, in a previous study in which 6 patients received no neo-adjuvant treatment a 60-90% (spontaneous) necrosis of the tumour was only seen in 1/14 tumour nodules.[3]

The accuracy of other diagnostic modalities, i.e. AFP and MRI, can be considered lower than the “gold-standard” of histology [6]. AFP may be false-positive from active regenerative liver tissue in inflammatory or cirrhotic liver, or false-negative with poorly differentiated tumours. In the presence of cirrhosis and a liver mass, AFP levels are virtually diagnostic only if they reach a level of more than 500 ng/ml [5]. As such, only 1/10 pre-therapy value in our study (patient #5) could be regarded as definitely tumour-related. This is probably related to the early stage of the tumours in this particular patient group. However, this makes the use of AFP as a marker for anti-tumoural activity of limited value. A clear decrease of AFP values after $^{131}$I-Lipiodol could therefore only in one patient (#5) be regarded as proof for anti-tumoural activity.

The lack of full lesion agreement between radiological modalities in 60% of our patients illustrates the difficulties of all imaging techniques [13], with more frequent false-negatives in small or microscopic tumour (such as patient #9) and possible false-positives in hyperplastic or dysplastic nodules (such as patient #10). In a recent publication on an unselected patient population of histologically verified hepatic tumours, using similar interpretation criteria as our study [14], a positive predictive value of 83% was found for MRI and 79% for CT-Lipiodol. Patient #10 is an example of a tumour that was retrospectively judged to be a possible radiological false-positive diagnosis, because the lack of the tissue correlate (normal, hyperplastic, dysplastic, tumoural, necrotic, fibrotic) was by consensus given more weight than the fact that the lesion was T2-hyperintense, gadolinium-hypervascular as well as confirmed by angiography and on Lipiodol-CT findings. On the contrary, in patient #1 the radiological disappearance of the lesion was given stronger evidence in favour of tumour than the histological findings. In our study we tried to minimise possible incorrect interpretation by 1) comparing only pre- with post-$^{131}$I-Lipiodol MRI studies to detect a TNM downstaging as an anti-tumoural criterium, and 2) avoiding a direct comparison between staging by histological and imaging data. Pre-therapy confirmation of diagnosis by biopsy, which could increase the accuracy of pre-$^{131}$I-Lipiodol diagnosis is not done in our institution because of the risk of tumour dissemination along the biopsy tract. However, the distinction between “atypical” or dysplastic macro-regenerative nodules and early HCC is histologically a challenge too because they represent a continuum spectrum of hepatocarcinogenesis. The differing findings on MRI and histology may be taken as an argument not in favor of reliable staging of HCC by MRI. In general, classical radiological criteria may not be ideal for assessing response to radionuclide therapy. Further study should address this important problem, since it is commonly viewed that millimetre sized (sub radiological) disease is optimal for radio-isotope radiotherapy.

In two patients (#5 and 6) post $^{131}$I-Lipiodol MRI showed an increase from 3 to 4 lesions, which would principally render these patients untransplantable. However, especially in view of the diagnostic shortcomings explained above, these criteria are never handled with absolutism. As stated before, transplant criteria in our patients were established on the pre $^{131}$I-Lipiodol MRI, also to avoid possible artefacts induced by the $^{131}$I-Lipiodol therapy.

The observed anti-tumoural effects in 50% of patients compares well with the observed tumour effect of chemoembolization showing a decrease in tumour size of 5-38% of patients [15]. It would be of interest to understand why the treatment is successful in some patients and others not. Some authors have found tumour size, i.e. below or above 5 cm tumour diameter, a decisive factor [16]. In our study there were only small sized lesions.
Others found that the calculated radiation dose did not correlate with survival in inoperable patients, but acknowledged the fact that this might have related to difficulties in determining the biodistribution and CT parameters [17]. Indeed, accurate dosimetry would be of great value in establishing a possible dose-response relationship. It is interesting to note that, except for one possible patient, no liver toxicity was noted in our study group regardless of selectivity of administration. This does allow the possibility of dose escalation.

In conclusion, with the use of stringent criteria on radiology, AFP and histology, this study shows evidence of an anti-tumoural effect in 50% of patients. This small and preliminary patient group does not yet allow a statistical evaluation of clinical parameters such as recurrence rates and long term survival, which may be viewed as the ultimate judgement on the clinical relevance of this treatment modality. Our data do support the evaluation on larger patient numbers to confirm the promising anti-tumoural activity of $^{131}$I-Lipiodol in HCC patients candidated for liver transplantation.
Figure 1.
Illustration of tumour targeting by intra-arterial $^{131}$I-Lipiodol therapy in hepatocellular carcinoma patients waiting for liver transplantation.
Figure 2.
Effect of $^{131}$I-Lipiodol therapy on hepatocellular carcinoma as evaluated by histological examination on the extraplasted liver. Note the central area of tumour necrosis (right, closed arrow), surrounded by a rim of viable residual tumour (left, open arrow).
REFERENCES

Paper 2:

$^{131}$I-Lipiodol therapy with cisplatin
COMBINING $^{131}$IODINE-LIPIODOL THERAPY WITH LOW-DOSE CISPLATIN AS RADIOSENSITISER: PRELIMINARY RESULTS IN HEPATOCELULAR CARCINOMA


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*European Journal of Nuclear Medicine and Molecular Imaging 2002; 29: 928-932*

**Purpose.** A prospective pilot trial was performed in 20 patients randomised to receive either $^{131}$I -Lipiodol therapy alone (n=10) or $^{131}$I -Lipiodol combined with a short low-dose cisplatin infusion (n=10), the aim being to evaluate the possible positive influence of a radiosensitiser on toxicity and tumour response.

**Methods and materials.** An activity of 1354-2128 MBq (mean 1824 MBq) [36.6-57.5 mCi (mean 49.3 mCi)] $^{131}$I–labelled Lipiodol was administered by selective instillation in the hepatic artery. Cisplatin was given in a dose of 30 mg/m$^2$ at day –1 and +6 (day 0: $^{131}$I - Lipiodol). The primary endpoint of this trial was toxicity of therapy; points of secondary interest were tumour response and survival at 6 months.

**Results.** With the use of cisplatin we found a higher percentage of stable or diminished tumour size (90%, vs 40% without). A benefit in group survival at 6 months was not evident. Low-grade stomatitis in one patient and minor changes in peripheral blood count were probably directly related to cisplatin but its administration is unlikely to be associated with an excess of serious side effects.

**Conclusion.** The use of low-dose cisplatin infusion as a radiosensitising agent in $^{131}$I-Lipiodol therapy for hepatocellular carcinoma seems safe and may be beneficial for tumour control. Larger patient groups are necessary for confirmation and to establish the future role of $^{131}$I-lipiodol in hepatocellular carcinoma.
INTRODUCTION

Several authors have used intra-arterial $^{131}$I-iodinized Lipiodol therapy in inoperable hepatocellular carcinoma (HCC) [1,2,3]. An objective tumour response of 32%-40% was achieved, but the impact on survival was modest, the rate being 25%-31% at one year. Additional strategies to improve these results would therefore be valuable. The use of higher administered activities of $^{131}$I-Lipiodol is limited by the radiation protection issues associated with the high-energetic gamma radiation of $^{131}$I.

Alternatively, low-dose chemotherapeutics could be employed as ‘radiosensitisers’ to enhance the radiation effect, in the same way as strontium-89 has been employed in combination with cisplatin in the therapy of bone metastases [4]. In HCC, Abrams and co-workers [5] reported a 43% response rate using cisplatin before and after external beam radiotherapy, and Chenoufi et al [6] reported a synergistic effect of cisplatin in-vitro, given either before or after $^{131}$I -Lipiodol.

In this study we therefore initiated a pilot trial using $^{131}$I -Lipiodol therapy alone or in combination with a short low-dose cisplatin intravenous infusion in patients with unresectable HCC to evaluate the safety and efficacy of the combined technique.

MATERIALS AND METHODS

Patients eligibility

The treatment protocol was approved by the ethical committee of University Hospital Ghent and patients gave their written informed consent. Between June 1999 and July 2001, 20 patients with inoperable HCC of the liver, with or without the presence of portal vein thrombosis, were randomised to receive either $^{131}$I-Lipiodol therapy alone (LIP group, n=10) or $^{131}$I -Lipiodol with cisplatin (LIP-CIS group, n=10). Diagnosis of HCC was made on the basis of either histology from biopsy or previous resection (n=14) or the combination of underlying cirrhosis with characteristic findings on magnetic resonance imaging (MRI) (hyperintensity on T2 and arterial gadolinium contrast enhancement).

Radionuclide therapy protocol

A total volume of 2-4 ml containing 1354-2128 MBq (mean 1824 MBq) [36.6-57.5 mCi (mean 49.3 mCi)] $^{131}$I-lipiodol (Lipiocis®, CIS bio international/Shering) was instilled selectively to the proper hepatic artery (n=34/45 treatments) or, for anatomical reasons, hyperselectively in the right and left hepatic arteries (n=11/45 treatments). Net administered activity was calculated by a NaI dose calibrator, based on the difference between the activity in the syringe before injection and the remaining activity in the syringe and catheter after injection. Cisplatin was given in a dose of 30 mg/m$^2$ at day –1 and day +6 (day 0: $^{131}$I -Lipiodol) as an intravenous infusion for 2.5 h, with an additional hydration scheme of 1-2 l NaCl 0.9% and 0.5 l mannitol, a bolus of 40 mg methylprednisolone, and ondansetron 2 times 8 mg per day. In conjunction with the angiography procedure, patients received a platelet infusion if baseline thrombocyte counts were below 50 x 10$^9$/l and whole blood packed cells if the haemoglobin level was below 8 g/dl. Retreatment with $^{131}$I-Lipiodol was performed 3, 6 and 9 months after the first injection.

Evaluation of endpoints

The primary endpoint of this trial was tolerance of treatment. Specific side effects were registered as common toxicity criteria (National Institute of Health CTC, version 2.0, March 1998). A side effect was regarded as such if the condition or symptoms occurred within 4 weeks after administration of $^{131}$I-Lipiodol with or without cisplatin. Liver enzymes, peripheral blood counts and creatinine were routinely monitored 7 and 14 days after treatment and in the case of a significant change or side effect.

Point of secondary interest were tumour response and group survival at 6 months after the first injection. Tumour response was classified according to WHO standards by MRI (n=16) or computed tomography (CT, n=4), performed 6 weeks after therapy and repeated after subsequent therapies.

Statistics

Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. Differences in group characteristics were assessed according to Kruskal-Wallis and the Fisher’s Exact Test (SPSS for Windows software, version 10.0). A P-value of <0.05 was considered statistically significant.
RESULTS

General patient characteristics

Table 1 lists the general and prognostic patient characteristics of the two groups. There were no statistical differences in these demographic and prognostic clinical classifications (Okuda, Stillwagon, CLIP)\(^7\). Only pre-therapy \(\alpha\)-fetoprotein (AFP) levels were statistically different in this patient sample (mean 75794 ng/ml in the LIP+CIS group vs 1161 ng/ml in the LIP group).

Table 1.
General and prognostic patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LIP Group</th>
<th>LIP+CIS Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>8/2</td>
<td>9/1</td>
</tr>
<tr>
<td>Age (^a)</td>
<td>60.9 +/- 10.7</td>
<td>58.3 +/- 8.8</td>
</tr>
<tr>
<td>Okuda classification (I/II) (^b)</td>
<td>5/5</td>
<td>6/4</td>
</tr>
<tr>
<td>Stillwagon classification (%favourable) (^c)</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>CLIP classification (0-2/3-6) (^d)</td>
<td>3/7</td>
<td>5/5</td>
</tr>
<tr>
<td>Alpha-fetoprotein (ng/dl) (^e)</td>
<td>1161 +/- 2281</td>
<td>75794 +/- 179486</td>
</tr>
<tr>
<td>Tumour extension (&lt; / &gt; 50% of liver) (^a, e)</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>Maximum tumour diameter (cm) (^a, e)</td>
<td>5.7 +/- 2.1</td>
<td>4.1 +/- 2.2</td>
</tr>
<tr>
<td>Portal vein thrombosis: trunk/right/left (^f)</td>
<td>2/1/0</td>
<td>1/2/1</td>
</tr>
</tbody>
</table>

\(^a\) Mean +/- standard deviation

\(^b\) Adverse criteria: Tumour >50% of liver volume; ascites present; albumin <3.0 g/dl; bilirubin >3.0 mg/dl. Stage I, no adverse criteria present; stage II, one or two adverse criteria present; stage III, three or four adverse criteria present.

\(^c\) Adverse criteria: Karnofsky score <80%, ascites present, albumin <3.0 g/dl, bilirubin >1.4 mg, SGOT >35 IU/l, alkaline phosphatase >95 IU/l. Favourable: no, one or two criteria present; Unfavourable: three or more criteria present.

\(^d\) Adverse criteria: Child-Pugh stage B; multinodular tumour and extension < 50%; AFP > 400 ng/dl; portal vein thrombosis: 1 point. Child-Pugh stage C; massive tumour or extension >50%: 2 points. Total score 0-6 points.

\(^e\) As measured on CT or MRI

\(^f\) As diagnosed on angiography at treatment

Clinical and laboratory changes after treatment

In total, 45\(^\text{131}\)I-Lipiodol therapies were given, 21 in the LIP group and 24 in the LIP-CIS group. Six patients received one therapy, seven patients two, three patients three and four patients four therapies. Clinical side effects were seen in 62% (28/45) of treatments (table 2). In the vast majority, 81% (22/28), these were tolerance grade 1 or CTC grade 1-2 (figure 1). In 19% (6/28) of cases we encountered tolerance grade 2 or 3 side effects. There were four cases of increased liver failure. Three patients, two in the LIP-CIS group and one in the LIP group, were characterised by increasing bilirubin levels (tolerance grade 2, CTC grade 3) without clinical liver failure. In the fourth, a LIP-CIS patient with a previous history of encephalopathy and a bilirubin level of 3.93 mg/dl before his (second) therapy, clinical liver failure occurred in the second week and progressed until death in the third week (tolerance grade 3, CTC grade 4). Other CTC grade 4 side effects were a haemorrhagic stomach ulceration diagnosed one week after treatment, and a subacute attack of abdominal pain of undetermined cause, possibly related to tumoural bleeding or rupture of a hepatic lesion, both of these in LIP-CIS patients.
Table 2.
Side effects after $^{131}$I –Lipiodol treatment in the LIP group (21 therapies) and LIP-CIS group (24 therapies)

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>LIP group</th>
<th>LIP+CIS group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7(33%)</td>
<td>6(25%)</td>
</tr>
<tr>
<td>Nausea (vomiting)</td>
<td>4(19%)</td>
<td>4(17%)</td>
</tr>
<tr>
<td>Abdominal discomfort, pain</td>
<td>5(24%)</td>
<td>2(8%)</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>0</td>
<td>1(4%)</td>
</tr>
<tr>
<td>Progression of liver failure</td>
<td>1(5%)</td>
<td>3(13%)</td>
</tr>
<tr>
<td>Subacute abdomen</td>
<td>0</td>
<td>1(4%)</td>
</tr>
<tr>
<td>Stomach ulceration</td>
<td>0</td>
<td>1(4%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>1(4%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1(5%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>LABORATORY:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised serum bilirubin and/or ALT</td>
<td>2(10%)</td>
<td>9(38%)</td>
</tr>
<tr>
<td>Raised lipase</td>
<td>1(5%)</td>
<td>1(4%)</td>
</tr>
<tr>
<td>Reduced blood count</td>
<td>1(5%)</td>
<td>8(33%)</td>
</tr>
<tr>
<td>Raised creatinine</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*a* Fourty-one paired observations: increase $> 50$

*b* Seven paired observations: increase $> 50$

*c* Thirty-nine paired observations: decrease $> 20$

*d* Thirty-five paired observations: increase $> 50$

Figure 1.
Clinical tolerance in 45 $^{131}$I –Lipiodol therapies

Light, left bars, LIP group;
dark, right bars, LIP-CIS group.
Grade 0: No side effects; Grade 1: minor side effects needing medication but no hospitalisation; Grade 2: moderate side-effects needing medication and hospitalisation; Grade 3: severe side effects, life threatening
Overall, laboratory changes were seen in 49% (22/45) of therapies (table 2). Minor transient, asymptomatic rises in bilirubin and/or alanine aminotransferase (ALT) (CTC grade 1) occurred in 55% (11/20) of patients, more often in the LIP-CIS group. Subtle reductions in the peripheral blood count were seen in seven patients (CTC grade 1), again more often in the LIP-CIS group. In one of these patients, haemoglobin dropped from 11.4 to 7.4 g/dl (CTC grade 3) related to a bleeding complication. In another patient leucocytes and platelet levels dropped from low baseline values of 2.11 and $44 \times 10^9/l$ to $1.53$ and $33 \times 10^9/l$, respectively, related to hypersplenism (CTC grade 2). There was no difference in the incidence of clinical and laboratory changes seen at the first or subsequent therapies.

**Treatment response and survival**

Table 3 shows the response to treatment in both groups. Overall we saw a radiological response (CR+PR) of 15%. Complete response (CR) was not seen in either of the groups. Partial response (PR) was seen in 1/10 (10%) of the LIP-CIS group and 2/10 (20%) of the LIP patients. Taking minor response (MR) and stable disease (SD) into consideration, a stable or diminished tumour mass was seen in 90% of LIP-CIS patients, versus 40% of LIP patients. However, due to the size of the patient groups this was not a statistically significant difference. The average duration of radiologically stable or responsive disease (PR or MR or SD) was 6.6 months overall, being 5.9 months in the LIP group and 6.9 months in the LIP-CIS group. In the patients with multiple treatments and responsive disease, maximum response was invariably seen after the second treatment, in LIP- and LIP-CIS patients alike. At termination of the inclusion period, 25 months after the first patient was included, all but one patient in the LIP group had died, while in the LIP-CIS group three patients were still alive after 7, 9 and 11 months. Kaplan-Meier survival curves showed similar survival rates between the groups, 80% and 70% at 3 months and 60% and 50% at 6-months in the LIP group and the LIP-CIS group, respectively (figure 2). Median survival time was 7.0 months (95% confidence interval 3.9-10.1 months) in the LIP group and 5.5 months (95% confidence interval 2.4-8.6 months) in the LIP-CIS group. There was no statistical difference in survival distribution between the two groups (p=0.59 according to log-rank test).
Table 3.
Treatment results in $^{131}$I-Lipiodol patients treated with (LIP-CIS) or without (LIP) cisplatin

<table>
<thead>
<tr>
<th>Patients</th>
<th>Pre-treatment</th>
<th>CT/MRI response</th>
<th>Duration of response (months)</th>
<th>Duration of survival (months)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>PD</td>
<td></td>
<td>16</td>
<td></td>
<td>Liver failure due to tumour growth</td>
</tr>
<tr>
<td>2</td>
<td>Lobe resection</td>
<td>SD</td>
<td>7.5</td>
<td>11.5</td>
<td>Liver failure due to tumour growth</td>
</tr>
<tr>
<td>3</td>
<td>PD</td>
<td></td>
<td>3.5</td>
<td></td>
<td>Biliary Obstruction</td>
</tr>
<tr>
<td>4</td>
<td>PD</td>
<td></td>
<td>8</td>
<td></td>
<td>Hemoperitoneum</td>
</tr>
<tr>
<td>5</td>
<td>Liver transplantation</td>
<td>PD</td>
<td>1.5</td>
<td></td>
<td>Liver failure due to tumour growth</td>
</tr>
<tr>
<td>6</td>
<td>PR</td>
<td></td>
<td>6</td>
<td>6</td>
<td>Liver failure due to cirrhosis+tumour</td>
</tr>
<tr>
<td>7</td>
<td>Chemo-embolisation</td>
<td>PR</td>
<td>8</td>
<td>9</td>
<td>Gastro-intestinal bleeding</td>
</tr>
<tr>
<td>8</td>
<td>PD</td>
<td></td>
<td>10</td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>PD</td>
<td></td>
<td>2</td>
<td></td>
<td>Liver failure due to cirrhosis+tumour</td>
</tr>
<tr>
<td>10</td>
<td>SD</td>
<td></td>
<td>2</td>
<td>7</td>
<td>Liver failure due to cirrhosis</td>
</tr>
<tr>
<td>LIP-CIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>MR</td>
<td></td>
<td>3</td>
<td>2.5</td>
<td>Liver failure due to cirrhosis</td>
</tr>
<tr>
<td>2</td>
<td>SD</td>
<td></td>
<td>5.5</td>
<td>7</td>
<td>Liver failure due to tumour growth</td>
</tr>
<tr>
<td>3</td>
<td>SD</td>
<td></td>
<td>2</td>
<td>2.5</td>
<td>Liver failure due to cirrhosis</td>
</tr>
<tr>
<td>4</td>
<td>Liver transplantation</td>
<td>PR</td>
<td>19</td>
<td>19</td>
<td>Failure of liver transplant</td>
</tr>
<tr>
<td>5</td>
<td>SD</td>
<td></td>
<td>4.5</td>
<td>5.5</td>
<td>Liver failure due to cirrhosis</td>
</tr>
<tr>
<td>6</td>
<td>Lobe resection</td>
<td>SD</td>
<td>7</td>
<td>7</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>SD</td>
<td></td>
<td>10</td>
<td>11</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>IV Chemotherapy</td>
<td>PD</td>
<td>3</td>
<td></td>
<td>Liver failure due to tumour growth</td>
</tr>
<tr>
<td>9</td>
<td>MR</td>
<td></td>
<td>6</td>
<td>9</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>Segmental resection</td>
<td>MR</td>
<td>5</td>
<td>5</td>
<td>Respiratory insufficiency</td>
</tr>
</tbody>
</table>

1 PR = Partial response; MR = minor response; SD = stable disease; PD = progressive disease

Figure 2.
Kaplan-Meier survival curves

*Thick line*, LIP-CIS group; *broken line*, LIP group
DISCUSSION

The moderate achievements of a 15% objective response and an overall survival of 55% at 6 months, which are in concordance with results reported by others [3], illustrate the extent to which inoperable HCC patients constitute a difficult treatment group and also the need to employ additional strategies to improve the efficacy of $^{131}$I-Lipiodol treatment.

The use of a radiosensitiser is attractive because it may increase tumour cell death by 30%-50% [6] without adding major toxicity to the treatment [4]. Cisplatin has been the referential radiosensitising agent. The precise biochemical mechanisms of the interaction with radiation remains a matter of debate [8] but most arguments point to an inhibition of repair of sublethal damage by cisplatin through DNA cross-linkage. Experimental data indicate a non-saturable dose-dependency and time-dependency with a tumour half-life of 94.4 h [9]. We chose to administer a moderate dose of 30 mg/m$^2$ cisplatin on day –1 and day +6 because:

1. Most studies in external radiotherapy have used a weekly cisplatin dose of 20-40 mg/m$^2$.
2. No clear benefit has been shown for a lower daily cisplatin dose of 5-6 mg/m$^2$ [10] and these lower daily cisplatin doses have been associated with sub-radiosensitising tumour concentrations [9].
3. The protocol has the merit of resembling the administration of 50 mg/m$^2$ cisplatin at day 0 and day +10 after $^{89}$Sr injection [4] but employs a lower dose because the combination with angiography could substantially add to the renal toxicity of cisplatin.
4. Cytotoxicity has been shown to be equal whether cisplatin was administered before or after $^{131}$I in-vitro [6]. Administration after $^{131}$I-Lipiodol would significantly increase the radiation burden for nursing and medical personnel.
5. Intra-arterial administration, such as has been used by others in HCC at a dose of 50 mg/m$^2$ weekly [5], would substantially increase the complexity of treatment.

Our preliminary results suggest a possible beneficial effect on tumour response but no difference in survival. This would correspond to the findings obtained in $^{89}$Sr with cisplatin [4]. In HCC, no literature data are available for comparison. The study of Abrams [5] was not controlled and therefore difficult to interpret. It is important to realise that the a priori survival expectancy of these patients with advanced liver cirrhosis, high tumour occupancy and portal vein thrombosis is very limited and thus strongly interferes with any differences in tumour response that may be achieved. Another important consideration when interpreting our results is the higher AFP level in the LIP-CIS group, which has been recognised as an important negative prognostic factor [7]. This could have skewed the efficacy data but taking this into account would be to the further advantage of the LIP-CIS group.

The fact that all 3 CTC grade 4 toxicity’s occurred in the LIP-CIS group is a particular point of concern. Progressive liver failure, stomach ulceration and possible tumour bleeding or rupture may well be caused by non-targeted deposition of $^{131}$I-Lipiodol, in either the liver or the stomach, through collateral circulation or arteriovenous shunting. However, these side effects lack specificity and may also have been caused by the end-stage liver cirrhosis and the tumour spread itself. Renal toxicity of cisplatin with radiotherapy has been observed to be independently additive and not related to radiosensitisation. Liver failure, stomach ulceration and acute abdomen are no typical side effects of cisplatin. Given the toxicity profiles of the agents used, any supra-additive toxicity would be most likely to be exposed by a higher level of renal function disorder in the LIP-CIS group; however, no such difference was observed.

On the basis of these results we plan to continue the randomisation in a larger patient group in order to confirm that the combination of $^{131}$I-Lipiodol therapy with low-dose cisplatin has beneficial effects on tumour response while not causing an excess number of serious side effects. Large-scale controlled trials on the use of radiosensitising agents with
radioisotopes and multi-modality treatments are required to establish the future role of $^{131}\text{I}$-Lipiodol in HCC.
Figure 3.
Images of palliative $^{131}$I-Lipiodol therapy

Figure 3A.
Angiographic distribution of the tumours and placement of catheter for injection of $^{131}$I-Lipiodol

Figure 3B.
Verification of tumour and tissue targeting by whole body scintigraphy one week after $^{131}$I-Lipiodol therapy

Figure 3C.
Verification of tumour and tissue targeting by Lipiodol-CT two weeks after $^{131}$I-Lipiodol therapy
REFERENCES


Paper 3:

Hyperselective administration of $^{131}$I-Lipiodol therapy
INTRA-ARTERIAL RADIONUCLIDE THERAPY OF LIVER TUMOURS: EFFECT OF SELECTIVITY OF CATHETERISATION AND $^{131}$I-IODIZED LIPIODOL DELIVERY ON TUMOUR UPTAKE AND RESPONSE

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Nuclear Medicine Communications 2002; 24: 391-396

Purpose. Several authors have demonstrated the good tolerance of hepatic intra-arterial $^{131}$I-iodinized Lipiodol therapy but report modest survival rates of 21-25% after one year in inoperable patients. This study explores the question if a more selective hepatic arterial instillation could be a strategy to increase tumoural uptake and response of $^{131}$I - Lipiodol.

Methods and materials. Between June 1999 and September 2001 we included 24 patients: 14 patients received a $^{131}$I–Lipiodol instillation selectively to the proper hepatic artery (“SEL” group); 10 patients received a hyperselective instillation in the right or left hepatic artery (“HYP-SEL” group). The individual $^{131}$I–Lipiodol activity as percentage of injected activity per volume tumour (% I.A./ml) was correlated with selectivity of instillation in 28 tumours and with tumour response in 24 tumours.

Results. Differences in tumour response between the SEL and HYP-SEL group were not significant. In general, we observed a $^{131}$I–Lipiodol uptake of 0.05-2.6 % of the injected dose per ml tumour volume. The uptake was significantly higher in responsive disease than stable or progressive disease (p=0.002). A large tumour volume was invariably related to low $^{131}$I–Lipiodol uptake and progressive disease (p=0.008).

Conclusion. In conclusion, our study does not support the general use of hyper- or superselective intra-arterial $^{131}$I-Lipiodol administration. This result may be extrapolated to similar types of intra-arterial, loco-regional hepatic radionuclide therapy.
INTRODUCTION

Hepatic intra-arterial \(^{131}\)I-iodinized Lipiodol therapy is an interesting treatment modality for hepatocellular carcinoma (HCC) \([1]\). Several authors have demonstrated its good tolerance as compared to classical chemo-embolisation \([2,3]\). In inoperable patients modest survival rates of 21-25\% after one year have been achieved \([2, 4, 5]\).

It would therefore be of interest to increase the tumour radiation dose. However, a phase I dose-escalation trial has never been performed in \(^{131}\)I-Lipiodol therapy and there is therefore uncertainty about the maximum activity that can be administrated safely. The liver has been determined as critical normal organ with an estimated radiation dose of 18.6 Gy for a standard administered activity of 2220 MBq (60 mCi) \([6]\). The tolerance dose of the liver has been estimated as 30 Gy for external irradiation \([7]\), but delivery of 30 Gy internally from intravenous injected colloidal phosphor-32 chromic phosphate did not cause side effects \([8]\).

The maximum tolerated dose may anyhow be significantly lower in severely cirrhotic livers. Moreover, the administration of higher doses of \(^{131}\)I-iodine, which emits high-energy gamma radiation, is limited by radioprotection issues, as there are undesirably long patient isolation periods and radiation exposure of personnel.

The present study addresses the question of whether hyperselective injection into the tumour supplying right or left hepatic artery is a therapeutic option to increase local activity and hence dose to the tumour in an attempt to increase tumoral uptake and response to \(^{131}\)I-Lipiodol.

MATERIALS AND METHODS

Patient eligibility

The \(^{131}\)I-Lipiodol program was approved by the ethical committee of our hospital. Patients with HCC that required neo-adjuvant or palliative therapy were eligible. Diagnosis of HCC was made on the basis of histology, from liver biopsy or previous resection specimen (n=11) or a combination of underlying cirrhosis and findings on MRI (n=14). Exclusion criteria for \(^{131}\)I-Lipiodol therapy were 1) Karnofsky performance scale < 60, 2) tumour stage III according to Okuda criteria and 3) the presence of extra-hepatic metastases. Between June 1999 and September 2001 we included 24 patients: 14 patients received a \(^{131}\)I–Lipiodol instillation selectively to the common (“proper”) hepatic artery (“SEL” group); 10 patients received a hyperselective instillation in the right or left hepatic artery (“HYP-SEL” group). Hyperselective catheterisation and \(^{131}\)I–Lipiodol instillation was only performed if 1) the liver tissue outside the targeted territory did not have evidence of tumour by any imaging modality and thus all visible tumours would be targeted, and 2) hyperselective catheterisation was technically feasible. All patients had a progressive, unifocal or paucifocal HCC with less than 10 tumours with one or more of at least 1 cm in diameter to ensure proper CT graphic and scintigraphic definition.

Radiotherapy protocol

The \(^{131}\)I-Lipiodol used in this study (Lipiocis\(^{\circ}\), CIS bio international, France) has a specific activity of 854-870 MBq/g (23-23.5 mCi/g) and radioactive concentration of 1.11 GBq/ml (30 mCi/ml). After hepatic catheterisation, a total volume of 2-4 ml containing a mean of 1345 MBq (49,8 mCi) was instilled through the catheter. Patients were admitted in radio-isolation for 6 days.

Dosimetry of \(^{131}\)I-Lipiodol therapy

Individual \(^{131}\)I–Lipiodol activity was calculated in 28 tumours (20 patients: n=1 tumour; 4 patients: n=2 tumours) from biplanar anterior-posterior total body scintigraphies at day 7. Scan speed of the total body scans was varied per patient according to the count rate to avoid pixel overflow. Irregular regions of interest (ROI) were drawn over the liver, tumour(s), background and a syringe in a Perspex phantom containing a standard activity of \(^{131}\)I and geometric mean of the total counts anteriorly and posteriorly in the ROI’s recorded. Uniform attenuation correction was performed using a standard factor derived from a phantom experiment. From these data we derived the tumoral activity, which was expressed as a background and decay corrected, calibrated percentage of injected activity (% I.A.). Tumour diameter was measured from the Lipiodol-enhanced post-therapy computerized tomography (CT), taken 1-2 weeks after therapy.

Tumour volume in ml, \(V_{\text{tumour}}\), was calculated from the equation...
$V_{tumour} = \frac{4}{3} \pi r_{max} r_{\perp}^2$

where $r_{max}$ is the maximum radius of the tumour, and $r_{\perp}$ is the perpendicular radius [9]. In the “SEL” group a total of 16 individual tumours were studied, in the “HYP-SEL” group 12.

**Evaluation of endpoints**

Response was assessable in 24 of the 28 tumours (14/16 in the SEL group and 10/12 in the HYP-SEL). In 4 tumour no follow-up radiology was done. Maximum tumour diameter before $^{131}$I-Lipiodol therapy was compared with 6 weeks after, on MRI ($n=17$) or CT ($n=7$), depending on availability. Complete response (CR) was defined as the disappearance of all known lesions. Partial response (PR) was a decrease of 50% or more in tumour load and no appearance of new lesions or progression of any known lesions. Minor response (MR) was defined as a decrease in tumour load between 25% and 50% and no appearance of new lesions or progression of any known lesions. Responsive disease (RD) was defined as CR + PR + MR. Stable disease (SD) was defined as 25% decrease or increase in tumour load. Progressive disease (PD) was defined as an increase of the tumour load by more than 25% or the appearance of new lesions.

**Statistics**

Statistical comparison of several independent samples of each variable between subgroups (“SEL” and “HYP-SEL”) was performed by one-way analysis of variance by using the Kruskal-Wallis test, using a standard software package (SPSS for Windows software, version 10.0). Differences in discrete variables such as the occurrence of side effects was performed by cross-tabulation and a Fisher’s exact test.

**RESULTS**

**Patient characteristics**

Table 1 lists the clinical characteristics of the patient groups. None of these variables were significantly different between the SEL and HYP-SEL group, making both groups comparable in degree of liver cirrhosis and HCC.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SEL Group</th>
<th>HYP-SEL Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/4</td>
<td>8/2</td>
</tr>
<tr>
<td>Age $^1$</td>
<td>62.6 (52-72)</td>
<td>57.5 (47-71)</td>
</tr>
<tr>
<td>Child-Pugh classification: A/B/C</td>
<td>7/6/1</td>
<td>7/2/1</td>
</tr>
<tr>
<td>Liver volume (ml) $^1$</td>
<td>1015 (766-1237)</td>
<td>1235 (822-1654)</td>
</tr>
<tr>
<td>Okuda classification: I/II</td>
<td>11/3</td>
<td>6/4</td>
</tr>
<tr>
<td>Pre-therapeutic AFP (ng/ml) $^{12}$</td>
<td>1140.4 (2.5-11160)</td>
<td>156.4 (1.8-763)</td>
</tr>
<tr>
<td>Tumour volume (ml) $^1$</td>
<td>65.2 (3.8-268)</td>
<td>46.5 (1.8-157)</td>
</tr>
</tbody>
</table>

SEL, selective instillation; HYP-SEL, hyperselective instillation

$^1$ The mean value (with the range in brackets) is given

$^{12}$ AFP, alpha-fetoprotein.
**Tumoural uptake**

Figure 1A-D shows the relationships between tumour volume, tumoural percentage of $^{131}$I–Lipiodol uptake and tumour outcome. Overall, we observed tumour volumes between 1.8 and 274 ml and a $^{131}$I–Lipiodol uptake of 0.05-2.6 % of the injected dose per ml tumour volume.

**Figure 1A-D.**

Relationship between uptake percentage of $^{131}$I–Lipiodol per ml tumour volume with tumour response (1A, upper left), hyperselective or selective instillation (1B, upper right), tumour volume (1C, lower left) and between tumour response and tumour volume (1D, lower right).

A proportion of patients were treated before $^{131}$I-Lipiodol. In the HYP-SEL group, 4/10 had previously undergone intra-arterial chemo-embolisation, consisting of 1 mg/kg cisplatin and 25 ml (non-radioactive) Lipiodol. In two patients this targeted the same vascular territory as the $^{131}$I-Lipiodol therapy, 10 and 12 months after. In one patient chemo-embolisation of the left hepatic artery was carried out 7 months before, while $^{131}$I-Lipiodol therapy targeted the right hepatic artery. In another patient a segmental tumourectomy was followed by chemo-embolisation in the right hepatic artery at 39, 33 and 15 months, the last time with temporary closure by gel foam. At $^{131}$I-Lipiodol therapy the right hepatic artery was occluded and the right lobe (with tumour) was injected from a pancreatico-duodenal collateral. In the SEL group two patients received chemo-embolisation in the same vascular
territorium 6 and 12 months before $^{131}$I-Lipiodol therapy. Tumoural uptake was not significantly different between patients who had undergone previous chemo-embolisation (9 tumours, mean 0.56 +/- 0.63 % I.A./ml) or not (19 tumours, 0.54 +/- 0.59 % I.A./ml).

In the HYP-SEL group 6/10 patients received a 100% instillation in the right hepatic artery and 1/10 a 100% instillation in the left hepatic artery. In 1/10 patients instillation was done near the right hepatic artery with a negligible reflux to the left system and no visible uptake in the left lobe on post-therapeutic scintigraphy. In 2/10 patients a 100% instillation was done in a segmental, tumour-feeding artery. In the SEL group 11/14 patients received a 100% injection in the common (proper) hepatic artery; 2/14 were injected 50/50% and 1/14 75/25% in right/left hepatic artery. Figure 1B shows that there seems a trend towards a higher ranged uptake with HYP-SEL administration (0.72 +/- 0.65 % I.A./ml, versus 0.43 +/- 0.51 % I.A./ml) but this was not a statistically significant difference.

Overall, responsive disease (RD = CR+PR+MR) was seen in 10/24 evaluable tumours or 50% (5/10) of HYP-SEL tumours and 35% (5/14) of SEL tumours. CR was seen in 1 HYP-SEL tumour (10%), PR in 1 HYP-SEL tumour (10%) and 2 SEL tumours (14%) and MR in 3 HYP-SEL tumours (30%) and 3 SEL tumours (21%). Stable disease (SD) was seen in 1 HYP-SEL tumour (10%) and 4 SEL tumours (29%). Progressive disease (PD) occurred in 4 HYP-SEL tumours (40%) and 5 SEL tumours (36%). Differences between these subgroups were not significant. As can be seen from figure 1A, responsive disease (RD) was associated with a significantly higher percentage of $^{131}$I–Lipiodol uptake than stable or progressive disease (SD/PD). The difference between RD and SD/PD was highly significant (p=0.002). Figure 1C impressively shows that with increasing tumour volumes, the $^{131}$I–Lipiodol uptake per unit volume sharply decreases. Figure 1D shows that high volume tumours were significantly associated with progressive disease (p=0.008).

Figure 2 shows illustrative examples of $^{131}$I–Lipiodol distribution after selective (left) and hyperselective (right) instillation. Selective focal uptake is seen in both, with an uptake of 0.67% and 0.43 % I.A. / ml. tumour respectively.

**Side effects**

As far as possible differences in tolerance, the major side effect was a temperature rise in 8 therapies, i.e. 3/10 (33%) of HYP-SEL therapies and 5/14 (36%) of SEL therapies. Other observed side effects were nausea (HYP-SEL: n=1, SEL: n=2), abdominal discomfort or pain (HYP-SEL: n=1, SEL: n=2) and diarrhoea (SEL: n=1). More serious side effects observed were increasing liver failure (HYP-SEL: n=1), a hemorrhagic gastric ulceration (SEL: n=1) and a pneumonitis syndrome of undefined origin occurring one day after therapy (SEL: n=1). Overall, side effects were seen in 4/10 (40%) HYP-SEL patients and 9/14 (64%) SEL patients. This was not significant different.

In the 9 progressive tumours, 2 bi-lobar and 3 uni-lobar disease in the SEL group and 3 uni-lobar tumours in the HYP-SEL group progressed accordingly. However, in one patient of the HYP-SEL group with a left lobe tumour and 100% instillation in the left hepatic artery, two satellite tumours were found in the right lobe at follow-up.

**DISCUSSION**

By loco-regional arterial administration of $^{131}$I–Lipiodol and preferential trapping in pre-capillary vessels of hypervascularized HCC tumours, it is possible to deliver a high tumour dose compared to generally administered radionuclides. Bringing the catheter closer to the tumour and instilling a higher amount of activity to the tumour instead of more generally to a larger liver volume could further increase the radiation dose to the tumour. Several authors have used either a selective [9,10] or hyper-/superselective [11-13] treatment.
approach, but a comparison of both modalities has never been performed. Our study has the advantage that identical procedures were undertaken with either selective or hyperselective $^{131}$I–Lipiodol administration while clinical and tumoural characteristics were similar. The retrospective nature of the study was inevitable at this stage, as the treatment of choice was based on clinical grounds, i.e. tumour distribution and liver vasculature, principally not leaving any tumours untreated while being so selective as possible.

Our analysis of uptake percentage, progression and side effects suggest that hyperselective $^{131}$I–Lipiodol instillation, as opposed to selective administration, is not necessary to achieve a higher activity in tumours. There is a trend towards some higher response (50% versus 35%) and mean percentage of uptake (0.72 % I.A./ml versus 0.43 % I.A./ml) but this is not statistically significant. This could be different in a larger sample size but we anticipate that the lack of statistical difference in our patient group will imply an otherwise limited difference in a larger group, not justifying greater investments in time, resources and patient comfort associated with more complicated, hyperselective procedures. Alternative isotopes such as yttrium-90, that has been used in microspheres [14], and rhenium-188, that has been used experimentally [15], do not carry high-energetic gamma rays and thus higher activities could be given more easily without radioprotection problems. Additionally, these isotopes have higher energy therapeutic beta rays, making the absorbed tumour dose higher in larger, visible tumours.

Moreover, we postulate that an activity that is slowly injected in the common proper hepatic artery is by a large proportion “sucked” into the tumour by its influence of neovascularisation and parasitic increased flow extending to the large vessels in which the $^{131}$I–Lipiodol is injected. Additionally, normal vessels may react to $^{131}$I–Lipiodol injection by vasoconstriction while pathological vessels do not, thereby increasing the gradient towards pathological liver segments anyway, regardless of hyperselective or selective administration. Besides this, there is a wide variation in normal liver vasculature, most importantly of the right hepatic artery, as well as pathological supply due to vascular anomalies such as arteriovenous malformations and portal hypertension or thrombosis. These conditions are not avoided by the selectivity of administration. Previous chemo-embolisation, although with an angiographically visible effect on the tumour vasculature in some, was not associated with lower uptake values, a fact possibly related to the fact that the embolisation was not permanent.

An important additional issue is the need for prophylactic diffuse liver treatment by selective injection into both hepatic arteries to reduce the risk of proliferating disease [16]. Raoul and co-workers described a case in which, after hyperselective instillation, a minute nodule outside the treated territory strongly progressed after therapy [17]. In our study, we had a similar situation of progression outside the treatment territory in one of the HYP-SEL patients, although no visible tumours were untreated in this case and a PD was also seen within the treatment territory. This is a further argument against hyperselectivity.

The present study does show that responsive disease is very much associated with higher $^{131}$I–Lipiodol uptake. This is to an extent in agreement with Novell et al [9] who found a higher tumour dose in patients with PR, but also in SD, contrary to PD. We also found high volume tumours invariably associated with progressive disease. This finding is in agreement with Yoo et al [11] who observed no meaningful tumour size reduction above a tumour diameter of 6 cm (approx. 113 ml) and Risse et al [18] who saw no responses in tumours larger than 8 cm (approx. 268 ml). Our study explains this size phenomenon as a manifestation of the same dose-response effect, as the incremental $^{131}$I–Lipiodol uptake was shown to sharply decrease with tumour volume. Importantly, this applied regardless of selectivity of administration. Our quantification of tumour dose, which only considers the tumoural % I.A./ml after one week, was chosen as a simple and straightforward method for the purpose of this study. Essential corrections were made for background activity similar to
others [9], standard uniform attenuation from a representative on-site phantom simulation, and count rate of the particular patient. Some authors [19] have used a tumour-to-non-tumour liver ratio on planar scintigraphy after 8 days, but this does not take uptake per unit tumour volume into consideration. Others [9-11, 13] have calculated a tumoural absorbed dose in Gray on the basis of the MIRD principle [20]. However several assumptions in the MIRD model are not applicable, i.e. a uniform distribution [21] and an uptake phase that can be ignored [22]. We used CT to measure the volume of the tumours because, instead of MRI, we could better delineate the area of Lipiodol uptake as the most accurate radiation distribution volume.

In conclusion, our study does not support the general use of hyper- or superselective intra-arterial \(^{131}\)I–Lipiodol administration. This result may be extrapolated to similar types of intra-arterial, loco-regional hepatic radionuclide therapy. The prominent dose-response relationship with tumour size, independent of selectivity of catheterisation, suggest moreover that large sized tumours should be treated additionally or alternatively.
Figure 2A-B
Examples of posttherapeutic anterior and posterior scintigraphies 7 days after $^{131}\text{I}$–Lipiodol.
Selective (2A, left) or hyperselectively (2B, right) administration. Percentage of injected activity per volume tumour was 0.67% and 0.43% respectively.
REFERENCES


Section II:

Thyroid function and pre-medication
Paper 4:

$^{131}$I therapy with rhTSH pre-medication
TUMOUR DOSIMETRY AND RESPONSE IN PATIENTS WITH METASTATIC DIFFERENTIATED THYROID CANCER USING RECOMBINANT HUMAN THYROTROPIN BEFORE RADIOIODINE THERAPY


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European Journal of Nuclear Medicine and Molecular Imaging 2002; 30: 367-373

Purpose. The development of recombinant human thyrotropin (rhTSH) has given clinicians new options for diagnostic follow-up and treatment of patients with differentiated thyroid cancer (DTC). This paper evaluates the tumour dosimetry and response following $^{131}$I treatment of metastatic thyroid cancer patients after rhTSH stimulation instead of classical thyroid hormone withdrawal-induced hypothyroidism.

Methods and materials. Nineteen consecutive $^{131}$I treatments in 16 patients were performed after rhTSH stimulation. All patients had undergone a near-total thyroidectomy followed by an ablative dosage of $^{131}$I. They all suffered from metastatic or recurrent disease showing tumoral $^{131}$I uptake on previous post-treatment scintigraphy. Dosimetric calculations were performed using $^{131}$I tumour uptake measurements from post-treatment $^{131}$I scintigrams and tumour volume estimations from radiological images. Response was assessed by comparing pre-treatment serum thyroglobulin (Tg) level with the Tg level 3 months post-treatment.

Results. In 18 out of 19 treatments, uptake of $^{131}$I in metastatic or recurrent lesions was seen. The median tumour radiation dose was 26.3 Gy (range 1.3–368 Gy), and the median effective half-life was 2.7 days (range 0.5–6.5 days). Eleven of 19 treatments (10/16 patients) were evaluable for response after 3 months. $^{131}$I therapy with rhTSH resulted in a biochemical partial response in 3/11 or 27% of treatments (two patients), biochemical stable disease in 2/11 or 18% of treatments (two patients) and biochemical progressive disease in 6/11 or 55% of treatments (six patients). Our study showed that although tumour doses in DTC patients treated with $^{131}$I after rhTSH were highly variable, 45% of treatments led to disease stabilisation or partial remission when using rhTSH in conjunction with $^{131}$I therapy, without serious side effects and with minimal impact on quality of life.

Conclusion. RhTSH is therefore adequately satisfactory as an adjuvant tool in therapeutic settings and is especially suitable in advanced recurrent or metastatic DTC patients who may be intolerant to TSH stimulation by levothyroxine withdrawal.
INTRODUCTION

Radioiodine is recommended extensively as a treatment modality for differentiated thyroid cancer (DTC)\[1\]. Iodine-131 (\(^{131}\)I) treatment of patients with metastatic DTC requires withdrawal of thyroid hormone (i.e. levothyroxine or L-T4) suppression therapy for 4–6 weeks to raise the endogenous thyroid stimulating hormone (TSH) level and thereby maximise selective radioiodine uptake by neoplastic cells. However, withdrawal of L-T4 induces symptoms of hypothyroidism that physically and psychologically constrain active people for prolonged periods, causing major disruption of the patient’s family, social and work life. This is particularly important considering that most patients with DTC are middle-aged and active \[2\]. A study by Dow et al. quantified the degree of symptoms and demonstrated that patients are significantly affected by hypothyroidism \[3\]. Additionally, hypothyroidism increases the risk of cardiac complications \[4\], may increase the risk of thyroid cancer growth \[5\] and is potentially a lethal factor in patients in very poor physical condition \[6\]. Furthermore, elderly patients may be especially prone to insufficient generation of adequate endogenous TSH levels. The availability of recombinant human TSH (rhTSH) provides an alternative means to elevate the TSH level without inducing hypothyroidism. In March 2000, the European authorities approved the clinical use of rhTSH to elevate TSH levels in patients on L-T4 suppressive therapy prior to thyroglobulin (Tg) testing in combination with diagnostic \(^{131}\)I scintigraphy. Successful studies on this diagnostic use of rhTSH \[7,8\], confirming the safety and efficacy of rhTSH in conjunction with \(^{131}\)I, have led to an increased interest in the use of rhTSH in preparing patients with metastatic or recurrent DTC for \(^{131}\)I therapy. Up to now, reports on the therapeutic efficacy of \(^{131}\)I after rhTSH stimulation have included only small series of patients without dosimetric results \[9,10\] and two single case reports with absorbed tumour dose \[11,12\]. The aim of this study was to evaluate the use of \(^{131}\)I therapy after rhTSH stimulation for metastatic and/or recurrent DTC in patients who may be especially intolerant to hypothyroidism, by measuring its efficacy using tumour dosimetry.

MATERIALS AND METHODS

Patient eligibility

In total, 16 consecutive patients were treated in two academic hospitals. Eleven patients (treatments 1–14) were treated at the University Medical Center Utrecht (The Netherlands) and five patients (treatments 15–19) were treated at the Ghent University Hospital (Belgium) between May 2000 and March 2002. Two patients were treated more than once (treatments 3, 6 and 10 and treatments 8 and 13), resulting in 19 treatments. Patient characteristics are shown in Table 1. All patients included in the study protocol previously underwent total or near-total thyroidectomy followed by radioiodine ablation. Post-ablative or post-therapy scintigraphy demonstrated uptake in metastases and/or local recurrences. After \(^{131}\)I ablation, 13 patients received one or more high therapeutic dosages of \(^{131}\)I, showing \(^{131}\)I uptake in recurrent or metastatic thyroid cancer tissue. The study was approved by the local ethics committee and all patients gave written informed consent.

Radionuclide therapy protocol

Patients were instructed to follow a low-iodine diet for 1 week (5 days before \(^{131}\)I administration and 2 days after \(^{131}\)I administration). RhTSH (0.9 mg)(Thyrogen, Genzyme Corp., Cambridge, Mass., USA) was given on two consecutive days, followed by a high therapeutic dosage (7,400 MBq) of \(^{131}\)I on the third day. Before the first injection of rhTSH (day 1), at administration of the therapeutic dosage of \(^{131}\)I (day 3) and 3 months after therapy, blood samples were taken for measurement of serum TSH, thyroglobulin and anti-thyroglobulin antibodies (Roche, Mannheim, Germany for the Utrecht patients; Immulite, BPC, The Netherlands for patients treated in Ghent).
Dosimetry of $^{131}I$ therapy

Post-treatment whole-body scintigraphy was performed with a dual-headed gamma camera (Vertex, ADAC) equipped with a high-energy parallel-hole collimator. Images were acquired in the whole-body acquisition mode with a scan speed of 15 cm/s. The energy window of both detectors was set at 360 keV with a window width of 15%. Simultaneously with patient scanning, a perspex phantom with a standard of known radioactivity was scanned whilst positioned between the legs of the patient in order to convert counts to radioactivity (MBq’s). The standard consisted of a 10-ml vial filled with a radioactive liquid of $^{131}I$ and stored in a perspex phantom. The phantom was hexagonal shaped in the transverse plane, with a distance of 14.2 cm to opposite corners. The axial length of the phantom was 15.4 cm. This geometry simulated the scatter process in the patient studies and gave a reasonable estimate of the detector efficiency. The anterior and posterior image data were stored in the computer for further analysis. Regions of interest were drawn over the metastatic lesions visible on radiological images and over a representative background area. In addition, regions were drawn over the standard and corresponding background area. The geometric mean ($N_{gem}$) of the net anterior and posterior lesion counts was calculated and converted to the real lesion counts by the following equation:

$$N_0 = N_{gem} \times \exp(\mu t/2) \times (\mu t/2)/\sinh (\mu t/2)$$  \hspace{1cm} (1)

where $N_0$ is the real number of counts, $t$ is the patient thickness, and $ft$ is the lesion thickness.

The same procedure was followed for the measured counts of the standard. The radioactivity in the lesion was calculated as follows:

$$A_{lesion}/A_{standard} = N_0_{lesion}/N_0_{standard}$$
$$A_{lesion} = A_{standard} \times N_0_{lesion}/N_0_{standard}$$  \hspace{1cm} (2)

Patients were scanned at 24, 48, 120, 216 and 336 h after injection of $^{131}I$ according to the described scanning procedure and the radioactivity calculated. Assuming an exponential washout for the iodine, the lesion radioactivity at these time points was fitted to a mono-exponential time function. The coefficient of this fitted function is the initial radioactivity $A_0$ (MBq) divided by the lesion mass. This results in the initial radioactivity concentration $C_0$ (MBq/g). The effective half-life $T_{eff}$ (days) can be calculated from the exponent.

Using the method described by Schlesinger et al. [13], the lesion dose was calculated as follows:

$$D = 1.44 \times T_{eff} \times 24 \times 0.11 \times C_0 \text{ (Gy)}$$  \hspace{1cm} (3)

where $T_{eff}$ is the effective half-life (days) and $C_0$ is the initial radioactivity concentration (MBq/g). We assumed that all non-penetrating radiation of $^{131}I$ (beta particles and conversion electrons) was completely absorbed in the lesion tissue and that all penetrating radiation (364 keV photons) had no contribution. The mass of residual or metastatic thyroid tissue was determined using radiological imaging (ultrasound $n=4$; chest X-ray $n=7$; CT $n=14$). Tumour volume was calculated using a spherical model where mass ($g$) = $4/3\pi r^3$. In cases where the lesion was more oval, the formula was modified for ellipsoids. As described by Furhang et al.[14], we calculated the absorbed dose to small lesions using an assumed 1 g mass, which would conservatively underestimate the tumour dose. Overestimation of the tumour absorbed dose may occur in tumours with a diameter of <0.5 cm [13]. In our patients the small lesions were all larger than 0.5 cm.

Evaluation of endpoints

Tg levels during L-T4 suppressive therapy (Tg-on) on day 1 were compared with Tg-on levels 3 months after the therapeutic dosage of $^{131}I$. Biochemically complete response (CR) was defined as the presence of undetectable Tg levels at 3 months (<1 µg/l for the Roche kit and <0.5 µg/l according to the Immulite kit). Partial response (PR) was defined as a >25% decrease in the Tg level, stable disease (SD) as a level between +25% and -25%, and progressive disease (PD) as a >25% increase in the Tg level. In cases of serum antithyroglobulin antibodies, Tg levels were not assessable.
Table 1
Patient characteristics.

<table>
<thead>
<tr>
<th>Treatment course</th>
<th>Primary TNM staging</th>
<th>Sex</th>
<th>Age at time of therapy</th>
<th>Type of thyroid cancer</th>
<th>Number of previous $^{131}$I therapies (cumulative dosage)</th>
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</table>

* patient entered study protocol 3 times, * patient entered study protocol 2 times
RESULTS

Side effects

Pre-treatment with rhTSH was very well tolerated. No serious side effects were noted. One patient (treatment 19) experienced increasing leg weakness and dysaesthesia probably attributable to a metastasis to a dorsal vertebra with spinal compression (Common Toxicity Criteria or CTC grade 2); corticosteroid administration quickly resolved these complaints. Mean serum TSH level at the time of the $^{131}$I administration was 141 mIU/l (range 51–258 mIU/l).

Tumour dosimetry

Tumour dosimetry is shown in Table 2. Dose calculation revealed a median tumour dose of 26.3 Gy (range 1.3–368 Gy). The median biological half-life was 4.1 days (range 0.6–34.7 days) and the median effective half-life was 2.7 days (range 0.5–6.5 days). A tumour absorbed dose >80 Gy was seen in only 5/25 tumours; accordingly, there was a dose of less than 80 Gy in 20/25 tumours. In one patient (treatment 7), it was impossible to calculate the dose to the metastases because of absence of $^{131}$I uptake in these metastases. It should be noted that this patient had undergone two previous radioiodine therapies that showed $^{131}$I uptake in lung and liver metastases on post-treatment scintigraphy.

Therapy response

Table 3 shows the results of the therapy. Eleven treatments (ten patients) were evaluable for response after 3 months. Eight treatments could not be evaluated for the following reasons: in five treatments (three patients), TgAb interfered with the correct interpretation of Tg levels; one patient (treatment 16) had a CR after additional surgery within the 3-month interval, and two patients (treatments 18 and 19) died prematurely within 3 months. Of the latter two patients, one (treatment 18) died of acute renal failure of unknown cause not related to the thyroid carcinoma, while the other (treatment 19) died of an unknown cause, possibly related to progressive thyroid carcinoma. $^{131}$I therapy with rhTSH resulted in a biochemical PR in 3/11 or 27% of treatments (two patients) and biochemical SD in 2/11 or 18% of treatments (two patients). PD was found in 6/11 or 55% of treatments (six patients). It should be noted, however, that none of these latter patients had a tumour dose of more than 30 Gy.
Table 2.
Tumour dosimetry

<table>
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<tr>
<th>Treatment course</th>
<th>Site of Metastatic Lesions</th>
<th>Radiological Imaging</th>
<th>Mass (gram)</th>
<th>Biological T1/2 (days)</th>
<th>Effective T1/2 (days)</th>
<th>C₀ (MBq/g)</th>
<th>Dose (Gy)</th>
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Table 3.
Outcome of $^{131}$I therapy with rhTSH

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<th>Anti-Tg pre-therapy $^a$</th>
<th>Tg-on 3 mts follow-up $^b$</th>
<th>Anti-Tg 3 mts follow-up $^b$</th>
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$^a$ Thyroglobulin and anti-Tg measurements (µg/l).

$^b$ SD, stable disease, PR, partial response, PD, progressive disease, NA, not assessable.
DISCUSSION

Several studies have confirmed that rhTSH promotes $^{131}$I uptake by normal thyroid residues, tumour remnants, recurrences, lymph node metastases and/or distant metastases of DTC in euthyroid patients during L-T4 suppression therapy [8,15]. We found a partial response in 27% (3/11 treatments) of the treatments. These results are somewhat less favourable compared with results found in other published studies. However, most of our patients were suffering from large metastases that may become radioresistant [16]. The inclusion of a control group of $^{131}$I therapy after L-T4 withdrawal would allow for better judgement of the relative merits of rhTSH, but such a group was not included at this stage because all patients were eligible for rhTSH preparation owing to their poor general condition or tumour-related limitations. Lippi et al. [9] reported the therapeutic use of rhTSH in the treatment of 12 patients suffering from metastatic DTC. Three to 12 months after therapy, serum Tg levels had fallen in four patients, whereas they had increased in another four patients; Tg levels remained stable in two patients. Luster et al. [10] described the use of rhTSH in $^{131}$I therapy in 11 patients. Five of 11 (45%) patients had decreased post-therapy Tg levels of at least 30% when compared with pre-therapy levels. In follow-up visits an additional three patients (27%) showed marked clinical improvement or decreased or stabilised tumour burden in whole-body scans when compared with pre-therapy scans. The other three patients died of progressive disease within 2 months, before follow-up assessment.

Maxon et al. [17] reported that 98% of tumours with an absorbed radiation dose of more than 80 Gy responded, whereas for radiation doses of less than 80 Gy the figure was only 20%. None of those with a radiation dose of less than 35 Gy responded. The importance of a high radiation dose was confirmed by our study, which showed a higher radiation dose in the group of patients with PR after $^{131}$I therapy. However, we also observed that lesions which seem to have a relatively low radiation dose may still regress following therapy. For example, in one of our patients (treatments 8), the tumour doses as measured in three metastatic lung lesions (fig.1A) varied from 41.4 to 87.1 Gy, i.e. below the desired 80 Gy in two out of three measured lesions. In this patient, response could be confirmed by a chest X-ray, which indicated shrinking of all lung metastases (fig.1B,C).

We found a median effective half-life of $^{131}$I of 2.7 days (range 0.5–6.5 days). Maxon et al. [17] found an effective half-life of 3.3±1.3 days for metastatic lesions of papillary DTC that responded to $^{131}$I treatment and 1.9±0.9 days for those that did not respond to treatment. These half-lifes are comparable to our data, suggesting that iodine kinetics in thyroid cancer tissue after rhTSH stimulation are not particularly di

There are several possible explanations for the relatively low tumour radiation dose in most of our patients. In hypothyroid patients, renal function and the renal clearance of iodine are markedly decreased, resulting in about 50% decrease in renal clearance of $^{131}$I and 50% increase in the bio-availability of $^{131}$I as compared with euthyroid patients receiving rhTSH [18]. Another explanation could be the continuation of L-T4 medication. Although all patients were advised to change to a low-iodine diet 5 days before treatment and continue on the diet 2 days after administration of $^{131}$I, it has to be recognised that thyroid hormone is a source of iodine. This could potentially reduce uptake in thyroid (cancer) tissue. Goslings [19] found that tumour uptake of radiiodine at 24 h increased by approximately 80% on a low-iodine diet,with an approximate 20% increase in the biological half-life of radiiodine in the tumour. The resulting estimates of radiation dose to tumour indicated approximately a doubling when the patients were prepared with the low-iodine diet. The recommended daily iodine intake varies between 150 and 300 µg. L-T4 (200 µg) contains 126 µg iodine, whereas triiodothyronine (T3, 50 µg) contains only 28 µg iodine. This raises the question if the use of
triiodothyronine might be preferable, since it contains three atoms of iodine compared with four in L-T4 and the daily dose is usually 25%. Alternatively, one could consider stopping L-T4 for a short time to minimise iodine intake [20,21]. Furthermore, variation in tumour characteristics in different patient groups, i.e. tumoural de-differentiation and consequently decreased radiiodine uptake, may be an important factor. This aspect could be particularly relevant in our patient group with advanced thyroid carcinoma. It also raises the question as to the potential influence of previous \( ^{131}\text{I} \) therapies on radiation dose. In one patient (treatments 8 and 13), a significantly lower tumour radiation dose was measured the second time she received therapy (table 2). This also applies to the other patient who received multiple therapies (treatments 3, 6 and 10). In the aforementioned patient we measured a decreasing tumour absorbed dose in the later therapies (7.0 Gy, 3.9 Gy and 3.5 Gy in successive \( ^{131}\text{I} \) therapies). CT imaging performed before the therapies showed an increase in size of the local recurrence. In the other patient CT indicated a decrease in tumour size as possible explanation. Further studies may indicate the importance of these factors in the use of rhTSH with \( ^{131}\text{I} \) treatment.

It is especially important to realise that in our difficult patient group, side effects were minimal and not serious. This should be viewed as a decisive advantage in patients with advanced DTC, who have an overall poorer general condition and shorter symptom-free survival.

In conclusion, our study showed that tumour doses in metastases of DTC patients treated with \( ^{131}\text{I} \) after rhTSH are highly variable. Still, in 45% of treatments a biochemical stabilisation or remission was observed. Further studies are warranted to examine whether radioiodine uptake after rhTSH stimulation can be modulated in order to further optimise this treatment, which holds great promise for probably all DTC patients treated with \( ^{131}\text{I} \). In our opinion, rhTSH can be used effectively in patients with advanced recurrent or metastatic DTC who would otherwise not have been able to receive \( ^{131}\text{I} \) therapy owing to either an inability to tolerate discontinuation of thyroid hormones or ineffectiveness of the withdrawal of L-T4 suppressive therapy in raising endogenous TSH.
Fig. 1A.
Whole body scintigram 48 hours after $^{131}$I therapy showing multiple lung metastases in treatment 8. Arrows indicated the tumours of which the radiation doses were calculated.
Fig. 1B.
Lung metastases before $^{131}$I therapy. Decrease in size of several lung metastases after therapy in treatment 8. Radiation doses were 55.7, 41.4 and 87.1 Gy for the upper, middle and lower tumour. Note that the largest tumour decrease is not in the tumour with the highest radiation dose.
REFERENCES


Paper 5:

Thyroid function after potassium iodide pre-medication in $^{131}$I-mIBG therapy
Purpose. In $^{131}$I-MIBG therapy, $^{131}$I-iodide can be released from the $^{131}$I-MIBG molecule. Hypothyroidism might result from the undesirable irradiation of the thyroid gland. To prevent this, stable iodide such as potassium iodide (KI) is given to oversaturate the thyroid before $^{131}$I-MIBG is administered.

Methods and materials. In the present study, the incidence of hypothyroidism (elevated TSH) was correlated with the thyroidal uptake of $^{131}$I and dose (MIRD dosimetry) after 35 individual treatments in 10 patients. $^{131}$I-MIBG therapy was performed using a modified dosage of 1.9-11.1 GBq (50-300 mCi) IV. Pre-medication with KI was done as recommended with a dose of 100 mg KI orally from 2 days before until 4 weeks after $^{131}$I-MIBG.

Results. The absorbed thyroidal dose amounted to a very variable range of 0.2 (patient # 1) up to 30.0 (patient 3) Gy with 7.1+/−7.9 Gy per treatment and 24.1+/−19.2 Gy per patient (mean+/−SD), despite the same and compliantly taken KI pre-medication protocol. Up to now, 4/10 or 40% of patients have developed hypothyroidism after a mean follow-up period of 11 months and a mean total administered dose of 18.7 GBq (505 mCi). A trend towards higher thyroidal doses was seen in the hypothyroid patients.

Conclusion. This study observes a general high inter- and intra-individual variability in radioiodide uptake in the thyroid after $^{131}$I-MIBG therapy despite KI pre-medication, as well as possible occurrence of hypothyroidism. A dose-response relationship needs confirmation on a larger cohort of patients to reach statistical value. An alternative thyroid cytoprotection strategy for possible long-term survivors may be considered.
INTRODUCTION

Radionuclide therapy with iodine-131-metaiodobenzylguanidine (\(^{131}\)I-MIBG) is a valuable treatment for neuro-endocrine tumours such as neuroblastoma and carcinoid tumour [7]. In view of the positive results, its wider application as an adjuvant modality to surgery and chemotherapy, especially in neuroblastoma, is being proposed [2,3].

The best known side effect is hematotoxicity, especially trombocytopenia, occurring shortly in the weeks following administration. Another possible side effects may be thyroidal damage caused by the unintentional irradiation of free \(^{131}\)I uptake dissociated from the \(^{131}\)I-MIBG complex. To limit thyroidal uptake of this free \(^{131}\)I, patients are pre-medicated with stable, non-radioactive iodide such as potassiumiodide (KI) [4] which creates an iodide oversaturation in the thyroid down-regulating the iodide uptake mechanism of the thyroid. In the UKCCSG study of \(^{131}\)I-MIBG therapy in neuroblastoma [5] it was found that the injected therapeutic activity included an average of 4.5\% free iodide corresponding with an activity of 0.5-1.0 GBq (13-27 mCi) thus emphasizing the importance of thyroid blockade. There is one study [6] systematically evaluating thyroid function in \(^{131}\)I-MIBG treated patients and this reported a high incidence of 82\% hypothyroidism in 2 year surviving neuroblastoma patients. It can be argued that this is acceptable with respect to the bad prognosis of patients while KI is well tolerated without side effects and hypothyroidism easily treated. However, in an upfront use of \(^{131}\)I-MIBG with extended survival of some of the patients, it is likely that long-term organ toxicities should be increasingly taken into consideration [7]. In the present study, we evaluated for the first time the observed thyroidal uptake as well as calculated thyroidal radiation dose in patients receiving repetitive \(^{131}\)I-MIBG treatments while on KI thyroid protection, to further substantiate the supposed correlation with the occurrence of hypothyroidism.

MATERIALS AND METHODS

Patient eligibility

Between February 1997 and November 1999 we treated 20 patients with \(^{131}\)I-MIBG with a total of 52 administrations. Ten patients with 35 treatments could be included for the analysis in the present study on the basis of 1) interpretable scintigraphic data for thyroid dosimetry, 2) TSH measurements during and after \(^{131}\)I-MIBG treatment and 3) survival for at least 3 months after repetitive \(^{131}\)I-MIBG treatments. Nine patients had to be excluded because of inadequate survival and one patient for non-compliance to the KI pre-medication protocol. In two of these patients thyroid dosimetry was unreliable because of tumour activity superimposing the thyroid while in one patient with a medullar thyroid carcinoma the thyroid was deliberately not blocked.

Radionuclide therapy protocol

Iodine-131-MIBG therapy was performed using a modified fixed dosage of 1.9-11.1 GBq (50-300 mCi) taking in account body weight and age, number of lesions, bone marrow involvement and kidney function and using a variable interval of 1-3 months between treatments according to the degree of hematotoxicity and (recurring) symptoms. The product was administered over a 2-hour intravenous infusion. Specific activity of the product was 1,48 GBq/mg. Efficiency of labeling was randomly checked with the use of instant thin layer chromatography (ITLC), allowing less than 5\% of free I-131-iodide.

Thyroid protection scheme

Subsequent uptake of radioiodide by the thyroid gland was inhibited by oral intake of 100 mg (50 mg for children under 5 years) potassiumiodide (KI) starting 2 days before therapy until 4 weeks after, slightly modified according to the guidelines of the European Association of Nuclear Medicine [4] which subscribes 100-200 mg 1 day before until 2 weeks after. Urinary iodide during KI administration was assessed randomly in all patients at least ones and in case of doubt of compliance, on the day of hospitalization for \(^{131}\)I-MIBG therapy and on a single urine sample, using an oxidation method according to Sandell-Kolthoff (Technicon, USA).

Thyroid function tests

Thyroid stimulating hormone (TSH) as well as free tri-iodothyronine (FT3) and thyroxin (FT4) were determined at least once during as well as in 3-6 months interval after \(^{131}\)I-MIBG therapy, using a standard electro-chemoluminescence method (Elecsys, USA). Hypothyroidism was defined as a raised TSH (>4.2 µU/ml)
with or without depressed FT4 (< 1.0 ng/dl) and/or FT3 (< 1.8 pg/ml). Thyreoglobulin and thyreoperoxidase antibodies were determined by chemoluminescence method (Immulite, U.S.A.). Values of respectively 0-40 U/ml and 0-35 U/ml were regarded as normal.

**Dosimetry of thyroidal radio-iodine uptake**

Cumulative 131I activity of the thyroid and whole-body was calculated from the area under the time-activity curve generated by three consecutive whole-body scintigraphy scans (at 2-3, 6-9 and 10-15 days) using a region of interest drawing. The geometric mean of the total counts in the anterior and posterior scans were corrected for background activity and calibrated by a I-131 standard of known activity contained in a phantom of similar geometry as the neck. No attenuation correction was employed. Absorbed dose to the thyroid and whole-body was calculated according to the Medical Internal Radiation Dose or MIRD formulism (MIRDDOSE© version 3.0, Oak Ridge, USA) using the cumulative activity generated from the scans and weight-adapted S-values obtained by a fit through the values of the different phantoms of various ages considered in the program.

**RESULTS**

Patients in this study consisted of 7 children and 3 adults while the indications for 131I-MIBG treatment were diffuse (table 1: patients # 1,2,10) or residual abdominal (patients # 3-5) stage IV neuroblastoma, carcinoid syndrome (patients # 6,7) or malignant pheochromocytoma (patients # 8,9). These patients received an average of 3.5 treatments; one patient (# 5) received two, five patients (# 2,4,6-8) three, three patients (# 1,9,10) four and one patient (# 3) six treatments.

The administered dose per treatment in this group varied between 1.9 GBq (50 mCi; neuroblastoma with heavily involved bone marrow and high transfusion need) and 11.1 GBq (300 mCi; maximum administered dose; malignant pheochromocytoma). The interval between treatments varied between 4 weeks (patient 1: palliative treatment for frequently recurring bone pain) and 20 weeks (patient 3: palliative treatment for less frequent recurring abdominal complaints). The total administered activity in the group ranged from 5.5 to 33.3 GBq (150-900 mCi) with a mean of 18.7 GBq (505 mCi) per patient or 5.3 GBq (144 mCi) per treatment.

The absorbed thyroidal dose amounted to a very variable range of 0.2 (patient # 1) up to 30.0 (patient # 3) Gy with 7.1 +/- 7.9 Gy per treatment and 24.1 +/- 19.2 Gy per patient (mean +/- SD), despite the same and compliantly taken KI pre-medication protocol. As can be seen from table 1, even within a same patient variable thyroidal doses were measured at different times despite similar preparation with KI (for example patients # 1 and 3).

Overall outcome to date is: 10% (1/10) complete remission (CR; patients # 4), 40% or 4/10 partial remission (PR; patients # 6-9), 10% or 1/10 stable residual disease (SRD; patient # 5), 10% or 1/10 progressive disease (PD; patients # 2,3) and 30% (3/10) patients dead by disease (DD; patient # 1,2,10). Up to now, 4/10 or 40% of patients have developed hypothyroidism after a mean follow-up period of 11 months after the first 131I-MIBG therapy.
## Table 1.

Patient characteristics

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**Notes:**
- Patient number: 1-12 / S: male; F: female / Age in years at first treatment
- Pathology: NB=neuroblastoma; CA=carcinoid syndrome; FC=malignant feochromocytoma
- Administered activity of $^{131}$I-MIBG in mCi; time interval with previous therapy in brackets
- Absorbed thyroidal radiation dose in Gy
- Absorbed whole-body radiation dose in Gy
- Outcome of patient to date: CR complete remission, PR partial remission, SRD stable residual disease, PD progressive disease, DD death by disease; number of months of evaluation after first $^{131}$I-MIBG treatment in brackets
- Outcome of thyroid to date: Hypo=hypothyroidism; Eu=euthyroidism; Number of months of evaluation after first $^{131}$I-MIBG treatment in brackets
The first patient is patient #1 in whom hypothyroidism was diagnosed 1 month after 4 treatments with a cumulative thyroidal dose of 19.8 Gy in 4 months. TSH at that time was > 100 µU/ml together with a low FT4 of 0.4 ng/dl and low FT3 of 1.1 pg/ml. Because of the progressive diffuse disease and short term survival expectancy thyroid hormone substitution was not initiated. The second patient, #3 became hypothyroid 1 month after the last treatment with a TSH of 28.7 µU/ml and normal FT4 (1.2 ng/dl) and FT3 (2.3 pg/ml). Two weeks later TSH was 66.2 µU/ml with a low FT4 (0.8 ng/dl) and yet normal FT3 (2.3 pg/ml). At that time substitution was started with subsequent normalization of thyroid hormone values. The total cumulative thyroid dose at that point was 56.4 Gy in 19 months but is probably underestimated because dosimetry data on four preceding treatments elsewhere are lacking (KI protection equally performed). The third, patient #10 became hypothyroid 1.5 month after 3 treatments with a cumulative thyroidal dose of 36.0 Gy in 4 months. At the time of diagnosis he had a raised TSH of 5.06 µU/ml but normal FT4 (1.7 ng/dl) and FT3 (2.9 pg/ml). This was not treated and the patient died 1.5 months later. The fourth patient #6 showed a raised TSH (5.5 µU/ml) with normal FT4 (0.9 ng/dl) and FT3 (2.4 pg/ml) 7.5 months after a cumulative thyroidal dose of 22.3 Gy in 5.5 months. Thyroid hormone substitution was started and TSH returned to normal. Figure 2 plots the cumulative total amount of thyroidal dose received in Gy in the euthyroid (n=6) and hypothyroid (n=4) group.

Anti-thyroid (anti-thyreoglobulin and anti-thyreoperoxidase) antibodies were negative in all four hypothyroid cases at the time of diagnosis of hypothyroidism (<10 U/ml and <20 U/ml respectively, normal values 0-40 U/ml and 0-35 U/ml).

A total of 10 urinary iodide measurements were made. All indicated a massive iodide overload with a mean of 14300 µgr/dl and a rather wide range of 1200-736-20 µgr/dl, especially also in the patients who developed hypothyroidism (14300, 10000, 2900 and 4050 µgr/dl respectively).

DISCUSSION

The principal finding of this study is the observation of a high inter- and intra-individual variability in thyroidal radioiodine uptake seen after therapeutic 131I-MIBG administrations, despite compliantly taken cold iodide pre-medication.

The protection of the thyroid by cold iodide pre-medication may be the resultant of several interacting mechanisms involved in the thyroid homeostasis: 1) the inhibition of iodide oxidation and tyrosine iodination (“organification”) by an acute increase of serum iodide, commonly called the “acute Wolff-Chaikoff effect” [8], which is however a transient phenomenon lasting approximately 48 hours; 2) its so-called “escape phenomenon”, most likely caused by a decrease in the active transport of excess plasma iodide into the thyroid [9]; 3) a flooding effect of the massive amount of circulating cold iodide, diluting the relatively minute amounts of radioiodine and its portion of thyroidal uptake. However, while radioiodine uptake relatively decreases, the absolute uptake calculated from thyroid radioiodine and serum or urinary iodide values may still be significant in situations of iodine overload. In patients with Graves’ hyperthyroidism undergoing a routine radioiodine uptake study, it was found that 24 hours radioiodine uptake still averaged 20% despite chronic administration of 10 mg of cold iodide while the proportion of non-organic, unbound radioiodine was only 14% of the total thyroidal content of radio-iodide [10]. This illustrates that thyroid blocking may never be complete and may also explain why perchlorate, another thyroid protective anion used in radionuclide therapy which washes out the non-organic (radio-)iodine, may not have an (additional) benefit. Picco et al [6] used a Lugol’s solution of 2-3 mg/kg/day 7 days before until 7 days after 131I-MIBG administration, which is a higher dose given in a shorter period than in our study. Although we did not compare different cold
iodide administration protocols, we do not think that increasing the KI dose will result differently. Because TSH is the predominant factor affecting iodide uptake, exogenous suppression of TSH levels might constitute a better alternative.

The great variability in observed thyroidal uptake between and even within patients needs to be addressed. The MIRD method is, although commonly used as in thyroid dosimetry, subject to potentially large errors inherent to the model assumptions on dose distribution \([11]\). However, we found that the calculated numbers corresponded well with the activity seen on the thyroid scans made after \(^{131}\text{I}-\text{MIBG}\) administration. Figure 1 illustrates this. Therefore, we think that the observed variability represents a true biological finding. Differences in radiopharmacokinetics of uptake, metabolism and excretion of \(^{131}\text{I}-\text{MIBG}\) could account for inter-individual, but less likely intra-individual variations. A variation of free \(^{131}\text{I}\) in the \(^{131}\text{I}-\text{MIBG}\) preparation is a distinct possibility since the free fraction progressively increases after production with limited shelf life and because we only randomly checked the percentage of this free \(^{131}\text{I}\).

**Figure 1 A-C.**
Illustration of thyroid dosimetry in \(^{131}\text{I}-\text{MIBG}\) therapy: near-complete (A, left) and partial (B, middle) blocking with thyroid doses of 1.4 Gy and 7.8 Gy respectively after KI pre-medication.
Comparison with a historical case of non-compliance to KI pre-medication (C, right): absence of thyroid blocking with a calculated thyroid dose of 66.3 Gy.
It is important to stress that with the small number of patient groups in our study, our data do not allow to establish a positive predictive value for development of hypothyroidism with any discriminatory statistical power. A dose-response relationship is suggested by figure 2 and this is indeed what may be expected. It would be necessary to extend this study in a larger cohort of patients such as in a multi-center $^{131}$I-MIBG trial. The observed incidence of hypothyroidism of 4/10 patients or 40% after a mean follow-up period of 11 months may be considered high but is lower than the observed incidence of 9/11 or 82% after a follow-up of 2 years in the study of Picco [6]. Although these authors typically found hypothyroidism occurring between 6-12 months after $^{131}$I-MIBG administration, it may be possible that the incidence in our patient group will still increase with a longer follow-up of individual patients.

**Figure 2.**
Box-and-whisker plot of the cumulative total amount of thyroidal dose in Gy (y-axis) in euthyroid (n=6) and hypothyroid (n=4) patients.

None of the 4 patients who became hypothyroid showed specific symptoms and substitution therapy was easily instituted. However, high levels of TSH have a known tumour promoting effect that must principally be taken into consideration too in evaluating the undesirability of hypothyroidism in these patients. We strongly advocate to perform regular thyroid hormone controls before, during and after $^{131}$I-MIBG therapy and include these routinely in the treatment protocols. Alternatively, TRF testing could also be performed to disclose non-symptomatic hypothyroidism. Patient # 1 received external radiotherapy to the neck 1 year before $^{131}$I-MIBG therapy; it is likely that this was at least a co-factor. Non-thyroidal illness may have accounted for the values seen in patient #10 who at the time of diagnosis only showed a slightly raised TSH. However, this is typically seen in a recovery phase of a disease and not in a pre-terminal condition in which cytokines will increasingly suppress TSH secretion and a low TSH as well as low FT4 and FT3 would result [12]. Nonetheless, in view of the multiple factors that can cause hypothyroidism in these patients,
cautious interpretation of etiology is necessary. Establishment of a dose-response relationship or not seems important in this respect too.

In conclusion, in 35 repetitive $^{131}$I-MIBG therapies in 10 patients, this study observed a high inter- and intra-individual radio-iodide uptake in the thyroid and variability in occurrence of hypothyroidism despite KI pre-medication. Using radionuclide dosimetry, a dose-effect relationship is suggested but cannot reach statistical discriminatory power in this small patient group. Multi-center upfront $^{131}$I-MIBG trials currently in progress give to opportunity to address this issue prospectively in a larger cohort of patients. An alternative thyroid cytoprotection strategy for possible long-term survivors may be considered.
REFERENCES

Paper 6:

Thyroid function after potassium iodide pre-medication in $^{131}$I-Lipiodol therapy
THYROID UPTAKE AND RADIATION DOSE AFTER $^{131}$I-LIPIODOL TREATMENT: IS THYROID BLOCKING BY POTASSIUM IODIDE NECESSARY?

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European Journal of Nuclear Medicine and Molecular Imaging 2002; 29:1311–1316

**Purpose.** In radionuclide therapy with iodine-131 labeled pharmaceuticals, free $^{131}$I may be released and trapped by the thyroid, causing an undesirable radiation burden. To prevent this, stable iodide such as potassium iodide (KI) can be given to saturate the thyroid before $^{131}$I is administered. The guidelines of the European Association of Nuclear Medicine do not, however, recommend special precautions when administering $^{131}$I-Lipiodol therapy for hepatocellular carcinoma. Nevertheless, some authors have reported $^{131}$I uptake in the thyroid as a consequence of such therapy.

**Methods and materials.** In this study, the influence of prophylactic KI on the thyroid uptake and dose (MIRD dosimetry) was prospectively investigated. $^{131}$I-Lipiodol was given as a slow bolus selectively in the proper hepatic artery or hyperselectively in the right and/or left hepatic artery. Patients were prospectively randomised into two groups. One group received KI in a dose of 100 mg per day starting 2 days before $^{131}$I-Lipiodol administration and continuing until 2 weeks after therapy (KI group; n=31), while the other group received no KI (non-KI group; n=37). Thyroid uptake was measured scintigraphically as a percentage of administered activity 7 days after $^{131}$I-Lipiodol (n=68 treatments). The absorbed radiation dose to the thyroid was assessed by scintigraphy after 7 and 14 days using a mono-exponential fitting model and MIRD dosimetry (n=40 treatments).

**Results.** The mean activity of $^{131}$I-Lipiodol administered was 1,835 MBq in a volume of 2 (n=17) or 4 (n=51) ml. Thyroid uptake was lower in the KI group, being 0.23%±0.06% of injected activity (n=31) compared with 0.42%±0.20% in the non-KI group (n=37); the mean thyroid dose was 5.5±1.6 Gy in the KI group (n=19) versus 11.9±5.9 Gy in the non-KI group (n=21). These differences were statistically significant (P<0.001). No effect of the amount of added cold Lipiodol (4 vs 2 ml total volume) or selectivity of 131 I-Lipiodol administration was evident (P>0.1).

**Conclusion.** $^{131}$I-Lipiodol is associated with a generally low thyroid uptake and dose that may be significantly decreased by KI pre-medication. The probability of hypothyroidism after a single treatment is, in view of the calculated thyroid dose, very low with or without KI. A long-term follow-up of patients will give more information on those who have received multiple treatments. Given the low cost and the very good tolerance of the KI treatment, the present use of KI may be recommended in these patients.
INTRODUCTION

Hepatocellular carcinoma (HCC) is a common disease worldwide but there are large differences in its incidence between the continents, e.g. it is endemic in Asia. Without treatment, HCC patients survive for only 1–6 months [1]. Liver transplantation and partial liver resection offer the best chance of cure, but these options are restricted to a small number of patients. Intra-arterial administered iodine-131-Lipiodol is an interesting treatment option in HCC [2].

In radionuclide therapy using radioiodine labeled molecules, $^{131}$I may be released from the complex and trapped by the thyroid, thereby causing unintentional irradiation. To prevent this, patients are pre-medicated with stable, non-radioactive iodine such as potassium iodide (KI), which leads to iodine saturation in the thyroid, thereby downregulating the iodine uptake mechanism of the thyroid.

Biodistribution studies of $^{131}$I-Lipiodol have reported a high uptake in liver tumours and to a lesser extent in the lungs, but no uptake in the thyroid. As a consequence, generally no special precautions are advocated for protection of the thyroid. Hence, several groups do not use cold iodide premedication when employing Lipiodol treatment [3, 4, 5]. Furthermore, KI is not recommended by the guidelines of the European Association of Nuclear Medicine [6]. On the other hand, some authors have reported visible thyroid uptake [7] or a high thyroid dose without KI [8]. Other groups employ thyroid protection by means of Lugol solution, starting 1 week before treatment [9].

In this study, we evaluated the potential benefit of KI pre-medication. We prospectively calculated the thyroid uptake and radiation dose in patients receiving one or more $^{131}$I-Lipiodol treatments, with or without KI pre-treatment.

MATERIALS AND METHODS

Patient eligibility

In this study, 42 patients (31 men, 11 women; mean age: 59 years; SD: 9 years) were included. All patients were treated in the Ghent University Hospital for hepatocellular carcinoma with $^{131}$I-Lipiodol, with a total of 68 administrations. $^{131}$I-Lipiodol was given as a slow bolus through a hepatic catheter, selectively in the hepatica propria (n=39) or hyper-selective in the right and/or left hepatic artery (n=29). The mean activity used was 1835 MBq (SD: 207 MBq) in a volume of 2 (n=17) or 4 (n=51) ml. In 28 treatments out of the 68, only one post-therapy scintigraphy (after 7 days) was available. Hence, thyroidal uptake after 2 weeks and the thyroidal dose could only be calculated for 40 treatments. The $^{131}$I-Lipiodol program was approved by the ethical committee of our hospital.

Radionuclide therapy protocol

A gross activity of 2220 MBq (60 mCi) $^{131}$I-Lipiodol (LIPIOCIS®, Schering CIS BIO International) per patient was provided in a standard volume of 2 ml. At random, samples were taken to measure the free iodide fraction by quality control, as described by the manufacturer. In the first 17 patients the provided volume of 2 ml was used for injection. In all other patients (n=51) an extra volume of 2ml of cold Lipiodol was added, bringing the total injected volume to 4ml. This larger volume could facilitate the hyperselective procedures by the interventional radiologist.

Thyroid protection scheme

KI was given in a dose of 100 mg per day, two days before the treatment until 2 weeks after the therapy. In total during the observation period, 31 treatments were associated with and 37 treatments without KI pre-medication. KI administration was verified during the hospitalization in isolation at day –1 till +6.

Total body scintigraphy and dosimetry

Biplanar anterior-posterior total body scintigraphic images were recorded 7 and 14 days after the therapy on an Elscint Helix camera using high energy parallel hole collimators. A syringe in a Perspex neck phantom, containing a standard activity of $^{131}$I, was scanned along with the patient. Scan speed was varied according to the retention of the $^{131}$I-Lipiodol on the basis of a prior planar scan to avoid pixel overflow.

For processing we used the HERMES® system (Nuclear Diagnostics, Sweden). Irregular regions of interests (ROI) were drawn over the thyroid, background and the $^{131}$I syringe anteriorly on the first scan. The ROIs were mirrored to the posterior image and copied to the subsequent scan. The background corrected
geometric mean of the total counts in the ROIs were used to calculate the total amount of net activity, using the $^{131}$I standard.

Thyroidal uptake was assessed by the percentage of activity in the thyroid measured on scintigraphy after 7 and 14 days:

\[
U_{1w} = \frac{\text{Calculated activity after 1 week}}{\text{Administered activity after a decay of 1 week}}
\]

\[
U_{2w} = \frac{\text{Calculated activity after 2 weeks}}{\text{Administered activity after a decay of 2 weeks}}
\]

Consequently, cumulative $^{131}$I activity of the thyroid was calculated from the area under the time-activity curve and represented by a single exponentional fit drawn through the data points of the two consecutive whole-body scintigraphy scans. Absorbed dose to the thyroid was calculated according to the MIRD (Medical Internal Radiation Dose) formalism, using the gender-dependent S-values generated by the MIRDDOSE® 3.0 (Oak Ridge, USA) software package [10].

Thyroid function

Thyroid stimulating hormone (TSH) as well as free tri-iodothyronine (FT3) and free thyroxin (FT4) were principally determined in patients having received 3 or more treatments during a 6-12 months interval after the first $^{131}$I-Lipiodol therapy, using a standard electro-chemoluminescence method (Elecsys, USA). Hypothyroidism was defined as a raised TSH (>4.2 µU/ml) with or without depressed FT4 (< 1.0 ng/dl) and/or FT3 (< 1.8 pg/ml).

Statistics

All calculated means, standard deviations and single-exponentional fits were calculated with the Excel® (Microsoft®) software. Wilcoxon tests, t-test and box plots were performed by means of the Medcalc® software.

RESULTS

The 42 patients (31 men and 11 women) included in this study received a total of 68 treatments resulting in average of 1.7 treatments per patient. Thirteen patients were treated neo-adjuvantly, i.e. before liver transplantation, and received one treatment each. The remainder were treated palliatively and received an average of 2.0 treatments and a range of 1 up to 5 treatments. Twelve patients received more than one treatment: four patients received two, six patients three and two patients four treatments. The interval between treatments was three months. Of all 68 treatments, 31 were associated with a KI thyroid protection scheme and 37 were not. In all patients receiving KI, TSH – before KI – was normal, minimizing the risk of inducing thyroid dysfunction by KI [11].

The mean net administered activity was 1835 MBq (SD: 207 MBq), as calculated from the difference between activity drawn up in the syringe and the residual activity in the catheter system after injection. The variation in net administered activity is explained by the high viscosity of the product leaving variable amounts of activity in the syringe, the use of one or more catheter systems with different diameters and thus variable retention in the catheter system after injection. There was no statistical difference (p=0.513) in administered activity between the KI group (mean: 1856 MBq) and non-KI group (mean: 1812 MBq).
As can be seen from figure 1A, thyroidal uptake on day 7 was significantly lower in the KI group (n=31), being 0.23 +/- 0.06 % of injected activity after 7 days, than in the non-KI group (n=37), being 0.42 +/- 0.20 % (p<0.001). Thyroid uptake on day 14 (figure 1B) was always lower than on day 7 and a similar difference was observed between the two groups: 0.18 +/- 0.04 % of injected activity after 14 days for the KI (n=19) group and 0.37 +/- 0.15 % for the non-KI (n=21) (p<0.001). From the single-exponential fit through the thyroid
activity points an effective half-life of 6.0 +/- 1.0 days was found in the KI group. In the non-KI group this was 6.3 +/- 1.2 days.

**Figure 2.**
Thyroid dose (Gy) in the KI and non-KI groups

With regard to the calculated thyroidal dose (figure 2), KI pre-medication resulted in a significantly (p<0.001) lower mean dose with decreased standard deviation: 5.5 +/- 1.6 Gy in the KI group (n=19) versus 11.9 +/- 5.9 Gy in the non-KI group (n=21).

No effect of the amount of added cold Lipiodol (2 versus 4 ml total volume) or selectivity of $^{131}$I-Lipiodol administration (selective in the hepatica propria or hyperselective in the right and/or left hepatic artery) was evident (p>0.1).

Visual observation of the thyroid on post-therapy scans was possible in 35/37 treatments of the non-KI group and in 23/31 cases of the KI group, which means a significant difference between the two groups (p<0.05). This result (thyroid seen on scintigraphy yes or no) corresponded with the statistical significant difference in thyroidal uptake and dose in the two groups. If the thyroid was seen on scintigraphy, it appeared more clearly at day 14 (figure 3).
Of the nine patients having three or more treatments, 6 were evaluated with thyroid function tests. After a mean follow-up of 8.4 months (range 6-12 months) none of these patients showed signs of thyroid dysfunction or occurrence of hypothyroidism, in agreement with the calculated doses.

**DISCUSSION**

Thyroid uptake of presumably free iodide has been reported in other forms of radioiodine treatment such as $^{131}$I-MIBG [12] and $^{131}$I-antiCD20 [13] therapy. Subsequent occurrence of high thyroidal radiation dose [14] and hypothyroidism [15, 16, 17] underlines the importance of further investigating the presumable link of hypothyroidism with the uptake of free radioiodide.

In the present study, KI pre-medication was associated with a significantly lower thyroidal uptake of radioiodine (0.23 +/- 0.06 % of injected activity after 7 days), compared to patients not pre-medicated with KI (0.42 +/- 0.20 % of injected activity after 7 days). The calculated thyroidal radiation dose was likewise significantly different: 5.5 +/- 1.6 Gy in the KI group versus 11.9 +/- 5.9 Gy in the non-KI group.

The literature on thyroid uptake in extra-thyroidal radioiodine therapy is scarce. In the UKCCSG study of $^{131}$I-MIBG therapy in neuroblastoma [18], it was found that the injected therapeutic activity included an average of 4.5% free radioiodide corresponding with an activity of 0.5-1.0 GBq (13-27 mCi), emphasizing the importance of thyroid blocking. In a previous study [19] of 52 $^{131}$I-MIBG treatments, we reported a high inter-individual and intra-individual variability of thyroid uptake in patients despite pre-medication with KI, as well as
the incidence of hypothyroidism after repeated $^{131}$I-MIBG treatments. In the present study we observed a high inter-individual variability only in patients not pre-medicated with KI. This variability decreased significantly in the KI group. We postulate that the reason for these differing results may lie in the stability of the radiopharmaceutical, in-vitro before administration and/or in-vivo after administration. Compared with $^{131}$I-MIBG which has a very short shelf life, $^{131}$I-Lipiodol is more stable, with the iodine being a natural component of the molecule. The high in-vivo stability of $^{131}$I-Lipiodol is exemplified by the generally low-grade thyroidal uptake seen with or without KI, in contrast to observations with $^{131}$I-MIBG.

Whether the thyroidal uptake is a result of the amount of free iodine already present in the product or after metabolisation cannot be ascertained from this study. The fact that the highest thyroidal uptake was consistently seen on the early scans (after 7 days) in our, as well as other studies [8], may be an argument in favour of an early phenomenon (free fraction in the administered product and/or enzymatic metabolisation of the molecule in the blood) rather than a slower organ metabolisation process, for example in the liver, with subsequent recirculation of the free iodine. Quality control in randomly taken samples of $^{131}$I-Lipiodol, showed that the fraction of free iodine was <0.1%. At a mean administered activity of 50 mCi, this results in about 50 μCi of free iodide. This amount of free iodine could not result in radiation doses of the range that we calculated. Hence, in vivo, it will be a combination of free iodine and released iodine by enzymatic degradation. A study of amounts of (radiolabeled) metabolites in blood and urine would provide more information on this subject. The intra-individual variability in our $^{131}$I-Lipiodol patients could not be properly assessed because only 12 patients received multiple treatments together with the fact that these patients usually had treatments both with KI and without KI due to the randomisation process.

The thyroidal radiation dose in the non-KI group in this study (11.9 +/- 5.9 Gy) is higher than recently reported in a group of patients not pre-medicated with KI [8]: 6.9 +/- 2.9 Gy (range: 1.5-13.0 Gy). These authors scanned after 7 and 35 days; they used a similar approach to calculate the thyroid dose but did not take into account the thyroid irradiation before day 7. In our calculations, we interpolated the time-activity curve to time point zero. This explains the possible underestimation of the thyroid dose in the previous study.

Some authors [3,4] have not visualized the thyroid on subsequent post-therapeutic scans at all. Differences in administered dose, mode of scintigraphy (planar, whole-body, duration of scanning) and scanning time point after administration may account for this. Variations of product quality and free fraction between different departments cannot be excluded. Responses to a questionnaire sent by the manufacturer to 11 users of $^{131}$I-Lipiodol (encompassing 667 patients) revealed that 33% of patients had a positive thyroid image without KI, 11% a positive thyroid image with KI, but that the majority of 56% had a negative thyroid image regardless of whether KI was administered (CIS BIO international, unpublished data).

Curiously, a massive amount of stable iodide that would be sufficient to block the thyroid is given in the form of contrast media (Omnipaque® 350 mg I/ml, Amersham) at the time of hepatic arteriography prior to $^{131}$I-Lipiodol administration. It has been shown from fall-out accidents that the 24-hr thyroid uptake percentage decreases sharply when KI is given in the period between 48-hr before and 2 hours after radioiodine: thus the percentage uptake fell from 26% in controls to 4.8% at 48 hours, 0.93% when it was given 24 hours before exposure, 0.34% when it was given at the same time as the exposure and 5.3% when it was given 2 hours after exposure [20]. Whatever the amount of free radioiodine circulating and “offered” for trapping by the thyroid, protection of the thyroid by cold iodide pre-medication may be the resultant of several interacting physiological mechanisms [21]. These are principally transient and partially due to “escape” phenomena involved in the thyroid homeostasis needed for a constant thyroidal hormone output in spite of varying (dietary) iodine supply [22]. For example, in patients with Graves’ hyperthyroidism undergoing a
routine radioiodine uptake study, it was found that 24 hour radioiodide uptake averaged 20% despite chronic administration of 10 mg of cold iodide, while the proportion of non-organic, unbound radioiodine was only 14% of the total thyroidal content of radioiodine [23]. We therefore assume that the significant difference we found between the KI and the non-KI group is related to a temporal difference in effect between KI, which is given daily and the contrast agent, which is given only once.

Finally, in accordance with the generally low thyroid uptake and radiation dose observed in our study after single treatments with or without KI (regardless of the statistically significant differences between the groups), we did not observe hypothyroidism in the six patients who were repeatedly treated and who received moderate cumulative thyroid doses. However, it is probably too early to draw definite conclusions in this respect, as post-irradiation hypothyroidism can occur many years after treatment. A long-term follow-up of our patients will provide more information on this subject.

In conclusion, 131I-Lipiodol treatment is associated with a generally low thyroidal uptake and dose. However, this may be significantly decreased by KI pre-medication. On the other hand, the probability of hypothyroidism after a single treatment is, in view of the calculated thyroid dose, very low with or without KI. A long-term follow-up of patients will give more information on those who have received multiple treatments. Given the low cost and the very good tolerance of the KI treatment, the present use of KI may be recommended in the majority of the patients.
REFERENCES


6. Monograph-[1-131]-Ethiodized oil therapy. European Association of Nuclear Medicine, Taskgroup Radionuclide Therapy, 2000 ([www.eanmrtc.org/Monograph/Lipiodol.htm](http://www.eanmrtc.org/Monograph/Lipiodol.htm)).


Section III:

Quality of life measurements
Paper 7:

Quality of life in radionuclide therapy
QUALITY OF LIFE ASSESSMENT IN RADIONUCLIDE THERAPY: A FEASIBILITY STUDY OF THE EORTC QLQ-C30 QUESTIONNAIRE IN PALLIATIVE 131I-LIPIODOL THERAPY


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European Journal of Nuclear Medicine and Molecular Imaging 2002; 29: 1374-1379

**Purpose.** The good tolerance of radionuclide therapy has frequently been proposed as a major advantage. Assessment of subjective well being and its induced changes by radionuclide therapy has up to now been largely confined to the field of bone pain palliation based on visual analog pain scales. This study explored the feasibility of using the EORTC QLQ-C30 questionnaire in palliative 131I-Lipiodol therapy for hepatocellular carcinoma (HCC).

**Methods and materials.** Questionnaires were completed during interviews in which all symptoms, co-morbidity and medication were assessed at baseline within 1 week before 131I-Lipiodol therapy, and subsequently after 1 and 3 months, in 20 patients treated with loco-regional, intra-arterial 131I-Lipiodol therapy with or without cisplatin.

**Results.** Principal observations were that (1) a number of important specific scales, i.e. overall quality of life, physical functioning and pain worsened between 0 and 3 months after 131I-Lipiodol therapy, irrespective of tumour response, and (2) the occurrence of clinical side-effects was associated with a negative impact on quality of life and physical functioning 1 and 3 month after 131I-Lipiodol.

**Conclusion.** The QLQ-C30 can be regarded as a feasible method for quality of life assessment in 131I-Lipiodol therapy for hepatocellular carcinoma and possibly in other radionuclide therapies. These observations should be related to the impact of other treatment modalities on quality of life.
INTRODUCTION
The good tolerance of radionuclide therapy has frequently been proposed as a major advantage compared with systemic chemotherapy [1]. Assessment of subjective well-being and the changes in it that are induced by radionuclide therapy has up to now largely been confined to the field of bone pain palliation, based on visual analogue pain scales [2, 3]. Palliative treatment, however, implies the preservation of quality of life (QoL) both through treatment efficacy in alleviating individual symptoms and through the impact on overall symptomatology. Since 1987, the European Organisation for Research and Treatment of Cancer (EORTC) has been developing a programme consisting of a core questionnaire, the EORTC QLQ-C30, that has been validated for a wide range of cancer patient populations [4, 5, 6]; in addition, 15 modular questionnaires have to date been developed for the evaluation of specific symptoms or problems.

This study explored the feasibility of using the EORTC QLQ-C30 in palliative iodine-131 Lipiodol therapy for hepatocellular carcinoma (HCC).

PATIENTS AND METHODS

Patient eligibility and characteristics
Between June 1999 and September 2001 we treated 26 patients with inoperable HCC. The ethical committee approved the treatment protocol and patients gave written informed consent. Twenty patients constituted the sample for the present feasibility study. Six were excluded from the study because they died before the study could be completed (n=4), because clinical follow-up was lacking (n=1) or because the patient refused to participate (n=1). All patients had a World Health Organisation (WHO) performance status of 0 to 2 and a Karnofsky score of ≥60. All patients had stage IVA disease according to the International Union Against Cancer 1992 criteria [7]. The majority of patients were men (80%) of Belgian (n=15) or Italian (n=5) origin, and the mean age was 61 years (range 45-73).

Radio-nuclide therapy protocol
On the second day of admission, an activity of 1,345-2,120 MBq (mean 1,816 MBq) [36.3-57.2 mCi (mean 49.0 mCi)] 131I-Lipiodol (Lipiocis, CIS bio international/Schering) was instilled selectively in the proper hepatic artery during hepatic angiography or, for anatomical reasons, hyperselectively in the right and left hepatic arteries. In 10 of the 20 patients, cisplatin, as a radiosensitiser, was given in a dose of 30 mg/m² at days -1 and +6 (day 0: 131I-Lipiodol) as an IV infusion over 2.5 h, with additional hydration, mannitol infusion, methylprednisolone and ondansetron. The other ten patients received only 131I-Lipiodol. In conjunction with the angiography procedure, patients received a platelet infusion if the baseline thrombocyte count was below 50×10⁹/l and whole blood packed cells if the haemoglobin level was below 8 g/dl. The thyroid was blocked with potassium iodide 100 mg once daily. Hospitalisation in radioisolation was continued until 5 days after administration of the 131I-Lipiodol.

Assessment of quality of life
The EORTC Quality of Life Study Group granted permission to employ the EORTC QLQ-C30 for this particular academic QoL study. The QLQ-C30 includes a total of 30 questions or "items" and is composed of scales that evaluate physical (five items), role (two items), emotional (four items), cognitive (two items), and social (two items) functioning, as well as global health/QoL scale. Higher scores on these scales represent better functioning. There are also three symptom scales measuring nausea and vomiting (two items), fatigue (three items), and pain (two items), and six single items assessing additional symptoms (dyspnoea, sleep disturbance, constipation, diarrhoea and loss of appetite) and perceived financial impact. Higher values on the symptom scales/items mean more symptomatology. Each question may be answered by "not at all", "a little", "quite a bit" or "very much" (so-called Lickert scale scores 1-4), except for the global health/QoL scale, which is a visual analogue scale from 1 ("very bad") to 7 ("excellent"). Before analysis, raw scores are linearly transformed to scales of 0 to 100. Questionnaires were completed during interviews in which all symptoms, co-morbidity and medication were assessed: (1) at baseline within 1 week before 131I-Lipiodol therapy, (2) after 1 month and (3) after 3 months. The score at 1 month was intended to correlate primarily with the occurrence of clinical side effects [8]. The score at 3 months was especially correlated with the tumour response [9], classified according to WHO standards [10] by magnetic resonance imaging (MRI, n=16) or computerised tomography (CT, n=4), performed 6 weeks after therapy.
Statistics
Overall changes between baseline and scores at 1 and 3 months were assessed by a paired-samples \( t \) test. Subgroup differences (additional cisplatin therapy or not, side effects or not, tumour response or stable/progressive disease) were assessed with the Wilcoxon signed rank test. A \( P \) value of <0.05 was considered statistically significant (SPSS Software, version 10.0).

RESULTS

Compliance
As stated above, 6/26 patients filled in the baseline questionnaire but did not do so subsequently at 1 and/or 3 months, resulting in an overall compliance of 77%.

Baseline symptoms and quality of life
Tables 1 and 2 show the percentage of patients having major problems on the functional and symptom scales. As can be seen, the most prominent feature was tiredness limiting work, hobbies and extended efforts.

Table 1.
EORTC QLQ-C30. Item and scale scores and distribution of patients reporting “quite a bit” or “very much” with regard to problems concerning functionality

<table>
<thead>
<tr>
<th>Scale/item</th>
<th>%</th>
<th>Scale/item</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning (PF2)</td>
<td></td>
<td>Emotional functioning (EF)</td>
<td></td>
</tr>
<tr>
<td>-Trouble doing strenuous activities</td>
<td>20%</td>
<td>-Did you feel tense?</td>
<td>5%</td>
</tr>
<tr>
<td>-Trouble taking a long walk</td>
<td>35%</td>
<td>-Did you worry?</td>
<td>40%</td>
</tr>
<tr>
<td>-Trouble taking a short walk</td>
<td>0%</td>
<td>-Did you feel irritable?</td>
<td>0%</td>
</tr>
<tr>
<td>-Bed- or chair ridden</td>
<td>10%</td>
<td>-Did you feel depressed?</td>
<td>10%</td>
</tr>
<tr>
<td>-Help with eating, dressing, toilet, washing</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Role functioning (RF)</td>
<td></td>
<td>Social functioning (SF)</td>
<td></td>
</tr>
<tr>
<td>-Limited in work</td>
<td>35%</td>
<td>-Interference with family life</td>
<td>5%</td>
</tr>
<tr>
<td>-Limited in hobbies</td>
<td>30%</td>
<td>-Interference with social life</td>
<td>10%</td>
</tr>
<tr>
<td>Cognitive functioning (CF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Difficulty in concentrating</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Difficulty in remembering</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EORTC QLQ-C30. Item and scale scores and distribution of patients reporting “quite a bit” or “very much” with regard to problems concerning symptoms

<table>
<thead>
<tr>
<th>Scale/item</th>
<th>%</th>
<th>Scale/item</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue (FA)</td>
<td></td>
<td>Single items</td>
<td></td>
</tr>
<tr>
<td>-Did you need to rest?</td>
<td>15%</td>
<td>-Were you short of breath?</td>
<td>0%</td>
</tr>
<tr>
<td>-Have you felt weak?</td>
<td>5%</td>
<td>-Have you had trouble sleeping?</td>
<td>5%</td>
</tr>
<tr>
<td>-Were you tired?</td>
<td>30%</td>
<td>-Have you been constipated?</td>
<td>5%</td>
</tr>
<tr>
<td>-Have you vomited?</td>
<td>0%</td>
<td>-Have you had diarrhoea?</td>
<td>5%</td>
</tr>
<tr>
<td>Emesis (NV)</td>
<td></td>
<td>-Have you lacked appetite?</td>
<td>0%</td>
</tr>
<tr>
<td>-Have you felt nauseated?</td>
<td>0%</td>
<td>-Disease caused financial difficulties?</td>
<td>0%</td>
</tr>
<tr>
<td>Pain (PA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Have you had pain?</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Did pain interfere with daily activities?</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Changes in symptoms and quality of life over time

Figure 1 shows the overall changes in the mean scores on the functional and symptom scales between baseline and 1 and 3 months after $^{131}$I-Lipiodol. Comparing the baseline score with the 1- and 3-month scores, we noted a significant deterioration in overall QoL ($P=0.002$ between 0 and 1 month, $P=0.007$ between 1 and 3 months), a significant deterioration in physical functioning ($P=0.005$ between 0 and 1 month, $P=0.006$ between 1 and 3 months) and a significant increase in pain complaints ($P=0.003$ between 0 and 1 month, $P=0.008$ between 1 and 3 months). Additionally, we found weak significant differences in fatigue, which increased between 0 and 3 months ($P=0.02$ only, and in nausea/vomiting, with an increase between 0 and 1 month ($P=0.03$) but a decrease between 1 and 3 months ($P=0.04$).

Figure 1.

Overall changes in functional (1A, upper) and symptom scales (1B, lower) between baseline (left-hand bars), 1 month (middle-hand bars) and 3 months (right-hand bars) after $^{131}$I-Lipiodol therapy

$^{1}p=0.002; ^{2}p=0.005; ^{3}p=0.006; ^{4}p=0.007$

$^{1}p=0.003; ^{2}p=0.008; ^{3}p=0.02; ^{4}p=0.03; ^{5}p=0.04$
Figure 2 shows the results in the tumour response subgroups. Of the 20 patients, 7 achieved a response (minor: n=3; partial: n=4; complete: n=0), compared to 13 patients with stable (n=7) or progressive (n=6) disease. In the no-response group, overall QoL scores marginally significantly worsened both between 0 and 1 month (P=0.03) and between 0 and 3 months (P=0.04), while for the response group the deterioration in QoL was only statistically significant between 0 and 3 months (P=0.04).

**Figure 2.** Changes in subgroups with (1A, upper) or without (1B, lower) tumour response baseline (left-hand bars), 1 month (middle-hand bars) and 3 months (right-hand bars) after $^{131}$I-Lipiodol therapy

Abbreviations are as defined in the legend to Fig. 1

1 $p=0.04$
Figure 3 shows the results in the subgroups with or without side effects. Twelve patients experienced clinical side effects: fever (n=6), nausea and loss of appetite (n=2), fever and nausea (n=1), abdominal pain (n=1), enteritis (n=1) and stomach ulceration (n=1). Only in the side effect subgroup was a statistically significant deterioration seen, i.e. in overall QoL (P=0.007 between 0 and 1 month; P=0.01 between 0 and 3 months) and in physical functioning (P=0.005 between 0 and 1 month; P=0.03 between 0 and 3 months).

**Figure 3.** Changes in subgroups with (1A, upper) or without (1B, lower) side effects baseline (left-hand bars), 1 month (middle-hand bars) and 3 months (right-hand bars) after $^{131}$I-Lipiodol therapy

Abbreviations are as defined in the legend to Fig. 1

$^1$ p=0.03; $^2$ p=0.04; $^3$ p=0.007; $^4$ p=0.01; $^4$ p=0.03
Figure 4 shows the scores of the patients who received additional low-dose cisplatin infusion as a radiosensitiser (n=10) and those who did not (n=10). Deterioration in QoL and physical functioning scores was seen in both subgroups and (just) reached statistical significance in the cisplatin group: P=0.04 between 0 and 1 month and P=0.03 between 0 and 3 months for overall QoL, and P=0.04 between 0 and 1 month and P=0.04 between 0 and 3 months for physical functioning.

**Figure 4.** Changes in subgroups with (1A, upper) or without (1B, lower) *cisplatin addition* baseline (left-hand bars), 1 month (middle-hand bars) and 3 months (right-hand bars) after ${}^{131}$I-Lipiodol therapy

Abbreviations are as defined in the legend to Fig. 1
DISCUSSION

The value of any cancer therapy may be determined from the observed tumour response, the impact on survival, the occurrence of side effects, the cost of the treatment and the effect of the treatment on QoL. Both cancer and its treatment are severely debilitating and the need to consider their impact upon health-related QoL when making patient management or treatment decisions is now well accepted [6]. The objective of palliative $^{131}$I-Lipiodol therapy is obviously an overall improvement in tumour-related symptoms and QoL through tumour stabilisation or response. Radionuclide therapy in general may be particularly well suited in this respect since it permits specific targeting, thereby limiting detrimental effects on normal organ systems. Tools such as the QLQ-C30 could provide important information on treatment efficacy and tolerance that would be of relevance to the decision to use this unique and specific therapeutic modality.
The principal finding of this study was that in spite of $^{131}$I-Lipiodol therapy, QoL worsened between 0 and 3 months, both overall and in the subgroups. Worsening of the QoL score, instead of the desired amelioration, has also been observed in other patient groups such as those undergoing surgery [8] or chemotherapy [11]. In our study, the worsening in QoL occurred irrespective of the observed tumour response, a fact which may have been related to the small size of the overall sample or of the response subgroups [9]. Worsening of pain is suggestive of tumour progression, and this is in accordance with the moderate response rate observed after one $^{131}$I-Lipiodol administration. In the present study the primary objective was to evaluate QoL parameters in relation to clinical data, and the observation that adverse clinical findings were consistently associated with a negative impact on QoL affirms the feasibility of using the QLQ-C30 for QoL assessment in $^{131}$I-Lipiodol therapy. It was not the object of this study to evaluate tumour response to the $^{131}$I-Lipiodol therapy itself, with or without cisplatin. Treatment assessment based on overall QLQ-C30 scores should preferably entail comparison with a control group of similar palliative HCC patients receiving best medical support alone [12]. The lack of a control group was unavoidable in our study since, during the period of study, all HCC patients treated at our institution received $^{131}$I-Lipiodol; a control group was not, however, essential for the purpose of this feasibility study.

Clinical side effects were associated with a statistically significant negative impact on QoL and physical functioning both between baseline and 1 month and between baseline and 3 months; this further affirms the feasibility of use of the QLQ-C30 in this patient group. Larger patient groups will be needed to further analyse the nature of the possible association of these QoL parameters with $^{131}$I-Lipiodol, cisplatin or radionuclide therapy in general. In view of the trend towards use of radionuclide therapy in association with other modalities, such as radical surgery, external radiotherapy and chemotherapy, it is important to stress that QoL parameters could provide controlled indicators of the positive or negative influence of these complementary modalities.

The 30 items of the questionnaire can be completed in about 10 min. As the questions are neutral and deal mostly with physical complaints, no psychological stress is induced, as illustrated by the fact that only one patient refused participation a priori, and none withdrew during the study. The attention of physicians to QoL aspects of the treatment invariably drew very positive responses from patients. The questionnaire is also very straightforward and rarely gave rise to requests for clarification from patients, which is an important consideration when using the questionnaire in an indirect way, such as by mail. We chose to perform the QoL assessment by interview rather than by mail. Obviously, our small sample allowed such an approach but the consequence was that the answers were "coloured" by the interaction between the respondent and the interviewer. Advantages of the interview technique are fewer dropouts and the possibility of distinguishing tumour-related symptoms from co-morbidity. In addition, motivation, personal and cultural differences (for example in the perception of what is signified by the answers "quite a bit" or "very much") and expectations about the therapy (patient bias) may be better appreciated. Disadvantages of interviewing are (a) the interview technique may be inadequate, (b) there may be (un)conscious influencing or prejudgement on the part of the interviewer (interviewer bias) and (c) the patient may have an incorrect perception of the interview, as reflected by a tendency to give socially desirable answers.

It has been stated that palliative interventions may be beneficial but do not necessarily treat the most important subjective symptoms [13]. Whether the symptoms addressed by the core questionnaire QLQ-C30 may be viewed as representative of those that are experienced by HCC patients receiving palliative $^{131}$I-Lipiodol therapy is therefore an important question. One study [14] that examined all the symptoms and problems occurring in 171 patients who received palliative treatment for a variety of cancers, established that the 63 different
symptoms identified were more completely covered by the QLQ-C30 than by other symptom/QoL scales. This suggests that the QLQ-C30 will also have been applicable in our patient group. We consider that most symptoms of liver failure and HCC are well covered by the QLQ-C30, although some symptoms of liver failure, such as icterus and sexual function, are not. Thus, a specific module on primary liver cancer that appears to be in an early developmental stage [6] could be an interesting supplement. Furthermore, a specific module dealing with issues related to radionuclide therapy would seem desirable, in view of the significant changes observed in the group experiencing side effects, the unique mechanism of action of radionuclide therapy and its different response patterns, the specific treatment condition of radioisolation and the psychological impact of radiation [15].

Other methodological issues are worthy of mention. For example, changes in scores over time and differences between groups may be more difficult to interpret than absolute scores when making comparisons with published data for other groups of patients or reference values of healthy persons (www.eortc.be/home/qol). It may be argued that only patients and controls of comparable age should be used as a reference group, rather than healthy young and old people. Another relevant point is that statistical significance of a change does not necessarily imply that it also has clinical significance [6,16]. However, the consistency between statistically significant items and clinical events that we observed makes it likely that the observed differences were disease related. Of course, the main limitation to our study was the small sample size and the consequent lack of statistical power in respect of several of the items; this especially affected the interpretation of marginally significant findings, e.g., regarding overall fatigue, overall nausea/vomiting, QoL in the response subgroup, and QoL and physical functioning in the cisplatin subgroup.

In conclusion, QoL assessment can deliver important information on disease status, symptoms and problems in a particular patient group and on the effectiveness of interventions aimed at improving or stabilising QoL in incurable cancer patients. Such assessment should probably be incorporated in every radionuclide therapy trial. The QLQ-C30 seems a feasible method of QoL assessment in 131I-Lipiodol therapy for HCC and possibly in other radionuclide therapies.
REFERENCES

Paper 8:

Anxiety in radionuclide therapy
DEPRESSION AND ANXIETY DURING ISOLATION AND RADIONUCLIDE THERAPY


Departments of Nuclear Medicine, Psychiatry and Medical Psychology, Ghent University Hospital, Ghent, Belgium.

Nuclear Medicine Communications 2003 in press

Purpose. The combination of a diagnosis of malignancy and hospitalisation, isolation and radioactivity of radionuclide therapy may have an important effect on the psychological equilibrium of patients and may hamper compliance and acceptability. We performed a psychiatric evaluation in patients admitted in isolation in order to study psycho-pathological manifestations and underlying personality-related vulnerabilities.

Methods and materials. During radioisolation, 48 patients (24 male, 24 female; mean age 57.8 years) with a malignant (n= 26) or non-malignant (n= 22) pathology who needed isolation for radionuclide therapy completed a series of questionnaires in order to assess anxiety (Spielberger State and Trait Anxiety Inventory; STAI), depression (Beck Depression Inventory; BDI), hopelessness (Beck Hopelessness Scale; BHS), personality characteristics (Temperament and Character Inventory; TCI) and coping strategies (Utrecht’s Coping List; UCL).

Results. Compared to patients with low state anxiety, patients who experienced a high level of state anxiety showed higher levels of depression (t=-2.10; P= 0.04) and hopelessness (t=-4.20; P= <0.001). Their personality was characterised by significantly higher scores on harm avoidance (t=-2.78; P= 0.008) and lower scores on self-directedness (t=3.12; P= 0.003). Coping strategies were more passive (t=-2.43; P= 0.02), avoiding (t=-2.15; P= 0.04) and less well aimed (t=2.64; P= 0.01). Surprisingly, the nature of disease (malignant versus non-malignant) was not influential on these results, nor was there a difference between males and females, age, years of education, having a relationship or not, or the duration of hospitalisation.

Conclusion. Thus, contrary to what may be expected in isolation with radionuclide therapy, subgroups such as women, elderly, cancer patients or lower educated people do not a priori exhibit a higher state anxiety level. Our study shows these levels to be closely related to individual personality traits and coping strategies that are inadequate for the situation. Screening for trait anxiety before admission can be easily done and may guide interventions aimed at increasing patient comfort and acceptability.
INTRODUCTION

Depending on the specific legislation in different countries, a substantial proportion of patients treated with radionuclide therapy spent a variable time in isolation. Being alone and suffering from a more or less life threatening pathology, while undergoing “nuclear therapy” making him or her radiating, may leave patients with considerable worries about their physical and psychological integrity, despite extensive patient information. Forbidding close contact with the most precious partner, children and other family members for a variable time after discharge because of “radioprotection”, may create an additive distress and threat, despite the concept of calculated minimal exposure and risks. Apart from the consideration of providing maximum patient comfort, it may be evident that patient compliance and treatment acceptance may thus be substantially hampered by high levels of anxiety implicitly related to this type of treatment.

Many studies have addressed the emotional adaptation to a diagnosis of serious disabling diseases such as cancer or neurodegenerative conditions [1,2]. Mood disorders and anxiety have been reported to be the two most frequent psychological disturbances within cancer populations [3,4]. Depressive feelings and hopelessness originating from stressful events are believed to determine for a major part patients’ quality of life. [5-7]. In patients with microbiological isolation, significantly higher levels of depression and anxiety have been found, especially in elder patients [8]. Isolation is known to induce anxiety and depressive feelings in bone marrow transplant patients [9,10] and has been found to cause emotional instability even in healthy volunteers. [11]. Currently, there is no literature available on the psychological impact of radionuclide therapy.

In this prospective study, we assessed the variables that are involved with the occurrence of anxious distress during isolation and radionuclide therapy. Based on these variables, our aim will be to develop a strategy of a priori selecting patients who are at risk of experiencing excess levels of anxiety and who may benefit from specific psychological support.

MATERIALS AND METHODS

Patient eligibility

Sixty-five adult patients hospitalised in the nuclear medicine isolation facility from April 2000 until June 2002 were approached to participate in the study. Since the 17-page questionnaire required the ability to focus attention for a substantial time period, patients with acute illness, mental deterioration or a Karnofski scale of less than 60% were excluded. Patients with a history of neuro-psychiatric illness were not included since these patients are more prone to anxiety and affective disorders.

Each patient received clear verbal and written information on his or her disease state and particularities of the radionuclide therapy procedure, including radioprotection, prior to admittance. This type of isolation implied that the patient could not leave the confinement of a standard room, equipped with a window and washing stand, a freezing-toilet, television and refrigerator, for a varying time period of three to six days. Entrance into the room was restricted only to hospital staff performing the necessary medical procedures, such as clinical investigation and treatment. Family and other visiting persons were not allowed into the room during the total duration of treatment, being in contact only from behind a door with lead glass and by telephone. All patients willing to participate gave their consent after thorough written explanation of the test procedure according to the instructions in the test manuals.

Psychological test protocol

The psychiatric assessment was made using validated self-rating questionnaires (Dutch language) in order to measure anxiety, mood, personality and coping. Anxiety is characterised by pervasive and unpleasant feelings of tension and dread in response to an impending danger, insecurity or an unknown and threatening situation. The Spielberger State and Trait Anxiety Inventory (STAI) [12], was used to assess levels of state...
anxiety (STAI-1[state]) and trait anxiety (STAI-2[trait]), through 20 items scored by Likert scale (i.e. “not at all”-“a little”-“quite a bit”-“very much”). State anxiety is defined as a transient momentary emotional status that results from situational stress that fluctuates in time and intensity. Trait anxiety refers to the predisposition of people to react with anxiety when a stressful situation arises. Mood state, i.e. levels of hopelessness and depression were measured respectively by the 20-item Beck Hopelessness Scale (BHS, yes or no answers) [13] and the 21-item Beck Depression Inventory (BDI, Likert scale answers) [14]. Loss of hope is derived from the feeling of loss of control and the ability of changing one’ destiny. Personality refers to stable and constant patterns of behaviour and reactions. Personality characteristics were evaluated with the Temperament and Character Inventory (TCI) which has 240 yes or no items that compose 25 subscales and 7 main scales: novelty seeking (i.e. explorative, curious, extravagant, impulsive, hot-tempered, quickly bored, sloppy), harm avoidance (i.e. careful, nervous, timid, distrustful, insecure, passive, worrying, pessimistic, inhibited, more in need of support, vulnerable to criticism), reward dependence (i.e. sensitive, loving, sentimental, dependent, social, intimate), persistence (i.e. diligent, persevering, ambitious, perfectionistic), self-directedness (i.e. mature, strong, responsible, reliable, constructive, resourceful, high self-esteem), cooperativeness (i.e. empathic, tolerant, compassionate, supportive, honest, respectful, forgiving, team player) and self-transcendence (i.e. unpretentious, satisfied, unselfish, spiritual, nature-oriented, self-conscious, modest, thankful, idealistic, adaptive) [15]. The way of dealing with situations (coping) was evaluated by means of the Utrecht’s Coping List (UCL) [16], a 47-item inventory (Likert scale) identifying 7 coping strategies: active (i.e. facing the problem constructively and aimed to solve it), palliative (i.e. distraction and pleasure seeking), avoiding (i.e. negating and undergoing the situation without action), social (i.e. seeking comfort and understanding from people), passive (i.e. fully absorbing the problem with pessimistic worrying), expressive (i.e. showing feelings such as anger and frustration to the outside world) and aimed (i.e. generating optimistic, relativating, encouraging thoughts) coping. The term coping is defined as dealing with or handling an uncomfortable or unfavourable situation with the object to, by individual cognitive and behavioural efforts, lower tension and ward off anxiety. The test is based on the principle that the person’s response to difficult or unpleasant events is generally similar and categorical.

Demographic and clinical variables were noted, including the nature of disease (malignant vs. non-malignant), age, gender, and duration of hospitalisation. Educational status was measured by assessing years of successfully participating school education (more or less than 10 years). Relational status was evaluated as having or lacking a stable relationship with a significant other for at least 6 months preceding the current treatment. All questionnaires were filled in at noon of day 1 of the isolation period, in order to rule out diurnal emotional variations.

Statistics
Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 10.0. Scores of the STAI-1[state] were correlated with the scores of STAI-2[trait] by two-tailed Pearson’s correlation. Comparison between the populations’ anxiety scores and demographic and clinical variables was made by two-tailed Pearson’s correlation and independent samples t-test. The level of anxiety was further stratified into two subgroups, i.e. “high” and “low” anxiety state, which were defined as higher or lower than the median score [17]. A comparison of psycho-pathological characteristics between these “higher” and “lower” anxiety groups was made by an independent sample t-test. Relationships between discrete variables (i.e. gender and malignancy or not) was analysed by chi-square cross-tabulation.

RESULTS

Patient compliance
Of the 65 patients, six patients refused to participate, because the personal questions confronted them too much with negative feelings. Another 11 patients did not fill in the complete set because of forgetfulness, secondary unwillingness or misunderstanding. The remaining 48 patients (74%) formed the study group.

State and trait anxiety
Figure 1 shows the distribution of the state anxiety (STAI-1[state]) scores on day 1. There was a wide range of scores between the minimum score of 20 points (all answers “not at all”) and maximum of 80 points (all answers “very much”). The mean score on the STAI1[state] was 39.5 (SD=11.5); that of the STAI-2[trait] 38.2 (SD=9.8). There was a good correlation within the whole research group between the levels of state (“STAI-1[state]”) and trait (“STAI-2[trait]”) anxiety (r=0.63; P=<0.01; two-tailed).
Figure 1.
Distribution of the state of anxiety STAI 1 score according to age.
Note the wide range of scores throughout the years between the minimum of 20, i.e. all answers “not at all”, and maximum of 80 points, i.e. all answers “very much”.

Baseline demographical and clinical characteristics
The study group consisted of 24 women and 24 men. Malignant disease was present in 26 patients, including 10 patients with thyroid carcinoma, treated by a per oral capsule containing 3700-7400 MBq (100-200 mCi) $^{131}$I, 12 patients with liver carcinoma treated with 1850 MBq (50 mCi) $^{131}$I-Lipiodol, and 4 patients with neuro-endocrine tumours treated with 7400 MBq (200 mCi) $^{131}$I-mIBG. The remaining 22 patients had a benign disease, i.e. hyperthyroidism treated with 555-1110 MBq (15-30 mCi) $^{131}$I. Non-malignant disease was present in 16 female and 6 male patients, whereas 18 men and 8 women suffered from a malignant disorder ($\chi^2=8.39; p=0.04$). The mean age of the total group was 57.8 years (SD=12.8 years), that of men 64.2 years (SD=8.2) and women 51.5 years (SD=13.5) differing significantly ($t=3.93; P<0.01$). These differences were due to the proportion of benign thyroid disease in younger females in this population.

Age did not correlate with state anxiety ($r=-0.03; P=0.87$) or other psycho-pathological variables. There was no significant difference in state anxiety or other psycho-pathological variables between male and female patients ($t=1.49; P=0.14$). The nature of the disease (malignant or non-malignant) had no significant effect on anxiety ($t=0.79; P=0.43$) or other psycho-pathological variables, nor had duration of hospitalisation ($t=-8.31; P=0.41$) (figure 2). Education level ($t=1.34; P=0.19$) and relational status ($t=0.04; P=0.97$) had no significant influence on state anxiety or other psycho-pathological variables.

Psycho-pathological characteristics
Four patients had STAI-1[state] scores that exactly matched the median score of the whole group. Since we aimed at developing intervention strategies for the ‘high anxiety’ group, these four patients were added to the ‘low anxiety’ group. This median split procedure resulted in a group of 26 patients with low level of state anxiety and another group of 22 patients with high levels of state anxiety. Concerning mood state, patients in the high-anxiety group, showed significantly higher scores on the BDI ($t=-2.10; P=0.04$) and BHS ($t=-4.20; P<0.001$) compared to low-anxiety patients. Concerning personality characteristics, the high state anxiety group scored significantly higher on harm avoidance ($t=-2.78; P=0.008$) and...
lower on self-directedness ($t=3.12; P=0.003$). Concerning coping strategies, the patients in the high anxiety group differed from less anxious patients in their scores on the UCL too. High anxiety patients scored higher on passive coping ($t=-2.43; P=0.02$), the use of avoiding strategies ($t=-2.15; P=0.04$) and scored less on cognitively aimed coping behaviour ($t=2.64; P=0.01$).

**Figure 2.**

Box-plots of state and trait anxiety scores in relation to gender, years of education (< vs > 10 yrs), nature of disease (malignant vs non-malignant) and days of hospitalisation (3 vs 6 d), showing no significant differences in anxiety scores.

Dark boxes=state anxiety (STAI 1) scores, Light boxes=trait anxiety (STAI 2) scores
DISCUSSION

In our patients, state anxiety was strongly related to trait anxiety, meaning that patients, who have a stronger tendency to demonstrate anxious reactions, have higher intensities of situational anxiety. This relation was previously demonstrated with regard to pre-operative state anxiety, in which one of the major predictors of state anxiety was trait anxiety [18]. This association makes it possible to identify, before admission and by the use of a psychological screening test such as the STAI, patients who are at risk of excess anxiety during radionuclide therapy isolation. Psychological intervention by cognitive and behavioural techniques (e.g. imagery induction, exposure induction) could easily be implemented before radioisolation to change negative automatic thoughts and dysfunctional appraisals, decrease passive coping and avoiding strategies and increase perception of control [19].

Following stratification of patients to high or low anxiety levels, we observed that patients who experienced a high level of state anxiety showed 1) higher levels of depression and hopelessness, 2) a personality characterised by higher harm avoidance and lower self-directedness, and 3) less aimed and more passive and avoiding coping strategies. Relationships between hopelessness and anxiety are well known [4,20]. Loss of hope is derived from the feeling of loss of control and the ability of changing one’s destiny. The loss of control generates anxious distress [4,5]. Depressed feelings are generally acquired by cognitive impairments such as a decreased possibility to plan and to direct ones own behaviour, by a decreased drive and initiative and by difficulties in decision-making. Possibly here, the situational anxiety stems partly from the inability to take up a combative and structured attitude.

Concerning personality, a specific pattern was found in the high anxiety group. People with high harm-avoidance scores are described as passive, negative, pessimistic and more rapidly anxious in distressing circumstances [15]. Along with a greater need for support and encouragement, a strong tense and anxious reaction in unknown and insecure situations is a well-known property of this personality characteristic [15]. High self-directedness implements a strong, confident and responsible reaction pattern. A lack of constructive problem solving strategies is characteristic for low self-directedness and a plausible source of highly anxious reactions.

Along the same lines were the findings on coping strategies. More anxious patients demonstrated more passive and more avoiding coping. These coping styles disable the more anxious patients to constructively deal with the difficult situation they are confronted with. A passive reaction pattern indicates that the individual is overwhelmed by the problems or circumstances. The main occupation is worrying, while gloomy perspectives prevent the person to take action and to do something about the situation. The reduced capacity of aimed coping strategies, providing reassuring and comforting thoughts to encourage one self and provide positive expectations and perspectives in order to feel stronger in the confrontation with a difficult period, is striking.

It is important to stress that certain personality characteristics cannot be viewed as simply positive or negative. In a dangerous situation such as high altitude, harm avoidance may be life saving. However, in the situation in which our patients find themselves with isolation, radioactivity and cancer this quality hampers the patient to evade excess levels of anxiety.

Surprisingly, high levels of anxiety were not related to age, gender, relational status, level of education, duration of hospitalisation or nature of disease. Especially, common sense and evidence [21] suggest that a malignant diagnosis has a more distressing effect than the diagnosis of a non-malignant pathology, but surprisingly this does not influence the anxiety level during radionuclide therapy isolation. Neither, a certain built up wisdom over life
apparently does not generate a specific defence mechanism, as age was not found to be influential either. Females, who have a higher risk of depression [2,22,23], did not report more depression and anxiety than males. A stable relationship with a significant partner (whether in marriage or not) has been described to be associated with a better psychological outcome in stressful situations such as cancer in some studies [24,25], but not all [20,26]. Higher educated people were found likely to demonstrate less anxiety and less depressive disorders [27], though not in all studies [20,26]. In our study group, these demographic variables were not related to anxiety and distress levels. Equally, duration of hospitalisation (3 vs. 6 days) produced no significant differences, although this does not rule out that anxiety may still increase to higher levels in longer admittance times beyond 6 days.

The relevance of psychological screening and guidance in radionuclide therapy may be diverse. In the patient they could contribute to feelings of relief, reassurance and increased quality of life. This may also be to the benefit of the hospital and department staff through positive publicity and acceptability of treatment. From an economical point of view, it would be meaningful to investigate whether managing more demanding patients in radionuclide therapy is reflected by increased hospital staff costs and/or exposure. On the other hand, it might be argued that admissions to the isolation facility are usually brief and the distress generated in susceptible patients is too short-lived to justify lengthy pre-treatment psychological approach. Moreover, a recent systematic review has been unable to find a consistent association between psychological coping and outcome of cancer. A fighting spirit or helplessness/hopelessness attitude were not particularly more related to the degree of recurrence or survival, although such a relation is biologically plausible and there is strong lay and professional support for psychological intervention therapy [28]. It will therefore be important to use well-defined and objective endpoints in examining the justification of psychological intervention in radionuclide therapy.

In conclusion, individual personality styles and coping strategies and not characteristics such as gender or nature of disease are associated with anxiety and depression in patients isolated for radionuclide therapy. Our study shows these levels to be closely related to individual personality traits and coping strategies that are inadequate for the situation. Further research studies will focus on the development of an instrument that can be used for screening patients at risk, and evaluation of possible means of interventions.
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Discussion, conclusions and suggestions for further study

As also observed in this thesis, tumoural uptake of radiopharmaceuticals is generally heterogeneous. The cells that receive a lower or no radiation dose may survive and cause tumour progression. This can be counteracted by employing combination strategies, such as with surgery, and/or additives to manipulate and increase the amount of lethal radiation to the tumours by the radionuclide. The papers 1-3 explore such techniques applied to the treatment of hepatocellular carcinoma by $^{131}$I-Lipiodol. Increasing the administered activity, within the boundaries of radioprotection, is another means to increase the radiation dose to the tumours, but the downside of this strategy is that the radiation dose to the normal tissues increases too. Therefore, decreasing side effects and increasing tolerance is another (supplementary) strategy to allow dose escalation. In the papers 4-6 thyroid uptake and function have been studied in relation to pre-medication techniques. In paper 4 this is the use of recombinant human TSH to stimulate thyroid tumour uptake while avoiding hypothyroidism. In paper 5-6 this is the use of potassium iodide to avoid thyroid uptake of free radioiodine in $^{131}$I-Lipiodol and $^{131}$I-mIBG therapy.

In paper 1, we investigated the anti-tumoural potential of neo-adjuvant $^{131}$I-Lipiodol therapy for HCC before liver transplantation. Trans-arterial loco-regional $^{131}$I-lipiodol therapy was earlier found to substantially reduce recurrence rates and increase disease-free survival in an adjuvant setting after partial hepatectomy. The neo-adjuvant indication was therefore a logical next step because 1) patients are put on the waiting list because of the shortage of donors and risk tumour progression if left untreated, and 2) the loco-regional treatment of the whole liver can control the disease in view of the multi-focal, partially sub-clinical nature of HCC. This proved successful, as in our study obvious anti-tumoural activity was observed in 5/10 (50%) of pre-transplant patients, using strict radiological and histological criteria, and all patients underwent subsequent liver transplantation. Evaluation on larger patient numbers would be necessary to confirm the promising anti-tumoural activity of $^{131}$I-lipiodol in these HCC patients, but this patient group may very well become a standard indication.

As, except for one possible patient, no liver toxicity was noted in this study group, there seems a possibility of dose escalation of administered $^{131}$I-Lipiodol activity. The development and use of $^{186}$Re-Lipiodol may be important to achieve this, as dose escalation of $^{131}$I-Lipiodol is very limited by radioprotection issues originating from the emission of high energetic gamma rays. However, as millimetre-sized disease is a prime target in this indication and prevents the occurrence of new tumours in the transplant waiting interval, a word of caution is in place and the two isotopes may not be viewed as simply one for the other.

The unique feature of a neo-adjuvant treatment group such as in this study is the opportunity to directly evaluate the effect of $^{131}$I-Lipiodol by histology. Indeed, not many studies have this possibility since most radionuclide therapy trials are for palliative, end-stage patients. This has also illustrated that important discrepancies in medical imaging modalities with respect to correct staging may occur. In our study, in several patients tumour size was unchanged while histology showed >90% necrosis. This may lead to serious misjudgement about the value of radionuclide therapy. On the other hand, it is important to compare treatment modalities in a standardised way, and this is still mostly done by CT. Positron emission or PET has a huge potential to evaluate tumour metabolism more functionally and quantitatively, for example substrate use such as glycolysis rate by FDG, DNA proliferation by radiolabeled nucleosides such as deoxyuridine, or annexin as apoptosis marker. This is especially true for radionuclide therapy. One of the few studies to date has evaluated the use of FDG-PET, CT and MRI in $^{90}$Y-glass microsphere treatment of colorectal cancer
metastases. These authors (Eur J Nucl Med 2002; 29:815-820) found a considerably higher sensitivity for “metabolic” response by PET than “anatomic” response by CT/MRI. Future studies in this field should be encouraged.

In paper 2, we investigated the possible positive influence of low-dose cisplatin as a radiosensitiser on toxicity and tumour response. The use of a radiosensitiser is attractive because it may increase tumour cell death by 30%-50% without adding major toxicity to the treatment. Cisplatin has been the referential radiosensitising agent. In our study, the use of low-dose cisplatin infusion as a radiosensitising agent in $^{131}$I-Lipiodol therapy for palliative hepatocellular carcinoma seemed safe and may be beneficial for tumour response, but had no statistically significant impact on survival in the small patient group. A particular difficulty in this study was that the patient group consisted of palliative treatment in end-stage liver cirrhosis, in whom the life expectancy is anyhow very limited regardless of treatment or not. The use of radiosensitiser may be more suitable for curative treatments, also because they include extra efforts in costs and manpower and the incremental gain in quality of life-maintained survival, with the agents currently available, may be small in patients with widespread disease. A large-scale (multicenter) study with a larger patient sample, lead by the French, is now underway that may answer the question whether there is a real benefit of cisplatin in palliative $^{131}$I-Lipiodol therapy. Hopefully this will include all aspects of tumour response, survival, incremental costs and impact on quality of life and compare this with a control arm of no cisplatin. Nevertheless, the use of radiosensitisers in radionuclide therapy is an exciting new field. No doubt we will see many more studies the coming years.

Paper 3 explored the question if a more selective hepatic arterial instillation could be a strategy to increase tumoural uptake, radiation dose and response of $^{131}$I-Lipiodol therapy for HCC. Our analysis of uptake percentage, progression and side effects suggests that hyperselective $^{131}$I-Lipiodol instillation, as opposed to selective administration, is not necessary to achieve a higher activity in tumours. We postulate that an activity that is slowly injected in the common proper hepatic artery is by a large proportion “sucked” into the tumour by its influence of neo-vascularisation and parasitic increased flow, extending to large as well as small vessels. Our study found a strong dose-response relationship: responsive disease was very much associated with higher $^{131}$I–Lipiodol uptake. The incremental $^{131}$I–Lipiodol uptake was shown to sharply decrease with tumour volume, and high volumes were invariably associated with progressive disease. The high correlation of percentage of tumoural uptake with tumour size and tumour response points to an additional possible advantage of $^{90}$Y, used as microspheres, and $^{188}$Re-Lipiodol as alternative isotopes. These isotopes emit higher energetic beta radiation, as compared to $^{131}$I, that may be more suitable for larger sized macroscopic tumours seen in the majority of patients who present for palliative treatment. Further studies with these isotopes should preferably be in prospective, randomised comparison to $^{131}$I-Lipiodol as the standard of treatment.

Paper 4 studied radiiodine kinetics in thyroid carcinoma following stimulation by humane recombinant TSH. The availability of recombinant human TSH (rhTSH) provides an alternative means to elevate the TSH level without inducing hypothyroidism. Our study showed that although tumour doses in thyroid carcinoma patients treated with $^{131}$I after rhTSH were highly variable, 45% of treatments led to disease stabilisation or partial remission, without serious side-effects and with minimal impact on quality of life. This is an important development for $^{131}$I therapy in patients with metastatic and/or recurrent disease, who may be especially intolerant to hypothyroidism causing major disruption of functionality and possible complications, including tumour progression.
The importance of a high radiation dose was confirmed by our study, which showed a higher radiation dose in the group of patients with PR after $^{131}$I therapy. Although Maxon has reported that almost all tumours responded after an absorbed radiation dose of more than 80 Gy, whereas none of those with a radiation dose of less than 35 Gy, we also observed that lesions which seem to have a relatively low radiation dose may still regress following therapy. Indeed, the calculated radiation dose is not the biological received dose; biological variables such as age, prior therapies, time to prior therapies, constitutional radiosensitivity, hypoxia, etc importantly affect the dose-response relationship of radionuclide therapy. For example, in hyperthyroidism, dosimetry-based $^{131}$I therapy has not been convincingly more effective than empirical $^{131}$I therapy. Moreover, variations in dose collection, i.e. organ volume, computational methods, attenuation and scatter correction and choice of time points make comparisons of dosimetry among studies generally not meaningful. Additional analysis of biological relevant factors in addition to more precise physical methods of dosimetry calculation will hopefully allow more improved dose-response estimations for effective clinical dosimetry.

The relatively low tumour radiation dose in most of our patients needs to be addressed and may be related several reasons, i.e. 1) preserved renal function and increased renal clearance of radioiodine compared to hypothyroidism, 2) iodine “contamination” through the continuation of thyroid hormone causing a lower radioiodine uptake, and/or 3) tumoural de-differentiation and decreased radioiodine uptake. Further areas of study may be to examine whether radioiodine uptake after rhTSH stimulation can be further modulated to increase the tumour dose, and which administered dose of rhTSH is most optimal and cost-effective.

In paper 5 and 6, the current practice of profylaxis of thyroidal radioiodine uptake by potassiumiodine pre-medication is documented. Hypothyroidism might result from the undesirable irradiation of the thyroid gland caused by unintentional release of free$^{131}$I from the molecule. Our study evaluated for the first time the observed thyroidal uptake as well as calculated thyroidal radiation dose in patients receiving repetitive $^{131}$I-mIBG treatments while on potassium iodide (KI) thyroid protection. We observed a generally high inter- and intra-individual variability in radioiodide uptake in the thyroid after $^{131}$I-mIBG therapy despite KI pre-medication. This illustrates that thyroid blocking by potassiumiodide is never complete. An important variation of free $^{131}$I in the $^{131}$I-mIBG preparation is a distinct possibility since the free fraction progressively increases after production and $^{131}$I-mIBG has a very limited shelf life. The possible occurrence of hypothyroidism implies that follow-up by regular thyroid hormone controls before, during and after $^{131}$I-mIBG therapy to detect early hypothyroidism is mandatory, and an alternative thyroid cytoprotection strategy for possible long-term survivors may be considered.

Potassium iodide (KI) is not recommended by the guidelines of the European Association of Nuclear Medicine in $^{131}$I-Lipiodol therapy, but some authors have reported visible thyroid uptake or a high thyroid radiation dose without KI. Our study found that $^{131}$I-Lipiodol is associated with a generally low thyroid uptake and dose that may be significantly decreased by KI pre-medication. The probability of hypothyroidism after a single treatment is however, in view of the calculated thyroid dose, very low with or without KI. Given the low cost and the very good tolerance of the KI treatment, the present use of KI may be recommended in these patients.

In paper 7 and 8, subjective patient parameters such as quality of life and anxiety are introduced to radionuclide therapy evaluation. Both cancer and its treatment are severely debilitating and the need to consider their impact upon health-related QoL when making patient management or treatment decisions is now well accepted. The good tolerance of radionuclide therapy has frequently been proposed as a major advantage compared with
systemic chemotherapy. Using the core EORTC quality of life questionnaire, QLQ-C30 and as observed in other treatment modalities, we found that overall quality of life, physical functioning and pain could worsen between 0 and 3 months after $^{131}$I-lipiodol therapy; the occurrence of clinical side effects was particularly associated with a negative impact on quality of life. The QLQ-C30 may be regarded as a feasible method for quality of life assessment in $^{131}$I-Lipiodol therapy for hepatocellular carcinoma and probably in other radionuclide therapies. These observations should be related to the impact of other treatment modalities and/or provide controlled indicators of the positive or negative influence of these modalities in a combination treatment scheme.

The parameter “quality adjusted (survival) time”, i.e. the extra survival time without loss of quality of life, or from an economical point of view, the “prize per quality adjusted time” in the evaluation of radionuclide therapy in comparison with other treatments is a consequent development. These parameters take into account the most important endpoints, i.e. survival, cost-effectiveness, side effects and quality of life impact in one single standardised parameter.

Mood disorders and anxiety have been reported to be the two most frequent psychological disturbances within cancer populations. Currently, there is no literature available on the psychological impact of radionuclide therapy. We observed that patients who experienced a high level of state anxiety showed 1) higher levels of depression and hopelessness, 2) a personality characterised by higher harm avoidance and lower self-directedness, and 3) less aimed and more passive and avoiding coping strategies. The nature of disease (malignant versus non-malignant) was not influential on these results, nor was there a difference between males and females, age, years of education, having a relationship or not, or the duration of hospitalisation. Thus, individual personality styles and coping strategies, and not characteristics such as gender or nature of disease, are associated with anxiety and depression in patients isolated for radionuclide therapy.

Further areas of study may be, from an oncological point of view, to investigate whether high anxiety and depression are associated with a more complicated and limited life expectancy in radionuclide therapy, especially since recent systematic review has been unable to find a consistent association between psychological coping and outcome of cancer. From an economical point of view, it should be investigated whether managing more demanding patients in radionuclide therapy is reflected by increased hospital staff costs and/or exposure. This may provide the correct incentives to screen and counsel patients before entering radio-isolation.

**An outlook on the future of radioiodine therapy**

Radioiodine therapy has been used for more than 60 years and its safety profile is very well known. Therefore developments in radioiodine may be viewed as just as important as development in other isotopes. A particular exciting prospect is to introduce genes (gene therapy) or reactivate existing genes in tumour cells (gene reactivation) that will cause the expression of the sodium/iodide symporter (NIS). The interested reader is referred to some excellent recent papers (Eur J Endocr 1999; 141:443-457; J Clin Endocrin & Metab 2002; 87:1247-1253; Gene Ther 2002; 9:1139-1145; Canc Res 2003; 63:1333-1338). Through this symporter, which is situated in the basolateral plasma membrane of the thyrocyte, radioidoine uptake is facilitated. This symporter can also be introduced in non-thyroid tumours. First experiments in breast, prostate, melanoma, colon, ovarian and of course thyroid cancer indicate this to be a realistic possibility. NIS infected tumour cells can be selectively killed by the induced accumulation of radioiodine. However, uptake, efflux and saturation kinetics of iodide in tumour cells, particularly those of extrathyroidal origin are likely to be different from those of normal thyroid cells. Nevertheless, this is an extremely exciting new
development and may be viewed as the ultimate means of combination therapy to manipulate radiiodine uptake and radiation dose, such as explored in various ways in this thesis.
SUMMARY

Faced with more aggressive tumour with higher proliferation rate, in which it is difficult to achieve a meaningful tumour response with an acceptable level of toxicity, it is pivotal for the further development of radionuclide therapy to extend its scope to combination treatments. The exploration of some of these concepts to established radioiodine therapy was the aim of this thesis.

In paper 1, we investigated the anti-tumoural potential of neo-adjuvant $^{131}$I-Lipiodol therapy for HCC before liver transplantation. Trans-arterial loco-regional $^{131}$I-lipiodol therapy for HCC has been found to substantially reduce recurrence rates and increase disease-free survival in an adjuvant setting after partial hepatectomy. For a neo-adjuvant setting before liver transplantation no data presently exist. $^{131}$I-Lipiodol is an attractive modality for this indication too because of its good tolerability and capacity to treat the whole liver in view of the multi-focal, partially subclinical nature of HCC. In our study, anti-tumoural activity was regarded as obvious with 1) a strong decrease of alpha-fetoprotein (AFP), comparing the highest recorded value before and after $^{131}$I-lipiodol and/or 2) a downstaging in TNM classification on the post-therapy MRI as compared to the pre-therapy MRI and/or 3) tumours with >50% necrosis on histopathology of the explanted liver, without previous chemoembolisation. Thus, an anti-tumoural activity was ascertained in 5/10 (50%) of patients. A follow-up study will evaluate a possible positive influence on disease-free survival.

In paper 2, we investigated the possible positive influence of low-dose cisplatin as a radiosensitiser on toxicity and tumour response. The use of a radiosensitiser is attractive because it may increase tumour cell death by 30%-50% without adding major toxicity to the treatment. Cisplatin has been the referential radiosensitising agent. In this randomised pilot study of $^{131}$I-lipiodol therapy for inoperable hepatocellular carcinoma (HCC), we found a higher percentage of stable or diminished tumour size with the combined use of low-dose cisplatin (90%, vs 40% without). However, a benefit in group survival at 6 months was not evident in this small pilot population. Low-grade stomatitis in one patient and minor changes in peripheral blood count in 7 patients were probably directly related to cisplatin, but its administration is unlikely to be associated with an excess of serious side-effects. The use of low-dose cisplatin infusion as a radiosensitisising agent in $^{131}$I-Lipiodol therapy for HCC seems safe and may be beneficial for tumour control.

Paper 3 explored the question if a more selective hepatic arterial instillation could be a strategy to increase tumoural uptake and response of $^{131}$I-Lipiodol therapy for HCC. We observed a $^{131}$I–Lipiodol uptake of 0.05-2.6 % of the injected dose per ml tumour volume that was significantly higher in responsive disease than stable or progressive disease (p=0.002). High tumour volume was invariably related to low $^{131}$I–Lipiodol uptake and progressive disease (p=0.008). Differences in tumour response between a selective or hyper-selective intra-arterial injection technique were not significant. These results do not support the general use of hyperselective intra-arterial $^{131}$I–Lipiodol administration.

Paper 4 studied the behaviour of iodine kinetics in thyroid carcinoma following stimulation by human recombinant TSH. The availability of recombinant human TSH (rhTSH) provides an alternative means to elevate the TSH level in $^{131}$I therapy for differentiated thyroid carcinoma (DTC) without inducing hypothyroidism. Up to now, reports on the therapeutic efficacy of $^{131}$I after rhTSH stimulation have included only small series of patients without dosimetric results. Our study evaluated the use of $^{131}$I therapy after rhTSH stimulation in patients with advanced metastatic DTC, who may be especially intolerant to hypothyroidism. We showed that although tumour doses in DTC patients treated with $^{131}$I after rhTSH were highly variable, 45% of treatments led to disease stabilisation or partial remission when using rhTSH in conjunction with $^{131}$I therapy, without serious side-effects and
with minimal impact on quality of life. In this patient group, preparation with rhTSH is to be preferred.

In paper 5 and 6, the current practice of prophylaxis of thyroidal radioiodine uptake by potassium iodine pre-medication is documented. Hypothyroidism might result from the undesirable irradiation of the thyroid gland caused by unintentional release of free $^{131}$I from the $^{131}$I-mIBG molecule. Our study evaluated for the first time the observed thyroid uptake as well as calculated thyroidal radiation dose in patients receiving repetitive $^{131}$I-mIBG treatments while on potassium iodide (KI) thyroid protection. We observed a generally high inter- and intra-individual variability in radioiodine uptake in the thyroid after $^{131}$I-mIBG therapy despite KI pre-medication, as well as possible occurrence of hypothyroidism. Alternative pre-medication strategies may be considered for some patient groups.

Potassium iodide (KI) is not recommended by the guidelines of the European Association of Nuclear Medicine in $^{131}$I-Lipiodol therapy, but some authors have reported visible thyroid uptake or a high thyroid radiation dose without KI. Our study prospectively calculated the thyroid uptake and radiation dose in patients receiving one or more $^{131}$I-Lipiodol treatments, with or without KI pre-treatment. We found that single $^{131}$I-Lipiodol administration is associated with a generally low thyroid uptake and dose that was, however, significantly decreased by KI pre-medication. Given the low cost and the very good tolerance of the KI treatment, its general use should be recommended in patients receiving $^{131}$I-Lipiodol therapy.

In paper 7 and 8, subjective patient parameters such as quality of life and anxiety are introduced to radionuclide therapy evaluation. Both cancer and its treatment are severely debilitating and the need to consider their impact upon health-related ‘quality of life’ (QoL) when making patient management or treatment decisions is now well accepted. The good tolerance of radionuclide therapy has frequently been proposed as a major advantage compared with systemic chemotherapy. Our study used the core EORTC quality of life questionnaire, QLQ-C30, in palliative $^{131}$I-Lipiodol therapy for hepatocellular carcinoma. We found that overall quality of life, physical functioning and pain significantly worsened between 0 and 3 months after $^{131}$I-lipiodol therapy, irrespective of tumour response. Particularly the occurrence of clinical side-effects was associated with a negative impact on quality of life. QLQ-C30 can be regarded as a feasible method for quality of life assessment in $^{131}$I-lipiodol.

Mood disorders and anxiety have been reported to be the two most frequent psychological disturbances within cancer populations. Currently, there is no literature available on the psychological impact of radionuclide therapy. In our prospective study, we assessed the variables that are involved with the occurrence of anxious distress during isolation and radionuclide therapy. Patients who experienced a high level of state anxiety during isolation showed 1) higher levels of depression and hopelessness, 2) a personality characterised by higher harm avoidance and lower self-directedness, and 3) less aimed and more passive and avoiding coping strategies. The nature of disease (malignant versus non-malignant) was not influential on these results, nor was there a difference between males and females, age, years of education, having a relationship or not, or the duration of hospitalisation. Thus, individual personality styles and coping strategies, and not characteristics such as gender or nature of disease, are associated with anxiety and depression in patients isolated for radionuclide therapy.

In the epilogue of the thesis, specific areas of further research applicable to the papers and methodological issues discussed. Finally, a view on the future of radioiodine therapy is provided.
SAMENVATTING

Indien men geconfronteerd wordt met agressievere tumoren waarbij de proliferatiesnelheid hoog is en het moeilijk is een betekenisvolle tumorrespons te bereiken met een acceptabel niveau van toxiciteit, en men wil dat ook bij deze tumoren radionuclide therapie een rol speelt, dan is het cruciaal om te komen tot combinatiebehandelingen en deze te evalueren volgens algemeen geaccepteerde eindpunten. The exploratie van een verbrede horizon in die richting met betrekking tot gevestigde radiojood therapie indicaties was de inzet van dit doctoraat.

In artikel 1, onderzochten we het anti-tumorale potentieel van neo-adjuvante $^{131}$I-Lipiodol therapie bij patiënten met het hepatocellulair carcinoom op de wachtlijst vóór levertransplantatie. Trans-arteriële locoregionale $^{131}$I-Lipiodol therapie werd namelijk eerder geassocieerd met een geringer aantal recidieven en verlengd ziektevrij overleven in adjuvant gebruik na partiële heptactomie voor HCC. Voor neo-adjuvant, pre-transplant patiënten bestaan geen data, maar ook deze indicatie lijkt aantrekkelijk vanwege de goede tolerantie voor $^{131}$I-Lipiodol en de mogelijkheid om de hele lever in één sessie te behandelen gezien het multi-focale, partieel subklisch gedrag van het HCC. In deze pilootstudie werd een antitumorale activiteit van $^{131}$I-Lipiodol als zéker beschouwd in het geval van 1) een sterke afname van alfa-foetoproteine (AFP) vóór t.o.v. na $^{131}$I-Lipiodol, en/of 2) een ‘downstaging’ in TNM classificatie op de posttherapie MRI vergeleken met de pretherapie MRI, en/of 3) tumoren met $>50\%$ necrose in het histologisch preparaat van de geëxplanteerde lever, zónder voorgeschiedenis van chemo-embolisatie. Een antitumorale activiteit werd aldus bij minstens 5/10 (50\%) van de patiënten verzekerd. Een vervolgstudie zal bepalen of dit ook gepaard gaat met een positieve invloed op de ziektevrije overleving.

In artikel 2 onderzochten we de eventuele positieve invloed van het gebruik van cisplatine als ‘radiosensitizer’ op toxiciteit en tumor respons. Het gebruik van een ‘radiosensitizer’ kan tumorceldood met 30-50\% verhogen zonder belangrijke bijkomende toxiciteit. Cisplatine is het standaardproduct. In deze gerandomiseerde pilootstudie bij het inoperabele hepatocellulair carcinoom (HCC) vonden we in de subgroep van $^{131}$I-Lipiodol met lage dosis cisplatine bij 9/10 patiënten (90\%) een stabilisering of afname van de tumormassa, terwijl dit bij 4/10 (40\%) van de patiënten zonder cisplatine was. Een verschil in overleving na 6 maanden werd echter bij deze kleine groep patiënten niet vastgesteld. Laaggradige stomatitis in één patiënt en lichte veranderingen in het perifeer bloedbeeld bij 7 patiënten hadden waarschijnlijk een directe relatie met het gebruik van cisplatine, maar het is weinig waarschijnlijk dat dergelijk gebruik tot ernstige bijwerkingen zou leiden. Cisplatine als een ‘radiosensitizer’ in $^{131}$I-Lipiodol therapie voor HCC lijkt veilig en kan bijdragen tot een verhoogde tumorcontrole.

Artikel 3 onderzocht de vraag of een meer selectieve hepatische injectie een algemene strategie zou kunnen zijn om de tumorale opname van $^{131}$I-Lipiodol en dus bestralingsdosis voor HCC tumoren te verhogen. Wij vonden in het algemeen een $^{131}$I–Lipiodol opname van 0.05-2.6 % van de geïnieceerde dosis per ml tumorvolume dat significant hoger was in respondereende tumoren t.o.v. progressieve tumoren (p=0.002). Een hoog tumorvolume was constant gerelateerd aan een lage $^{131}$I–Lipiodol opname en progressieve ziekte (p=0.008). Verschillen tussen de groep met selectieve of hyperselectieve toediening waren echter niet significant. Deze resultaten ondersteunen geen algemeen gebruik van hyperselectieve intra-arteriële $^{131}$I–Lipiodol toediening.

Artikel 4 bestudeerde de kinetiek van radiojood in gedifferentieerd schildkliercarcinoom na stimulatie met humaan recombinant TSH (rhTSH). De beschikbaarheid van recombinant humaan TSH (rhTSH) levert een alternatief om de TSH spiegel te verhogen in $^{131}$I therapie voor gedifferentieerd thyroid carcinoom (DTC), zonder hypothyreoïdie te induceren. Tot nu toe hebben de studies omtrent de therapeutische
efficaciteit van $^{131}$I na rhTSH stimulatie slechts kleine series zonder dosimetrische resultaten geïncludeerd. Deze studie evalueerde de $^{131}$I therapie na rhTSH stimulatie bij patiënten met gevorderd metastatisch DTC, die bijzonder intolerant voor hypothyreoidie kunnen zijn. Alhoewel de tumordossissen van $^{131}$I na rhTSH zeer variabel waren, leidde toch 45% van de behandelingen tot een ziektestabilisatie of partiële remissie, zonder belangrijke bijwerkingen en met een minimale impact op kwaliteit van leven. Bij deze groep van patiënten is de voorbereiding met rhTSH te prefereren.

In de artikelen 6 en 7 onderzochten we algemene klinische praktijk van profylaxe van opname van ongebonden radiojood in de schildklier door kaliumiodide. Hypothyreoidie kan veroorzaakt worden door de ongewenste bestraling van de schildklier bij ontkoppeling van vrij $^{131}$I uit de molecula. Een eerste studie evalueerde de geobserveerde schildklieropname en de berekende dosis in patiënten na meerdere $^{131}$I-mIBG therapieën onder kaliumiodide (KI) thyroid protectie. We stelden een in het algemeen grote inter- en intra-individuele variabiliteit in radiojod opname in de schildklier vast ondanks KI, alsook het optreden van hypothyreoidie in deze patiëntengroep. Alternatieve premedicatie strategieën zouden aldus bij bepaalde patiëntengroepen kunnen worden overwogen.

Kaliumiodide (KI) is niet aanbevolen in de richtlijnen van de Europese Associatie van Nucleaire Geneeskunde bij $^{131}$I-Lipiodol therapie, ondanks het feit dat sommige auteurs een zichtbare schildklieropname op scan of hoge berekende schildklierdosis hebben vastgesteld zonder gebruik van KI. Deze studie berekende prospectief de schildklieropname en bestralingsdosis in patiënten na één of meerdere $^{131}$I-Lipiodol therapieën, met of zonder KI pretherapie. Wij vonden dat een enkele $^{131}$I-Lipiodol toediening geassocieerd is met een algemeen lage schildklieropname en -dosis die weliswaar significant verlaagd kon worden met gebruik van KI. Gezien de lage kosten en zeer goede tolerantie voor KI, is het gebruik bij patiënten behandeld met $^{131}$I-Lipiodol in het algemeen aanbevolen.

In de artikelen 7 en 8 introceren we subjectieve patiënt parameters als ‘kwaliteit van leven’ en stress als valabele eindpunten in de evaluatie van radionuclide therapie. Zowel kanker als de behandeling ervan zijn namelijk ernstig verzwakkend en de noodzaak om met de impact van gezondheidsgerelateerde ‘kwaliteit van leven’ (QoL) rekening te houden is nu goed geaccepteerd. De goede tolerantie van radionuclide therapie is vaak als een belangrijk voordeel beschouwd, vergeleken met systemische chemotherapie. Deze studie gebruikte de basis EORTC vragenlijst, de QLQ-C30 in palliatieve $^{131}$I-Lipiodol therapie voor hepatocellulair carcinoom. We vonden dat de ‘overall’ QoL, lichamelijk functioneren en pijnklachten significant verslechterden tussen 0 en 3 maanden na $^{131}$I-Lipiodol therapie, onafhankelijk van tumor respons. Vooral het optreden van klinische bijwerkingen was geassocieerd met een negatieve impact op QoL. QLQ-C30 kan beschouwd worden als een bruikbare methode voor QoL beoordeling in $^{131}$I-Lipiodol therapie.

Op dit moment is er geen literatuur beschikbaar omtrent de psychologische impact van de radionuclide therapie zelf. In deze prospectieve studie bepaalden wij de variabelen die zijn betrokken bij het optreden van angsttoestanden gedurende isolatie en radionuclide therapie. Bij patiënten met een hoog angstniveau tijdens opname observeerden wij 1) een hoog niveau van depressie en hopeloosheid, 2) een leedvermijdende en weinig zelfsturende persoonlijkheid, en 3) een minder gerichte en meer passieve ‘coping’ strategie. De aard van de ziekte (maligne versus niet-maligne) beïnvloedde deze resultaten niet, evenmin als het geslacht, leeftijd, aantal jaren van opleiding, al of niet een relatie, of de duur van de hospitalisatie. Angst en depressie tijdens isolatie voor radionuclide therapie zijn geassocieerd met individuele persoonlijkheidsstijlen en niet met karakteristieken zoals geslacht of aard van de ziekte.

In de epiloog van dit doctoraat worden specifieke gebieden voor verder onderzoek en methodologische overwegingen besproken, gevolgd door een afsluitende blik in een mogelijke toekomst van radiojood therapie.
RESUME

Confronté à une tumeur plus agressive avec un taux plus élevé de prolifération, dans lequel il est difficile réalisez une réponse significative de tumeur avec un niveau acceptable de la toxicité, il est pivotal pour le développement de la thérapie de radionucléide pour prolonger sa portée aux traitements de combinaison. L'exploration de certains de ces concepts à la thérapie établie de radioiodé était le but de cette thèse.

En papier 1, nous avons étudié le potentiel anti-tumoral de la thérapie de néo-adjuvant 131I-Lipiodol pour HCC avant la transplantation de foie. L’administration intra-artérielle hépatique de 131I-Lipiodol pour le HCC a démontré un effet substantiel sur la réduction des taux de récidive et l’augmentation de l’intervalle de survie sans récidive en utilisation adjuvante après une résection chirurgicale partielle. Pour une utilisation néo-adjuvante, dans le cadre pré-transplantatoire, aucune donnée n’existe actuellement. Le traitement par administration intra-artérielle hépatique du 131I-Lipiodol est une modalité attrayante pour cette indication en raison de sa bonne tolérance et de sa capacité à traiter le foie entier étant donné la nature multi-focale partiellement infra-clinique du HCC. Dans notre étude pilote, l’activité antitumorale a été considérée comme évidente avec 1) une diminution forte d’alfa-foetoproteine (AFP), comparant la plus forte valeur enregistrée avant et après 131I-Lipiodol et/ou 2) une sous-stadification dans la classification TNM sur l’IRM après thérapie en comparaison de l’IRM en pré-thérapie et/ou 3) les tumeurs avec >50% nécrose sur l'histopathologie du foie, n’ayant pas reçu de chimioembolisation préalable. Ainsi, une activité anti-tumorale a été vérifiée dans 5/10 (50%) des malades. Une étude de suivi évaluera la possibilité d’une influence positive sur l’intervalle de survie sans récidive.

En papier 2, nous avons étudié l'influence positive possible du cisplatin comme un agent radiosensibilisant sur la toxicité et la réponse de tumeur. L'utilisation d'un radiosensibilisant est intéressant parce qu'il peut augmenter la mort de cellules tumorales de 30%-50% sans ajouter de toxicité majeure au traitement. Le Cisplatin a été l'agent de référence. Dans notre étude pilote randomisée, de la thérapie à l' 131I-lipiodol pour le carcinome hépatocellulaire (HCC) inopérable, nous avons trouvé un plus fort pourcentage de stabilisation ou diminution de la taille tumorale avec l’utilisation de cisplatin à faible dose (90%, contre 40% sans cisplatin). Cependant, la population était trop petite pour apprécier le bénéfice en terme de survie à 6 mois. Nous avons observé une stomatite de faible grade et des changements mineurs dans les taux sanguins périphériques chez 7 patients probablement en relation directe avec le cisplatin, mais son administration n’est vraisemblablement pas à associer à un excès d’effets secondaires sérieux. L'utilisation de perfusion de faible dose de cisplatin comme un agent radiosensibilisant dans la thérapie à 131I-Lipiodol pour le HCC semble sûre et contribuer au contrôle de la tumeur.

Papier 3 a exploré la question de savoir si une administration artérielle hépatique plus sélective pouvait être une stratégie générale pour augmenter la fixation tumorale et la réponse au 131I-Lipiodol pour le HCC.

Nous avons observé une fixation de l’ 131I-Lipiodol entre 0.05-2.6 % de la dose injectée par ml de tumeur qui était significativement plus fort pour les malades qui répondaient au traitement que pour ceux dont la maladie était stable ou en progression (p=0.002). Les volumes tumoraux les plus importants étaient ceux qui invariablement fixaient le moins l’ 131I-Lipiodol et ayant une progression de la maladie (p=0.008). Les différences dans la réponse tumorale entre les groupes recevant des injections par techniques sélective ou hypersélective n'étaient pas significatives. Donc, notre étude ne soutient pas l'usage général de l’administration artérielle hépatique du 131I-Lipiodol plus sélective.

Le papier 4 a étudié le comportement de la cinétique d'iode dans le carcinome thyroïde après stimulation par TSH de recombinaison humanitaire. La disponibilité de la TSH humaine
recombinante (rhTSH) pour le carcinome différencié de la thyroïde (CDT) fournit un moyen alternatif pour élever le niveau de TSH sans induire une hypothyroïdie. Jusqu'alors, les rapports sur l'efficacité thérapeutique de $^{131}$I après la stimulation par rhTSH ont inclus seulement de petites séries de malades sans résultats de dosimétrie. Notre étude a évalué l'utilisation de la thérapie $^{131}$I après la stimulation par rhTSH dans les CDT métastatiques avancées, qui peut être particulièrement intolérants à l'hypothyroïdie. Nous avons montré que bien que les doses délivrées aux tumeurs chez les patients CTD traités avec $^{131}$I après rhTSH étaient extrêmement variables, 45% des traitements ont mené à la stabilisation de maladie ou à la rémission partielle en utilisant la rhTSH conjointement avec $^{131}$I thérapie, sans effets secondaires sérieux et avec un impact minimal sur la qualité de vie. Dans cette population, préparation avec rhTSH est préférable.

En papier 5 et 6, la pratique courante des prophylaxies de la prise thyroïdienne de radioiode par l'iode de potassium (KI) est documentée. L'hypothyroïdie pourrait résulter de l'irradiation indésirable de la glande de thyroïde causée par le relarguage involontaire de $^{131}$I libre par la molécule $^{131}$I-mIBG. Notre étude a évalué pour la première fois la fixation thyroïdienne ainsi que le calcul de la dose d’irradiation thyroïdienne des traitements répétitifs à la $^{131}$I-mIBG avec protection de la thyroïde par l'iode de potassium (KI). Nous avons observé généralement une haute variabilité inter et intra-individuelle dans la fixation de l’iode radioactif au niveau thyroïdien après la thérapie $^{131}$I-mIBG en dépit de la prémédication de KI, ainsi que la survenue possible d’hypothyroïdie. Les stratégies alternatives de prémédication peuvent être considérées pour quelques groupes patients.

L’iodure de potassium (KI) n’est pas recommandé par l’Association européenne de Médecine Nucléaire dans la thérapie $^{131}$I-Lipiodol, mais quelques auteurs ont rapporté la fixation thyroïdienne ou une forte dose d’irradiation de la thyroïde sans KI. Notre étude a calculé la fixation thyroïdienne et la dose d’irradiation chez les malades recevant un ou plusieurs traitements de $^{131}$I-Lipiodol, avec ou sans KI. Nous avons trouvé que un seul traitement de $^{131}$I-Lipiodol était associé avec une fixation de la thyroïde généralement basse et que la dose peut être significativement diminuée par la prémédication de KI. Etant donné le coût faible et la très bonne tolérance du traitement de KI, son usage dans la thérapie $^{131}$I–Lipiodol devrait être recommandé.

En papier 7 et 8, des paramètres patients subjectifs tels que la qualité de la vie et l'inquiétude sont présentés à l'évaluation de thérapie de radionucléide. Le cancer et son traitement sont tous les deux sévèrement affaiblissants et le besoin de considérer leur influence sur la 'qualité de vie' relative à la santé lors de la prise en charge des malades et des décisions de leur traitement sont maintenant bien acceptés. La bonne tolérance de la thérapie par les radionucléides a fréquemment été proposée comme un avantage majeur comparé à chimiothérapie systémique. Notre étude a utilisé l’essentiel du questionnaire de qualité de vie de l’EORTC, QLQ-C30, dans la thérapie palliative à $^{131}$I-Lipiodol pour le carcinome de hépatocellulaire. Nous avons trouvé que la qualité de vie globale, les capacités physiques et la douleur s'aggraveraient significativement entre 0 et 3 mois après la thérapie à $^{131}$I-lipiodol, quelle que soit la réponse tumorale. Particulièrement la survenue d’effets secondaires étaient associés à un impact négatif sur la qualité de vie. QLQ-C30 peut être considéré comme une méthode faisable pour l’évaluation de qualité de vie dans la thérapie à $^{131}$I-lipiodol.

L’anxiété et les troubles de l’humeur ont été rapportés pour être les deux plus fréquents dérangements psychologiques dans les populations de cancer. Actuellement, il n’y a pas de littérature disponible sur l’impact psychologique de la thérapie avec des radionucléides. Dans notre étude prospective, nous avons évalué les variables qui sont impliquées dans la survenue de la détresse anxieuse pendant la thérapie avec isolement. Nous avons observé que les malades qui ont éprouvé un niveau supérieur d'anxiété dans l’isolement, ont montré 1) les niveaux supérieurs de dépression et de désespoir, 2) une personnalité caractérisée par un événement de tout malheur et une prise en charge de même moindre, et 3) une ‘coping’ plus
désœuvrée, plus passive et non direct. La nature de la maladie (maligne contre non maligne) n’influait pas sur ces résultats, pas plus qu’il n’y avaient une différence entre les hommes et les femmes, l’âge, les années d’éducation, ayant une relation ou pas, ou la durée d’hospitalisation. Ainsi, les personnalités individualistes, et non pas les caractéristiques tel que le sexe ou la nature de la maladie, sont associées avec l’anxiété et la dépression chez les malades isolés pour la thérapie avec les radionucléides.

Dans l’épilogue de la thèse, des domaines d’avantage de recherche applicables aux papiers et des issues méthodologiques sont discutés. En conclusion, une vue du futur de la thérapie de radioiode est fournie.
Dankwoord

Bij het schrijven van het dankwoord komt het besef dat veel mensen in meer of mindere mate een bijdrage hebben geleverd. Een dankwoord wordt dan sowieso iets willekeurigs. Daarom wil ik in de eerste plaats dank zeggen aan al die mensen die op één of andere manier betrokken zijn geweest bij dit doctoraat en er een positieve bijdrage aan hebben geleverd. Met iets grotere nadruk wil ik hier diegenen vermelden zonder wie dit doctoraat niet in deze vorm tot stand gekomen was.

In de eerste plaats mijn ouders, Jos en Erica en mijn broer Michael voor hun groot vertrouwen, steun en interesse tijdens al mijn universitaire studies.

Mijn grootvader, wijlen “opa Veldman” voor onvergetelijke zondagmiddagen met koffie en speculaas.

Mijn studievriend Dr Patrick Flamen, voor de introductie in de wereld van de nucleaire geneeskunde.

Mijn opleider, Prof Dr Pierre Blockx, voor de opportuniteiten die hij mij geboden heeft in de opleiding nucleaire geneeskunde.

Mijn promotor, Prof Dr Rudi Dierckx voor zijn gedrevenheid en toewijding aan de nucleaire geneeskunde.

De klinisch fysici Lic Myriam Monsieurs en Ir Klaus Bacher voor veel rekenwerk en het mij doen appreciëren van de verschillen en overeenkomsten tussen een fantoom en een patiënt.

Dr Geneviève Laureys voor haar interesse in mIBG therapie en toevertrouwen van haar patiënten.

De collega’s van het Leverteam UZ Gent voor de fijne samenwerking in de Lipiodol therapie. In het bijzonder ook de collega’s radiologen, Dr Luc Defreyne en Dr Peter van Langenhove en hun team voor hun grote bereidwilligheid tot het uitvoeren van de levercatheterisaties.

Dr Kurt Audenaert voor een waardevol psychologisch inzicht.

Speciale hulde aan Dr Frederic De Winter† voor zijn enthousiaste bijdrage bij het opzetten van de $^{131}$I-Lipiodol therapie. Technici en verpleging van Poli 7 voor, onder andere, de vele “GN REK” posttherapie scans. De verpleging van 9K12/4K2 voor hun onverschrokken taakuitvoering op de isolatiekamers. Alle experts stralingsbescherming van de ‘kamers’ (Myriam Monsieurs, Walter Verweire, Jean-Pierre Van Haelst, Filip De Vos) voor hun controle van ‘open’ bronnen die beter gesloten hadden gebleven.

De collega’s van de ‘Therapy committée’ van de Europese Associatie van Nucleaire Geneeskunde, voor inspiratie.

Dr John De Klerk, voor de plezierige samenwerking in de studies met recombinant TSH, iets waar we ons broek niet aan gescheurd hebben.

De leden na de Examenjury voor constructieve commentaren.

Voor oneindige liefde en steun dank ik mijn grote dierbaren: Ellen, Sebastiaan en Marthe.
CURRICULUM VITAE


Naast diverse lidmaatschappen van nationale en internationale verenigingen zijn als bijzonderheden te vermelden het alumnischap van de Vlerick Leuven Management School (sinds 2001) en lidmaatschap van de Radionuclide Therapie Commissie van de Europese Vereniging voor Nucleaire Geneeskunde (sinds 2000). Hij is to heden (co)-auteur van 26 internationale A-publicaties. Zijn speciale interesses liggen in de therapeutische toepassingen, intra-operatieve detectie, pediatrie en PET.