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BIOMEDICAL IMAGING AND THERAPY FOR PERSONALIZED HEALTHCARE

Internal Dosimetry Task Force Report on:

Treatment Planning For Molecular Radiotherapy: Potential And Prospects

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CONTENTS

ACKNOWLEDGEMENTS

We are indebted to Sonia Niederkofler for her assistance in the organisation of this report.

ACRONYMS

BED – biologically effective dose
BSSD – Basic safety standards directive of Council directive 2013/59 Euratom
CR – Complete Response
CT – Computed Tomography
DTC – Differentiated Thyroid Cancer
EBRT – External Beam Radiation Therapy
EDTMP - ethylenediamine tetra methylene phosphonic acid
FDA – United States Food and Drug Administration
HCC – Hepatocellular Carcinoma
HEDP - Hydroxyethylidene Diphosphonic Acid
IDTF – EANM Internal Dosimetry Task Force
ICRP – International Commission on Radiological Protection
MAA – Macroaggregated albumin
MDP - Methylene diphosphonate
mIBG – Metaiodobenzylguanidine
MIRD – Medical Internal Radiation Dose
MRT – Molecular radiotherapy
NIS – sodium/iodide symporter
NTCP – Normal tissue complication probability
ORR – Overall Response Rate
PET – Positron Emission Tomography
PFS – Progression-Free Survival
PNET – Pancreatic Neuroendocrine Tumours
PRRT – Peptide Receptor Radionuclide Therapy
PSA – Prostate-Specific Antigen
PSMA – Prostate Specific Membrane Antigen
RBE – Relative Biological Effect
rhTSH – recombinant human TSH
RIT – Radioimmunotherapy
RNT – Radionuclide therapytherapy
SPECT – Single Photon Emission Computed Tomography
SNMMI – Society of Nuclear Medicine and Molecular Imaging
TARE – Transarterial Radioembolisation
TATE - (Tyr^3)-octreotate
TCP – Tumour Control Probability
TOC – (Phe^1-Tyr^3)-octreotide
TOF – Time Of Flight
TSH – Thyroid-Stimulating Hormone

EXECUTIVE SUMMARY

» Cancer and benign diseases have been treated with radiopharmaceuticals since the 1940s. A forthcoming European council directive (council directive 2013/59 Euratom) mandates that treatments should be planned according to the radiation doses delivered to individual patients, as is the case for external beam radiotherapy. The directive also specifies that verification of the radiation doses delivered should be performed.

» In recent years the number and range of radiotherapeutics available has expanded significantly. Many new agents are in development or in early phase clinical trials. These will provide new treatment options for many cancers, particularly following unsuccessful treatments with conventional chemotherapeutics or relapse and will have a significant impact on the costs of healthcare.

» A survey of practice in Europe has shown a very wide range of practice in terms of treatment prescriptions, not just between different centres but also between different centres in the same countries. Although the Basic Safety Standards directive mandates the involvement of medical physics experts in therapeutic procedures, of those that responded this is not currently the case for 1 in 3 cases.

» In almost all therapeutic procedures considered, the ability to perform image-based patient-specific dosimetry has been demonstrated. This allows verification of the absorbed doses delivered to tumours, target volumes and healthy organs. Patient-specific treatment planning is also feasible in all cases, either from tracer studies with the therapeutic radionuclide, with surrogate imaging radionuclides as 'companion diagnostics', or within an 'adaptive planning' strategy in the case of multiple administrations.

» Molecular radiotherapy (MRT) is a highly multidisciplinary area requiring a range of trained staff to provide a comprehensive service. All therapy procedures have demonstrated the potential to be highly effective. Dosimetry-based individualisation of treatment is likely to significantly improve this effectiveness, although must be adequately resourced.

INTRODUCTION

Cancer and benign diseases have been treated with radiopharmaceuticals since the 1940s. Although internal dosimetry was initially investigated for benign and malignant thyroid disease with radioiodine, this was subsequently omitted and for over 60 years radiotherapeutic administrations have been primarily governed by fixed levels of activity, sometimes modified by patient weight or body surface area.

The aim of this report is to examine the potential for personalised, dosimetry-based treatment planning and verification of the absorbed dose delivered. The main sections evaluate whether dosimetry is feasible for the therapeutic procedures currently used, examine the evidence for absorbed dose-effect correlations, and speculate on how personalised treatment planning may be further developed. The results of a Europe wide survey on current practice in MRT are also presented which serves to demonstrate the range of practices currently offered and the need to promote European standardisation and optimisation. Finally, consideration is given to the resources needed to deliver a comprehensive therapy service.

The European directive 2013/59/Euratom (1) is concerned with basic safety standards for protection against the dangers arising from exposure to ionising radiation. Of particular relevance to medical procedures is the need for justification of medical exposures and the recording and reporting of absorbed doses from medical procedures. The general principle of optimisation is applied to radiotherapeutic procedures in terms of patient dosimetry:

Article 56 Optimisation

'For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.'

The term 'radiotherapeutic' is specifically defined as 'including nuclear medicine for therapeutic purposes' (Definition 81).

This form of treatment has been known by many names. In general the most widely used term has been radionuclide therapy. In recent years the term 'molecular radiotherapy' (MRT) has gained acceptance to describe the use of radiotherapeutics informed by patient-specific absorbed dose calculations, as this acknowledges that for any given procedure, for any given patient, treatment outcome is dependent on the absorbed doses delivered to tumours, target volumes and to healthy organs. However, it should be noted that not all therapy procedures employ a molecular process, a notable exception being the use of ^{90}Y microspheres for hepatocellular carcinoma and liver metastases. In this respect, this generic term emulates that of 'molecular imaging' which is also widely applied to functional imaging procedures. In this report 'radionuclide therapy' is used as a general term to refer to treatment with radiopharmaceuticals, and the term 'molecular radiotherapy' is used where dosimetry is a key element.

BACKGROUND TO RADIONUCLIDE THERAPY

Radionuclide therapy exploits the energy released by unstable, artificially produced nuclei to damage and ultimately kill cancer cells. Most radionuclide therapeutic procedures employ electron (β-) emitters, which usually release their energy within the range of millimetres of tissue. More recently, α emitters – which deposit a higher energy per length of tissue - are also being used in clinics as well as in preclinical trials.

Unsealed sources of radioactivity can be injected intravenously or released locally, as in the case of intrathecal, intra-arterial, intra-tumoural, intra-peritoneal or intra-articular treatments. Initial reports of radionuclide therapy in humans date back to the period between 1938 and 1939, when several patients suffering from chronic myeloid and lymphoid leukaemia were treated with repeated oral administrations of ^{32}P sodium phosphate, which accumulates in blood cells (2).

In the case of intravenous administrations, the prerequisite for an effective treatment which also minimises side effects is the selectivity for the desired target. It is no coincidence that, for several decades starting from the forties, the field of radionuclide therapy was essentially dominated by the treatments of thyroid cancer and hyperthyroidism with ^{131}I NaI, which exploits an extremely selective mechanism to enter the thyrocytes.

Nowadays the panel of possible mechanisms and targets identified for delivering radionuclide treatments has expanded tremendously. Single isotopes mimicking the function of native elements can be injected in pharmaceutically accepted salt forms (e.g. $Na_3{}^{32}PO_4$, $Na^{131}I$, $^{89}SrCl_2$ $^{223}RaCl_2$), conjugated to small molecules (e.g. mIBG) or coordinated in molecules such as diphosphonates (e.g. EDTMP, HEDP, MDP), peptides (e.g. TOC, TATE, PSMA) or antibodies (e.g. ibritumomab, tositumomab, etc).

This increment of radionuclide therapy applications has brought the attention of both the scientific community and the institutional bodies to the need for planning and verification of the absorbed dose delivered to individual patients, as is currently standard practice in external beam radiotherapy (EBRT). However, while many decades of development have led to treatment planning and dosimetry for EBRT being relatively straightforward (3, 4), this represents a challenge for radionuclide treatments given systemically (i.e. internal dosimetry), whose biodistribution and ultimate targeting is greatly heterogeneous among individuals and whose therapeutic effect is exerted over a long period of time (days or weeks in many cases, depending on both biological and physical properties of the radiopharmaceuticals).

Nuclear medicine has the intrinsic potential of allowing pre- and post-therapeutic ***in- vivo*** biodistribution studies. By applying a computational analysis on radioactivity distribution in organs and tumour lesions over time, internal dosimetry allows the desired dose estimations in these body compartments to be obtained. Such dosimetry studies can profoundly inform the planning and delivery of radionuclide treatments.

References – Introduction and Background

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SURVEY ON THE IMPLEMENTATION OF THERAPY AND DOSIMETRY PROCEDURES IN EUROPE

To date there has been little investigation of the extent and implementation of MRT and dosimetry throughout Europe for either clinical routine or research. A survey was therefore conducted between June 2016 and September 2016 to obtain an initial overview of current practices. The primary route of dissemination was via European Association of Nuclear Medicine (EANM) national delegates although it was also distributed via national networks for medical physicists and nuclear medicine.

The survey concerned therapy procedures performed during the year 2015. Eighteen different therapy procedures were explicitly considered, as listed in Figure 1. There were also additional pages for "Therapy using alpha emitting radionuclides other than ^{223}Ra", and for "Therapy using other radiopharmaceuticals". The total number of responders was 208, distributed over 26 European countries. Here we provide a short summary of the results of the survey that will be reported in their entirety in a separate publication.

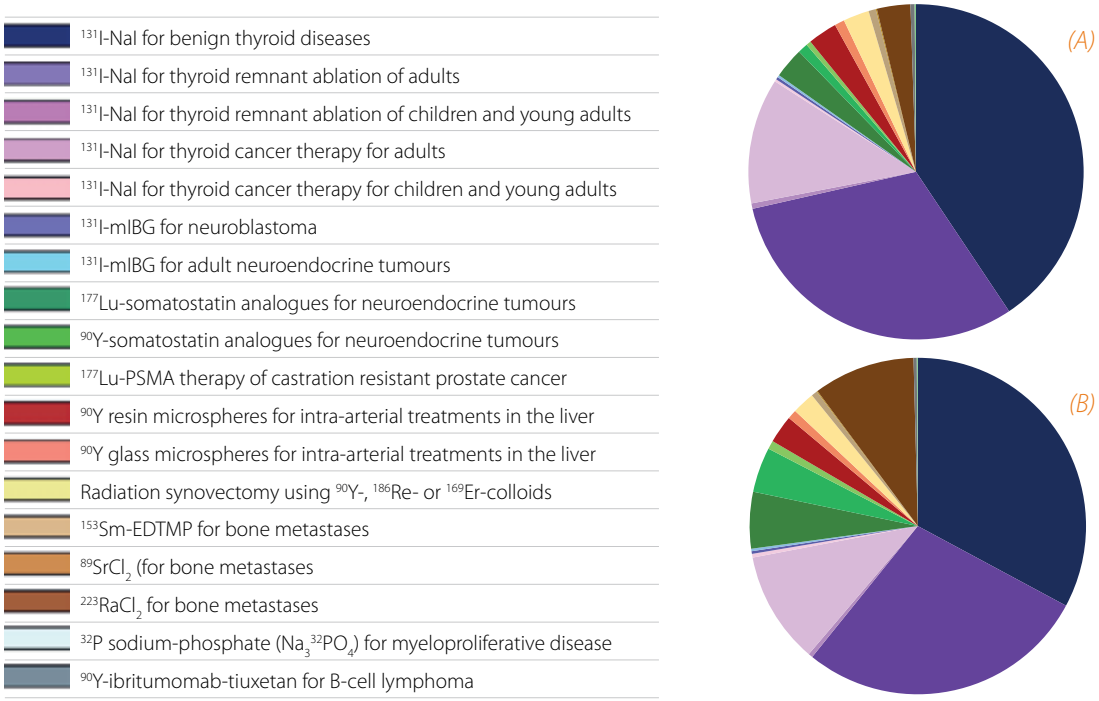


Figure 1. *The proportion of (A) the total number of treated patients, (B) the total number of administered therapies that comprised the different kinds of therapies*

NUMBER OF PATIENTS AND NUMBER OF TREATMENTS

Figure 1 shows the proportion of the number of treated patients and the number of administered therapies that comprised the different procedures in 2015. In total, in all countries and the 208 centres, 34,838 patients were treated with a total number of administrations of 42,853, as a result of some procedures being repeated. Therapies involving ^{131}I represented 84% of the treated patients, and 71% of the number of treatments given. Of the total treatments, 11% consisted of ^{177}Lu/^{90}Y somatostatin receptor PRRT or ^{177}Lu PSMA, and 10% of $^{223}RaCl_2$. The therapies that were most disseminated among the countries were those involving ^{131}I-NaI for the treatment of benign thyroid diseases and for thyroid ablation of adults, which together comprised 71% of the treated patients and 60% of the given treatments.

INVOLVEMENT OF MEDICAL PHYSICIST

The level of involvement of a medical physicist was asked for, and in 68% of the cases a medical physicist was always involved or involved in the majority of treatments. In the remaining 32% of cases a medical physicist was never involved or involved in a minority of treatments. Responses above 80% were obtained for ^{177}Lu PSMA therapy of castration resistant prostate cancer, ^{90}Y somatostatin receptor PRRT, ^{32}P sodium-phosphate for myeloproliferative diseases, ^{131}I mIBG for neuroblastoma, and ^{90}Y microspheres. It is worth noting that a 100% response was not obtained for any procedure.

POST-THERAPY IMAGING

Post-therapy imaging was performed always or in the majority of treatments in 69% of the cases. However, more than 50% of the centres reported that post-therapy imaging was never performed, or performed in the minority of cases for therapies such as ^{131}I NaI for benign thyroid diseases, radiation synovectomy$^{89}SrCl_2$ or $^{223}RaCl_2$ for bone metastases, ^{32}P phosphate for myeloproliferative diseases, and ^{90}Y-ibritumomab-tiuxetan for B cell lymphoma.

ABSORBED-DOSE PLANNING

The absorbed dose was reported to be individually planned for each patient either always or in the majority of treatments in only 36% of cases. In 63% of cases, absorbed dose planning was never carried out, or carried out in a minority of treatments. The highest number of responses were obtained for ^{90}Y-labeled microspheres, 82% (resin) and 84% (glass), and for ^{131}I-NaI for benign thyroid diseases (54%).

POST-THERAPY DOSIMETRY

Post-therapy dosimetry was performed always or in the majority of treatments in only 26% of the cases. More than 50% of the centres indicated that post-therapy dosimetry was performed always or in the majority of cases for ^{177}Lu PSMA (100%) and ^{131}I mIBG for neuroblastoma (59%). For PRRT with ^{90}Y or ^{177}Lu and ^{131}I mIBG for adult neuroendocrine tumours this percentage was approximately 40%.

SATISFACTION ON THE IMPLEMENTATION OF PATIENT-SPECIFIC DOSIMETRY

Fifty-five percent of the responders indicated that they were not satisfied with the current implementation of patient-specific dosimetry in their centre. The main limiting factors were identified as: "Shortage of knowledge and know-how", "Shortage of medical physicists working in nuclear medicine", "Shortage of other staff", "Limited access to scanner or other equipment needed", "Limited access to dedicated software", with an approximately equal distribution of responses. It is interesting to note that 12% of participating centres identified the "Lack of legislative requirement to perform dosimetry" as the main limiting factor.

CONCLUSION

The results of this survey indicate the need for central registries for MRT and for the implementation of dosimetry. Although the level of response varied between countries, the results nevertheless demonstrated a lack of harmonisation and implementation of individual-patient based internal dosimetry.

DOSIMETRY FOR THERAPY PROCEDURES

As also reflected in the survey, the complexities of Molecular Radiotherapy are exacerbated by the number of different procedures, the range of radionuclides and radiopharmaceuticals and the wide variations in patient status. This section reviews the main therapy procedures currently in use. While the goal of the survey was to provide a report as complete as possible on the implementation of dosimetry for a wide range of therapy procedures performed in Europe, this section by necessity covers in detail only a sub-set of such therapies. However, conclusions drawn here may be readily applied to other radiopharmaceuticals using the same radionuclides. The procedures described for imaging and dosimetry are equally applicable to verification of the absorbed doses delivered to tumours, target volumes and healthy tissues.

For each section a brief introduction is given, followed by the current effectiveness of the treatment, the potential for quantitative imaging that underpins organ and tumour dosimetry and existing evidence for absorbed dose-effect correlations. The potential for personalised dosimetry-based treatment planning is then considered. Finally, issues specific to the treatment are considered along with questions that merit further investigation.

^{131}I NaI for the treatment of benign thyroid disease

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

Oral administration of ^{131}I for benign thyroid disease (hyperthyroidism) has been carried out since 1941, when the first effective therapy was performed by Saul Hertz (1). Hyperthyroidism is a consequence of an excessive production and secretion of thyroid hormones T3 and T4. The main causes of hyperthyroidism which are a clear indication for radioiodine treatment include autoimmune hyperthyroidism (Graves' disease), solitary hyperfunctioning thyroid nodule (autonomous adenoma), and multinodular goitre. Administration of ^{131}I NaI is not the only treatment and other options, such as administration of anti-thyroid drugs and surgery are usually considered (2). Procedure guidelines given by the EANM (3) and the Society of Nuclear Medicine and Molecular Imaging (SNMIM) (4) are available to advise clinicians on how to perform the treatment of benign thyroid disease with ^{131}I NaI.

EFFECTIVENESS

The aim of radioiodine therapy for Graves' disease, autonomous adenoma and toxic multinodular goitre is that patients achieve a non-hyperthyroid condition. This means that patients may become euthyroid or hypothyroid, which is compensated with the administration of L-thyroxine. In the case of nontoxic multinodular goitre, the main aim is the reduction of the thyroid volume. The goal of radioiodine therapy – elimination of hyperthyroidism and shrinkage of thyroid volume – is achieved in 80% of patients regardless of the approach to administration used. For calculated activities, success rates for radioiodine treatment have been reported to be higher (3-5).

IMAGING

Radioiodine uptake is usually imaged with anterior gamma-camera imaging using a high-energy parallel-hole collimator. The count rate is increased with a thick crystal (1/2 inch or 5/8 inch) (6). Corrections for scatter and camera dead-time may be necessary (7). Quantitative SPECT/CT ^{131}I imaging is not common practice but is possible, and can offer accurate quantification (7). To determine the target mass, ultrasound imaging is recommended (3, 5), although an anterior view after administering ^{99m}Tc pertechnetate is also used.

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

Within the range of administered activities of ^{131}I NaI, low absorbed doses to normal tissues are delivered (4). Thus, normal tissue dosimetry is not usually required.

TARGET DOSIMETRY

In some cases fixed activities are delivered, whereas in other cases administered activities are calculated with different methods:

(1) Measurement of thyroidal volume and/or radioiodine uptake measurement after 24 h.
(2) Measurement of thyroidal volume, radioiodine uptake, and individual radioiodine half-life by at least two uptake measurements, for example, after 24 h and 5 days.

To determine the absorbed dose to the target, the Quimby-Marinelli method has been widely used (8). Moreover, the EANM Dosimetry Committee has released standard operational procedures for dosimetry prior to radioiodine therapy (6).

ABSORBED DOSE-EFFECT

Treatments aimed to deliver an absorbed dose prescribed to the target have shown high success rates (9).

Graves' disease

The success rate has proved to be dependent on the absorbed dose prescribed to the target (10, 11). Moreover, function-orientated radioiodine treatments have aimed to deliver an absorbed dose to achieve euthyroidism. A common approach is to deliver an ablative absorbed dose to the thyroid (12).

Autonomous adenoma

Delivery of absorbed doses of 300 Gy and 400 Gy to the solitary hyperfunctioning nodule has shown similar high success rates (> 90%) in the elimination of its functional autonomy (13).

Multinodular goitre

In toxic multinodular goitre, intended absorbed doses above 150 Gy have resulted in success rates higher than 90% (14, 15). Cure rates could be maintained with absorbed doses around 120 Gy (15). In the case of nontoxic multinodular goitre a notable volume reduction was observed (>50%) (16).

DOSIMETRY-BASED TREATMENT PLANNING

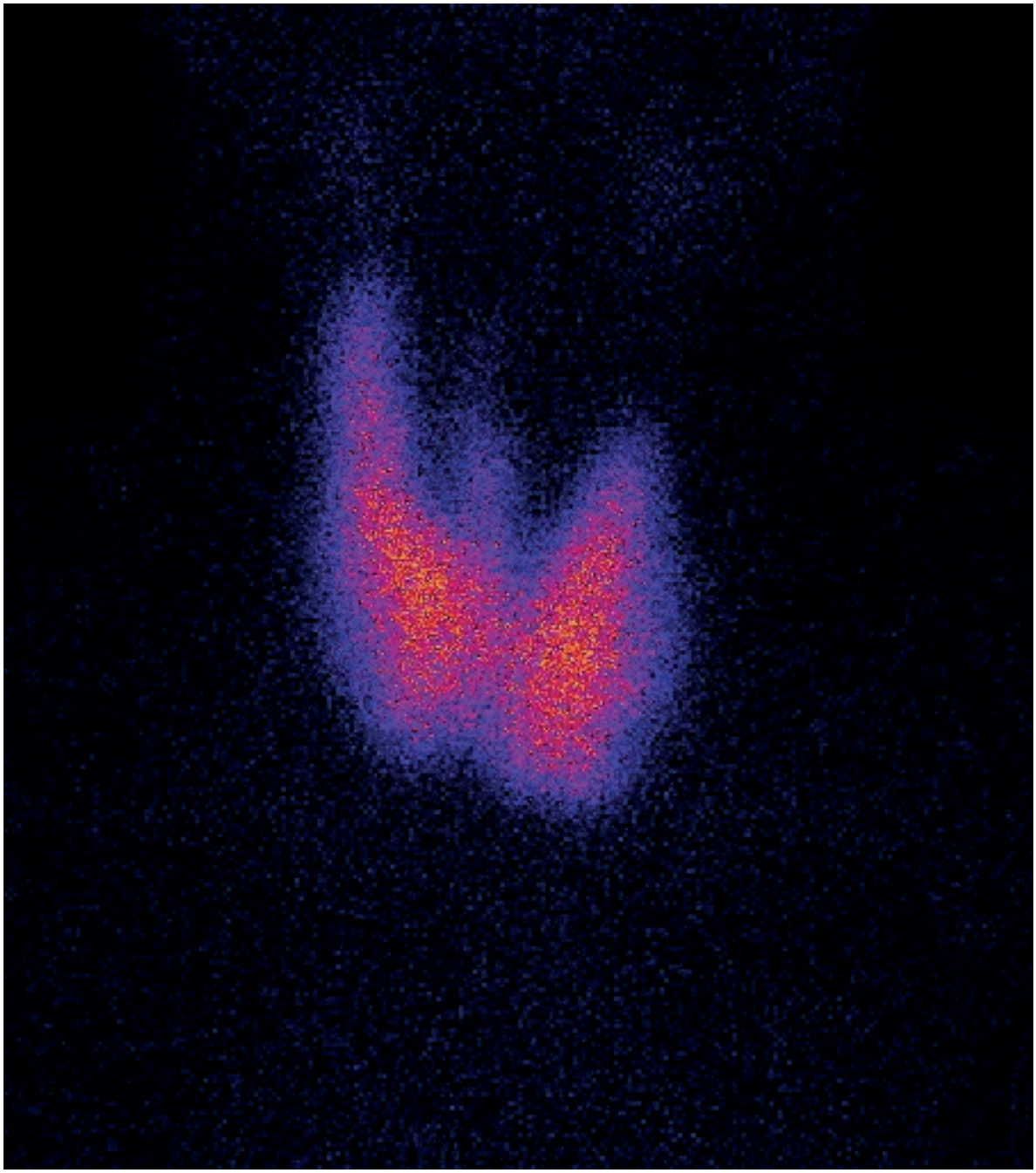
Determination of the activity to administer in order to deliver a prescribed absorbed dose to the target is feasible, and has been widely reported (3). The target mass can be determined by ultrasound. Following the administration of a tracer of ^{131}I NaI, thyroid uptake with time has to be assessed (6). If the uptake is determined with a thyroid probe, 2 MBq are sufficient, and up to 10 MBq may be needed if a gamma camera is used. Higher activities are not recommended due to the so-called 'stunning' effect (6). The potential for semi-individualised treatment planning has been investigated using a mean half-life and patient specific uptake values (17). A model to calculate the optimal absorbed dose to deliver based on the normal tissue complication probability (NTCP) was developed and verified (18).

ISSUES TO CONSIDER

Conventionally, 2D dosimetry has been the standard procedure. However, SPECT/CT acquisitions are widely available nowadays, which enables 3D dosimetry. Moreover, guidelines for SPECT dosimetry with radioiodine following the MIRD formalism are available (7).

NEED FOR INVESTIGATION

Further evaluation of the optimal absorbed doses is warranted, including mass reduction during treatment and possible differences in radioiodine biokinetics prior to and during therapy. The role of recombinant human TSH (rhTSH) prior to the treatment and its potential effect on dosimetry is also in need of evaluation (19). A key question is whether a dosimetry based approach can maximise the number of patients rendered euthyroid rather than hypothyroid, thereby mitigating the need for lifelong medication. Multi-centre trials are necessary to investigate this.



Tc-99m image of thyroid prior to treatment of Graves' disease with radioiodine

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^{131}I NaI for the treatment of differentiated thyroid cancer (DTC) with ablative intent and in the case of recurrent disease

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

Administration of ^{131}I NaI for DTC treatment has been in common use since the 1940s. The activity to administer is customarily determined (1). In comparison with normal thyroid cells, thyroid cancer cells have a reduced expression of the sodium/iodide symporter (NIS), which determines iodine uptake from the blood (2). Therefore, to improve radioiodine uptake, high thyroid-stimulating hormone (TSH) levels are achieved before ^{131}I NaI treatment by hormone withdrawal or recombinant human TSH (rhTSH) administration.

EFFECTIVENESS

The effectiveness of the treatment is usually evaluated by measuring thyroglobulin levels and sometimes also by acquiring a whole-body scan between 6 and 12 months after the treatment. High rates of success, of about 90% or higher, can be expected for treatments with ablative intent (3). In the presence of metastases, a 10-year overall cause-specific survival of about 85% has been reported (4).

IMAGING

Radioiodine uptake in thyroid remnants and metastases can be determined with anterior gamma-camera imaging or SPECT/CT imaging which affords more accurate quantification (5). Corrections for scatter and camera dead-time may be necessary (5). PET/CT imaging can also be performed using ^{124}I NaI, which may advantageous for determination of remnant mass and small metastases (6).

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

In the treatment of recurrent disease, when high activities are given, red-marrow absorbed dose may be of concern (4, 7). EANM guidelines recommend determining red-marrow absorbed dose from whole-body and blood dosimetry (7), and a constraint of 2 Gy is considered when using this methodology (8). Pneumonitis and pulmonary fibrosis are possible concerns in the presence of diffuse lung metastases, and absorbed dose-rate methods have been suggested based on the whole-body retention threshold of 2.96 GBq at 48 hours post-treatment (9). Salivary glands may show side-effects such as sialadenitis and xerostomia, which are markedly less frequent for the case of ablative treatments (10). Currently, there is no absorbed-dose constraint reported for the salivary glands, although toxicity has been reported for notably lower absorbed doses than the constraints used in external beam radiotherapy (11).

TUMOUR DOSIMETRY

Several studies, most of them acquiring planar images, have reported absorbed doses to remnants and metastases with values ranging from <10 Gy to 1000 Gy (12-15).

ABSORBED DOSE-EFFECT

Several studies have investigated correlations between the absorbed doses delivered to remnants and metastases and response, resulting in a wide range of absorbed doses to achieve a successful ablation. For instance, absorbed doses to remnants higher than 49 Gy (12), 90 Gy (15) and 300 Gy (14) have been reported. For metastases, absorbed doses of over 40 Gy (15) and 80 Gy (14) have been documented.

DOSIMETRY-BASED TREATMENT PLANNING

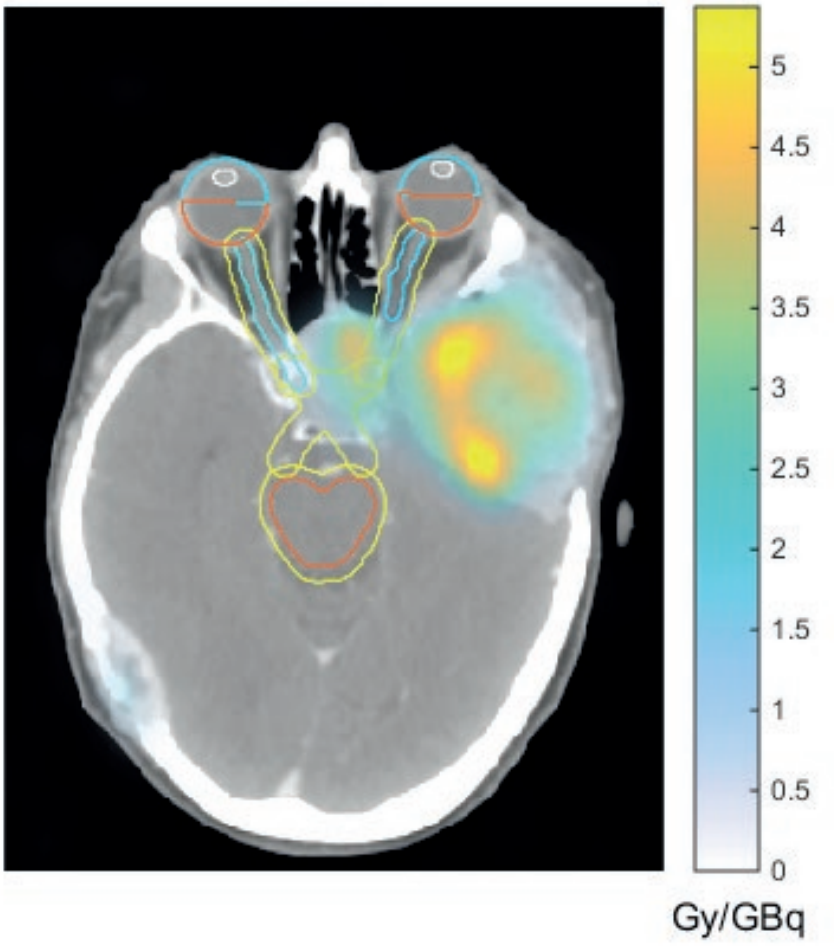
Currently, in the treatment of DTC there are no well-established values for absorbed doses to remnants and metastases which may be used as prescription values. Thus, this treatment is performed by administration of a fixed activity of ^{131}I NaI ranging between 1.11 GBq and 7.4 GBq, depending on the stage of the disease. In the case of recurrent disease, the administered activity may be calculated based on the absorbed dose constraints of the normal tissue (usually red marrow) (7). Initial pre-therapy planning would require a tracer activity of ^{131}I NaI or ^{124}I NaI (7, 15).

ISSUES TO CONSIDER

Determination of radioiodine uptake and mass of remnants and of small metastases is a challenging task. Recovery coefficients and thresholding techniques can be used in SPECT/CT imaging (16). The superior resolution of ^{124}I PET/CT imaging may be an alternative way to estimate these values (15). Treatments performed after administration of rhTSH show different radioiodine biokinetics from those performed after thyroid hormone withdrawal (17), which may have to be considered if treatment planning is performed. For iodine-positive bone metastases, pronounced intra-tumour non-uniformity of iodine uptake may affect dose-response relationships if mean absorbed dose values are used (18). In the case of patients with metastatic disease, when high activities are delivered, appropriate radiation protection measures should be undertaken if patients are moved from the isolation rooms to the gamma camera to acquire images.

NEED FOR INVESTIGATION

Although an absorbed dose-effect correlation has been reported in single-centre studies, the outcome of the treatment can be successful in patients who receive a very low remnant-absorbed dose of only a few Gy (12, 15). This situation calls for further investigation of the influence on the treatment outcome of other factors, such as the stage of the disease, the surgery procedure followed, and the remnant's mass. Multi-centre clinical trials are necessary to gather the evidence required to optimise treatments. The stunning effect has been described as a decrease in the uptake of ^{131}I NaI during the therapeutic course after a previous administration of a tracer of ^{131}I NaI (13). However, there is no completely accepted explanation for this effect (19) and further investigation is warranted. The use of external beam radiotherapy as an adjuvant therapy of the radioiodine therapy in the case of metastatic disease is also an issue to be investigated (20).



Absorbed dose distribution for a treatment planning study with I-131 iodine and SPECT/CT imaging for a 55 year old female with a large bone metastasis in the skull

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^{131}I mIBG for the treatment of neuroblastoma in children and young adults

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

The metaiodobenzylguanidine (mIBG) molecule is an aralkyl-guanidine which structurally resembles norepinephrine (also called noradrenaline), a monoamine secreted by the adrenal medulla. Therefore, tumours expressing the norepinephrine transporter show mIBG uptake capacity. In 1980 the labelling of mIBG with ^{131}I was reported to have a diagnostic use in the imaging of the adrenal medulla (1) and in 1984 the first therapeutic use for neuroblastoma was performed. The specific activity of the ^{131}I mIBG used for therapy usually ranges from 1.11 GBq/mg to 1.85 GBq/mg. This means that approximately only 1 in every 2000 molecules of mIBG is labelled with ^{131}I. The prescription of ^{131}I mIBG for neuroblastoma is sometimes made according to the whole-body absorbed dose, which can be considered more advanced than the majority of therapy procedures.

EFFECTIVENESS

Therapy with ^{131}I mIBG is usually delivered to children with more advanced stages of neuroblastoma, and its effectiveness has been studied. For instance, similar results to those of chemotherapy in stage III and stage IV patients were found in a phase I/II study (2), and more recently a response rate of 58% after individualised ^{131}I mIBG therapy was reported (3).

IMAGING

Conjugate view imaging can be used for determination of ^{131}I mIBG uptake in lesions, although SPECT/CT imaging is advisable for quantification and to visualise the 3D distribution of uptake. Corrections for scatter and camera dead-time may be necessary (4).

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

If stem cell rescue is not scheduled, the main organ at risk is usually the bone marrow, with an absorbed dose constraint of 2 Gy (5). If there is bone marrow involvement, imaging is necessary to perform dosimetry. Otherwise, a blood-based method can be used, which includes blood and whole-body dosimetry. As blood extractions may be distressing to children, an alternative is to determine whole-body absorbed dose by dose-rate measurements, which can be related to red-marrow absorbed dose. When high activities of ^{131}I mIBG are administered, the liver can be considered as an organ-at-risk, for which image-based dosimetry is necessary.

TUMOUR DOSIMETRY

Tumour dosimetry has been performed with both SPECT and planar imaging. A wide range of absorbed doses have been reported, varying from <5 Gy to > 300 Gy. (3, 6).

ABSORBED DOSE-EFFECT

A correlation between the tumour absorbed dose and the response to treatment has been reported. Progressive disease was seen only in those patients whose tumours received less than 17 Gy and the partial response was much higher in those receiving more than 70 Gy (7). With regard to toxicity, a correlation between the whole-body absorbed dose and neutropenia has been shown (8).

DOSIMETRY-BASED TREATMENT PLANNING

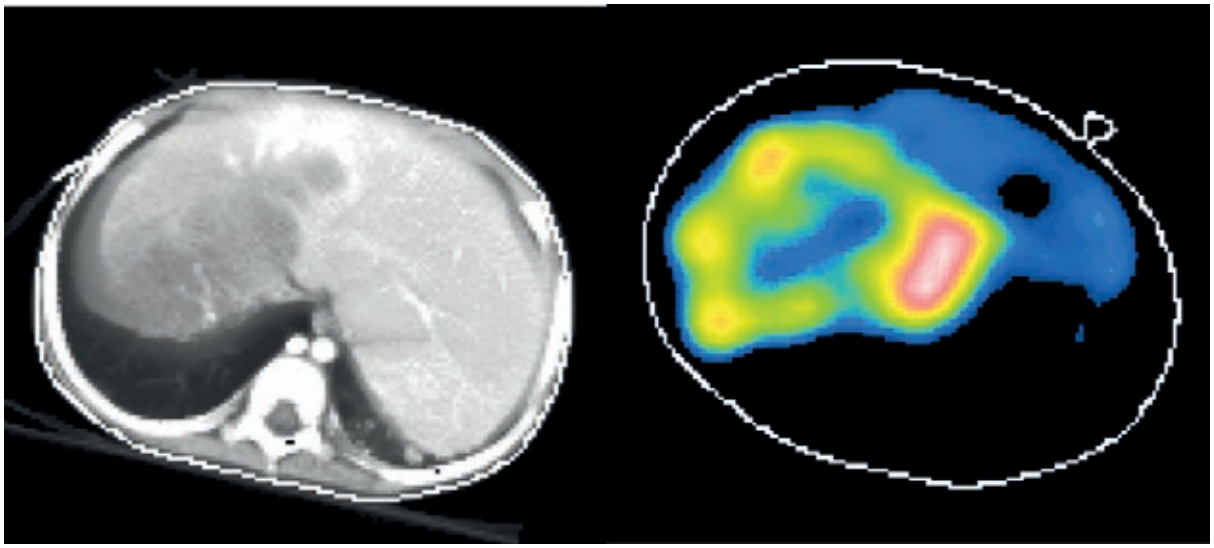
Treatments are often prescribed according to a whole-body absorbed dose. An increasingly common protocol is to deliver a whole-body absorbed dose of 4 Gy in two administrations of activity separated by 2 weeks, followed by a stem cell rescue. The first administration is delivered according to a body mass-based prescription of 444 MBq/kg (9). If there is no stem cell rescue available, a ^{131}I mIBG tracer study may be performed to deliver a given red-marrow or whole-body absorbed dose. There are to date no prescription values for the tumour absorbed dose.

ISSUES TO CONSIDER

^{123}I mIBG imaging is often performed for diagnostic assessment before therapy, and using this scan could be considered for treatment planning.' Before performing SPECT/CT based dosimetry, it may be necessary to perform a whole-body scan to determine all the uptake regions during the ^{131}I mIBG treatment. Patients are hospitalised in isolation rooms, so if patients are moved to the gamma camera room during the isolation period, appropriate radiation protection measures should be undertaken. For the elimination of the ^{131}I mIBG from the whole body, three to five phases can be considered (8). For tumour and liver dosimetry the uptake phase and possibly several washout phases should be taken into account. Therefore, dose-rate measurements and gamma camera acquisitions have to be well distributed through the whole washout of the ^{131}I mIBG.

NEED FOR INVESTIGATION

Numerous studies have demonstrated that quantitative imaging of ^{131}I and tumour dosimetry is feasible, which may lead to treatment regimens based on the absorbed doses delivered to tumours and to organs-at-risk, as is routine for external beam radiotherapy. A deeper radiobiological knowledge may also help to establish those treatment regimens. Further possibilities for development include the use of no-carrier added mIBG with a notably higher specific activity, which has been shown to improve the tumour uptake of radiolabelled molecules, and combination treatments of ^{131}I mIBG with chemotherapy or external beam radiotherapy.



CT and I-123 SPECT of neuroblastoma

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^{131}I mIBG for the treatment of neuro-endocrine tumours in adults

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

The basis for the treatment of neuroendocrine tumours in adults with ^{131}I mIBG is the same as for the treatment of neuroblastoma, that is, tumours expressing the norepinephrine transporter may show mIBG uptake capacity. ^{131}I mIBG is used primarily to treat phaecromocytoma, paraganglioma, medullary thyroid carcinoma and neuroendocrine carcinomas, although its use has also been reported in less frequent neuroendocrine tumours, such as islet cell carcinoma and Merkel cell carcinoma (1). The first therapeutic use was reported in 1984 for the treatment of phaeocromocytoma (2). Unlike neuroblastoma treatment, administered activities are usually not based on patient mass and single or multiple activities ranging between 3.7 GBq and 18.5 GBq are delivered.

EFFECTIVENESS

The effectiveness of ^{131}I mIBG in the treatment of neuroendocrine tumours in adults has been reported in several studies. In the case of phaeocromocytoma and paraganglioma, response rates between 30% and 47% for morphologic response and 75%–90% for symptomatic response have been reported. Approximately 30% of the metastases demonstrated objective response to therapy and in 40% of the cases tumours remained stable. In the case of medullary thyroid carcinoma, an objective response of 30% has been reported, and in the case of carcinoid tumours symptomatic responses in the range of 50%–75% (1).

IMAGING

Conjugate view imaging can be used for determination of ^{131}I mIBG uptake in lesions, although SPECT/CT imaging is advisable for quantification and to visualise the 3D distribution of uptake. Corrections for scatter and camera dead-time may be necessary (3).

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

The basis for normal tissue dosimetry is the same as in the case of neuroblastoma. Red marrow toxicity is the common dose-limiting factor (4). Stem cell rescue is less frequent than for neuroblastoma, but it can also be performed (2).

TUMOUR DOSIMETRY

As with the case of neuroblastoma, mostly using planar imaging a very wide range of values for tumour absorbed doses, between a few Gy and more than one hundred Gy, has been reported (5, 6).

ABSORBED DOSE-EFFECT

In a study for the treatment of the phaeocromocytoma, an absorbed dose higher than 150 Gy was considered necessary to cause beneficial effects (5). Moreover, for the higher administered activities a better response has been observed, which may possibly be explained under the assumption that higher tumour absorbed doses were delivered (6).

DOSIMETRY-BASED TREATMENT PLANNING

Considering an absorbed-dose limit of 2 Gy for the red marrow, a dosimetric study with a tracer could be performed to determine the red-marrow absorbed dose per administered activity. Using this value, the activity of ^{131}I mIBG can be prescribed so as not to exceed the red marrow toxicity. Alternatively, the treatment can be fractionated and the activity in subsequent activity administrations determined from the biokinetics of the first administration (7). There are as yet no prescription values for the tumour absorbed dose.

ISSUES TO CONSIDER

As with the case of neuroblastoma, it may be useful to acquire a diagnostic or whole-body scan to determine the uptake regions. Radiation protection measures must also be undertaken if an inpatient is moved to the gamma camera, and it is also important to take into account all washout phases for whole-body, organs-at-risk and tumour dosimetry.

NEED FOR INVESTIGATION

As with neuroblastoma, it is necessary to investigate treatment regimens based on absorbed doses delivered to tumours and to organs-at-risk, including concepts of radiobiology, as is routine for external beam radiotherapy. The use of no-carrier added mIBG and combination of ^{131}I mIBG treatments with chemotherapy or external beam radiotherapy also needs to be investigated.

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^{177}Lu-DOTATATE for the treatment of neuroendocrine tumours

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

^{177}Lu-DOTATATE is a radiolabelled somatostatin analogue developed for treatment of patients with somatostatin receptor positive neuroendocrine tumours. Being a somatostatin analogue, ^{177}Lu-DOTATATE is taken up by areas of increased somatostatin receptor density. In 2005 results of the first large clinical study of ^{177}Lu-DOTATATE were reported (1). This was a study with a fractionated approach where patients in most cases were given 7.4 GBq four times with a 6 to 10 weeks interval. No dose-limiting toxicity was observed and this schedule has been widely adopted since it is considered both safe and effective. This is currently the most frequent treatment protocol; patients are treated with 4 therapy cycles with an activity of 7.4 GBq each time with concomitant infusion of amino-acids to reduce renal uptake. However, protocols delivering cycles of 7.4 GBq, until a maximum prescribed absorbed dose to the kidneys and the bone marrow is reached, are under investigation (2).

EFFECTIVENESS

The results of the randomised NETTER-1 phase III study of patients with somatostatin receptor positive midgut neuroendocrine tumours showed that ^{177}Lu-DOTATATE leads to markedly longer progression-free and overall survival and a significantly higher response rate relative to cold somatostatin (3).

IMAGING

Even though the photon yield is relatively low, the high amount of activity administered makes quantitative imaging of ^{177}Lu possible. It has been demonstrated that gamma camera imaging is feasible (4) and that activity can be quantified to within 20% accuracy, depending on the volume imaged. Medium energy general purpose collimators and energy window centred at 208 keV is recommended (5).

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

The absorbed dose to normal tissues has been estimated in several studies based on sequential quantitative imaging, blood sampling and in one case urine collection (4, 6, 7). Kidneys and (more seldom) bone marrow were reported to be the dose limiting organs. In these studies the main route of excretion was found to be via the kidneys. These studies also showed that absorbed doses delivered to kidneys vary by an order of magnitude from 0.2 - 2.0 Gy/GBq.

TUMOUR DOSIMETRY

A limited number of studies have investigated absorbed doses to measureable metastases using gamma camera imaging. In one study a range of absorbed doses were calculated from SPECT/CT imaging, and reported between 10 – 340 Gy from a standard administration (8).

ABSORBED DOSE-EFFECT

A clear correlation between tumour absorbed doses and the response to the treatment was reported in pancreatic neuroendocrine tumours (PNETs) (8). With regard to toxicity, treatment related kidney toxicity has not been reported, despite long follow-up for patients receiving a kidney dose over 28 Gy, indicating that this may be a conservative limit (9).

DOSIMETRY-BASED TREATMENT PLANNING

Treatments may be performed prescribing a maximum total dose to the kidneys and the bone marrow. The safety of 8 or more cycles has recently been described in a small patient group (10). While the maximum absorbed dose for kidneys is commonly set at limits used in EBRT, the threshold dose for late kidney toxicity for ^{177}Lu-DOTATATE treatment is uncertain. The threshold dose for hematologic toxicity is set at 2 Gy, equivalent to practice in ^{131}I NaI therapy of thyroid cancer.

NEED FOR INVESTIGATION

Although it has been demonstrated that patient-specific absorbed doses for Lu-177 can be calculated and can have a clinical benefit, the optimal protocol and standardised dosimetry methods are yet to be established. The short range of the beta emissions necessitates an investigation of small scale dosimetry and microdosimetry, both for normal and tumour tissue. The absorbed dose limits for normal tissue and the desirable absorbed dose to the tumours also still need to be determined. The absorbed dose-based treatment with ^{177}Lu-DOTATATE for patients with somatostatin positive neuroendocrine tumours can increase the efficacy of the treatment to the patient and make later external beam radiotherapy possible. Numerous studies have demonstrated that quantitative imaging of ^{177}Lu and dosimetry is feasible which leads to treatment regimens based on the absorbed doses delivered to organs-at-risk, as is routine for external beam radiotherapy. Further possibilities for development include the use of carrier free DOTATATE and combination treatments with ^{131}I-mIBG, chemotherapy or external beam radiotherapy.

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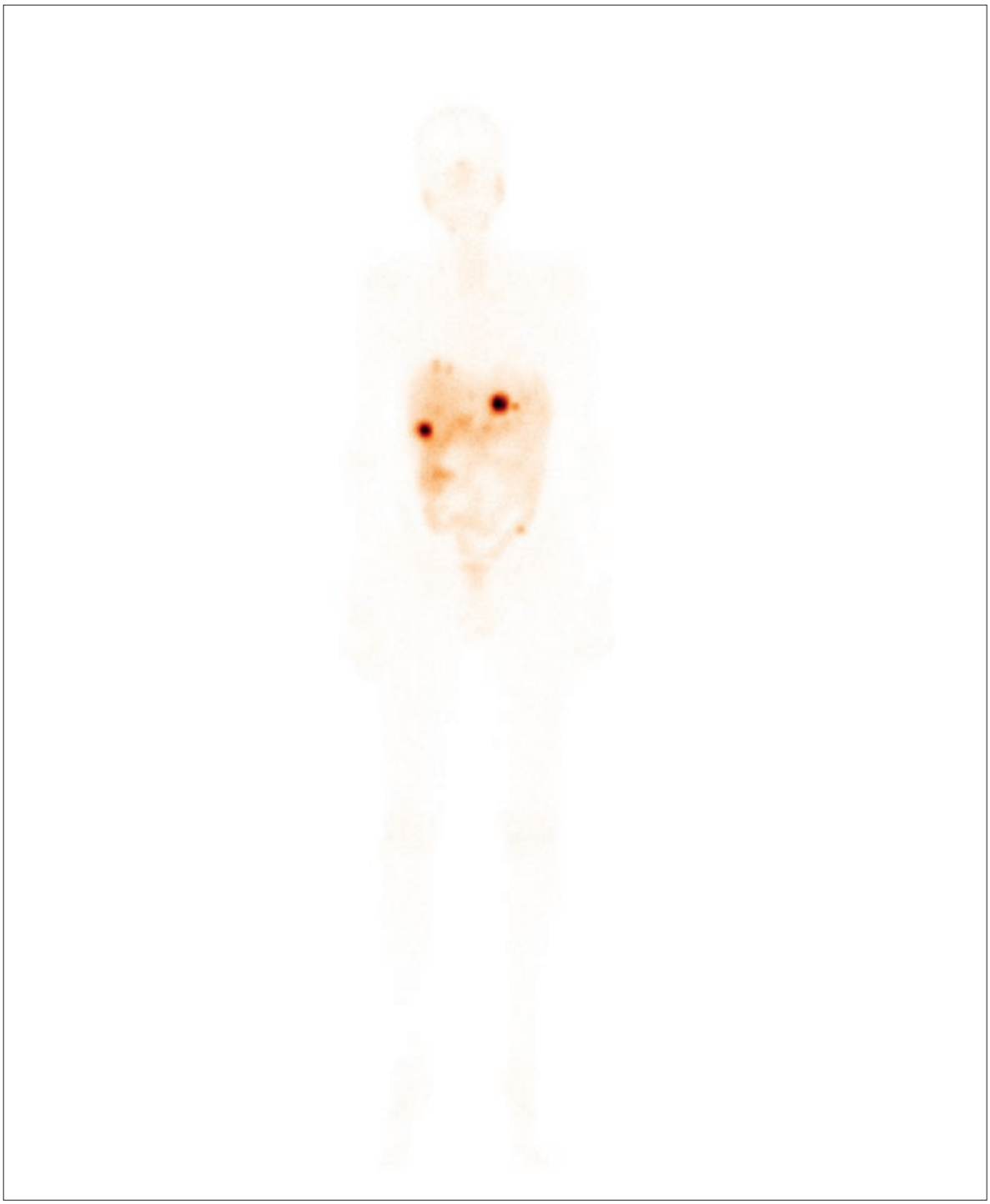

Anterior whole-body image acquired 24 h post infusion of 177Lu-Dotatate

^{90}Y somatostatin analogues for the treatment of neuro-endocrine tumours

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

^{90}Y-DOTATOC was the first somatostatin analogue developed for treatment of patients with somatostatin receptor positive neuroendocrine tumours. Phase 1 clinical trials were dosimetry guided by using prospective ^{86}Y-DOTATOC quantitative PET imaging (1). The conclusion in this study was that individual patient dosimetry was needed as both kidney and tumour absorbed doses showed extreme variability. In the phase 2 trial for this compound no dosimetry was performed and patients were administered with a single or several administrations of 3.7 GBq/m^2 (2). Treatment protocols are mostly based on fixed activity or activity per body surface area (typically at 1.85 - 3.7 GBq/m^2) administration schemes, which are repeated with a 6-8 week interval, depending on response and quite often adapted to (bone marrow) toxicity after previous treatment. This leads to the huge range in reported cumulative activities of 1.1 – 26.5 GBq (3).

EFFECTIVENESS

In the clinical phase 2 single-centre open-label trial overall 60% of the patients showed clinical response, biochemical response, and/or morphologic disease control after a single administration of 3.7 GBq/m^2 ^{90}Y-DOTATOC with amino-acid infusion (2). No randomised comparative studies have been performed for ^{90}Y DOTATOC. Several studies have been performed to compare ^{90}Y-labeled somatostatin receptor peptide alone with a combination of ^{90}Y and ^{177}Lu peptides (4, 5). These combination therapies were based on equal administered activity of both radionuclides, whereas over its cumulative decay ^{90}Y emits 2.5 times the energy emitted by ^{177}Lu (6).

IMAGING

As ^{90}Y is a pure beta-emitter, direct imaging of the therapy compound is only possible by using its induced bremsstrahlung spectrum in planar whole body or SPECT (7). Peri-therapeutic PET imaging can also be performed by using the 0.003%/decay positron emission from ^{90}Y, which has been shown to be feasible for quantifying the uptake in the renal cortex (8). Theragnostic companion compounds have been used to prospectively quantify the ^{90}Y DOTATOC biodistribution, with the gamma-emitter ^{111}In-DOTATATE (9) or the PET emitter ^{86}Y-DOTATATE (10). When using a surrogate peptide it is of great importance to use the same amount and type of peptide as used in the therapeutic setting, or otherwise correct for the difference in pharmacokinetics and binding affinity (11).

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

Both single ^{90}Y-DOTATOC therapy and combination treatment with ^{90}Y and ^{177}Lu peptides have led to permanent and sometimes even fatal renal toxicity (grade 4 and 5) (2, 5). Kidneys are considered to be the critical organ after therapy. When the peptide is cleared by the primary renal filter elements (the glomeruli), radiolabelled peptides are reabsorbed and remain in the secondary filter elements (proximal tubuli). Dosimetry performed in 18 patients with ^{86}Y-DOTATOC PET quantification showed interpatient variability of a factor 4, the absorbed dose per activity ranged between 1.2 – 5.1 Gy/GBq (1), a comparable variability was observed for the ^{111}In-DOTATOC based dosimetry: 1.3 – 4.9 Gy/GBq (9). Bone marrow dosimetry is performed less often. Image-based methods were used with ^{86}Y-DOTATOC and a correlation was observed with ^{111}In-DTPA-Octreotide thoracic spine uptake (12). In 21 patients the bone marrow absorbed dose ranged between 0.3 and 1.7 Gy for the full therapy of 370 MBq.

TUMOUR DOSIMETRY

Tumour dosimetry is seldom performed for ^{90}Y-DOTATOC, most probably due to the highly metastasised nature of the tumours. Nevertheless it has been performed using In-111 DOTATOC as a companion diagnostic (13) and in the initial phase 1 clinical trial, using ^{86}Y DOTATOC (14).

ABSORBED DOSE-EFFECT

Longer follow-up in a sub-group of patients treated in Belgium revealed a dose-response relation between renal toxicity and the Biologically Effective Dose (BED) when based on the actual kidney volume instead of the standard size (15). It was observed that the activity and hence absorbed dose per treatment cycle significantly influenced the incidence of renal toxicity (16). Late stage renal toxicity was shown to follow a classic sigmoidal shaped dose-effect curve with the BED (17). The threshold for late renal toxicity was found around a BED of 40 Gy for patients without additional risk factors for renal disease, including high blood pressure, diabetes, or prior chemotherapy. Reduction in tumour volume was shown to be significant above tumour absorbed doses of 200 Gy (14).

DOSIMETRY-BASED TREATMENT PLANNING

One study repeated administrations according to the 1.85 GBq/m^2 dosing scheme until a threshold dose of 37 Gy BED was reached, thereby preventing renal toxicity (18). The BED has been semi-empirically defined in MIRD pamphlet 20 by using a sub-lethal damage repair half-life of 2.8 h and the radiobiology parameter $\alpha/\beta = 2.5$ Gy for late renal toxicity (16). A multi-factorial dose-effect model for blood platelet response was defined, using prior platelet counts as additional weighting factor, leading to a correlation between the weighted bone marrow dose and platelet count nadir after therapy (12).

ISSUES TO CONSIDER

^{90}Y is a pure high energy beta emitter (mean energy 0.93 MeV), while a minute fraction (0.0032%) leads to internal pair production photons at 511 keV. Quantitative imaging of ^{90}Y is complex and prospective imaging with surrogate markers may deviate from the actual biodistribution.

NEED FOR INVESTIGATION

Despite the clear relation between occurrence of late renal toxicity and absorbed dose this has not lead to clinical protocols using this concept. The longer range of the high-energy beta-particles from ^{90}Y results in relatively homogeneous dose distributions within uptake volumes. Still inhomogeneous uptake in tumours, by e.g. necrosis, could lead to inhomogeneity in dose distribution. This partly explains the high absorbed doses that are needed to lead to tumour volume reduction, but this needs to be further investigated. The radiation sensitivity of neuroendocrine tumours is not well known, but it is not considered to be extremely radio-resistant, considering the tumour dose of 50 Gy in neo-adjuvant external beam radiotherapy (19).

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Beta emitters for bone pain palliation

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

Several beta-emitting agents exist for treatment of cancer metastatic to bone; the most commonly used are strontium-89-chloride ($^{89}SrCl_2$), samarium-153-EDTMP (^{153}Sm-EDTMP), rhenium-186-HEDP (^{186}Re-HEDP) and rhenium-188-HEDP (^{188}Re-HEDP). The ligands seek the bone matrix and accumulate in areas of increased osteoblastic activity. The radiopharmaceuticals are mainly used for patients with castration-resistant prostate cancer, as bone metastases from prostate cancer are predominately osteoblastic. However, the applications have included treatment of skeletal metastases from prostate, breast, and lung cancer. The administration is most often based on delivery of a fixed amount of radioactivity or an adjusted amount corresponding to patient body weight (1). Fractionated therapy is sometimes given. The agents have traditionally been used for pain palliation, and there is some evidence to suggest they may provide complete relief for months (2).

EFFECTIVENESS

Response has primarily been measured as pain relief experienced. The different radiopharmaceuticals have demonstrated similar pain reduction rates, of approx. 50-70 % (3). In addition; quality of life, analgesia consumption, time to symptomatic skeletal events, and the time to increase in alkaline phosphatase or prostate-specific antigen level can be monitored. Studies of survival have been sparse. However, the ALSYMPCA results for ^{223}Ra dichloride have encouraged trials investigating survival data as endpoints.

IMAGING

The radioisotopes ^{153}Sm and ^{188}Re (and to a lesser degree ^{186}Re) emit photons suitable for gamma camera imaging (Table 1). Both low energy and high energy collimators have been utilized; the latter was previously suggested to reduce bremsstrahlung contribution (4-6). If tumour quantitation is to be performed, 3D imaging is recommended (7). The low yield of photons makes direct quantitative imaging of ^{89}Sr challenging. The lack of a carrier molecule also prevents the use of a surrogate radioisotope for imaging purposes.

Table 1. Physical characteristics

Radioisotope	Half-life (d)	Maximum β-energy (MeV)	γ-emission (MeV)
^{89}Sr	50.5	1.46	Nil (0.01%)
^{153}Sm	1.9	0.81	0.103 (29%)
^{186}Re	3.7	1.07	0.137 (9%)
^{188}Re	0.7	2.12	0.155 (15%)

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

The most common adverse events are myelotoxic. These can be evaluated by leukocytopenia and thrombocytopenia grading. In general, bone surfaces and red bone marrow have been reported to receive the highest absorbed doses for ^{153}Sm-EDTMP, ^{186}Re-HEDP and ^{188}Re-HEDP (4, 5, 8). This is in accordance with myelosuppression being the activity-limiting side effect for bone-seeking radiopharmaceuticals. While the urine, bladder and kidneys will also be exposed through urinary excretion, the absorbed doses are too low for these organs to be considered dose-limiting. Normal tissue dosimetry has mainly been based on sequential planar imaging, and the reported dose ranges have varied. For $^{89}SrCl_2$ the absorbed doses to normal tissues has been estimated with the International Commission on Radiological Protection (ICRP) model. In addition to the organs described, the lower gastrointestinal tract will also receive an absorbed dose contribution from clearance for this treatment (9).

TUMOUR DOSIMETRY

Several studies have demonstrated considerable variation in absorbed doses to metastases using gamma camera imaging. For example, a range of approx. 3 Gy - 60 Gy for an administration of 222 MBq/kg ^{153}Sm-EDTMP was reported when state-of-the-art dosimetry was performed (6).

ABSORBED DOSE-EFFECT

For ^{153}Sm-EDTMP, a significant dose–response relationship for transient tumour volume shrinkage has been reported (6). The red marrow absorbed dose estimated by SPECT/CT has been shown to be predictive of myelotoxicity for the same treatment (10).

DOSIMETRY-BASED TREATMENT PLANNING

The range in absorbed doses delivered by the treatments demonstrates a potential use for dosimetry to predict toxicity or response. For ^{153}Sm-EDTMP, ^{186}Re-HEDP and ^{186}Re-HEDP quantitative imaging is feasible, and a fractionated regimen would allow 'adaptive planning' whereby the next activity given is based on the dosimetric results from the preceding administration. Furthermore, the rate of retention of ^{99m}Tc-MDP in bone has been demonstrated to estimate the ^{153}Sm-EDTMP retention rate (10, 11). This can provide a simple method to predict lesion and red marrow doses.

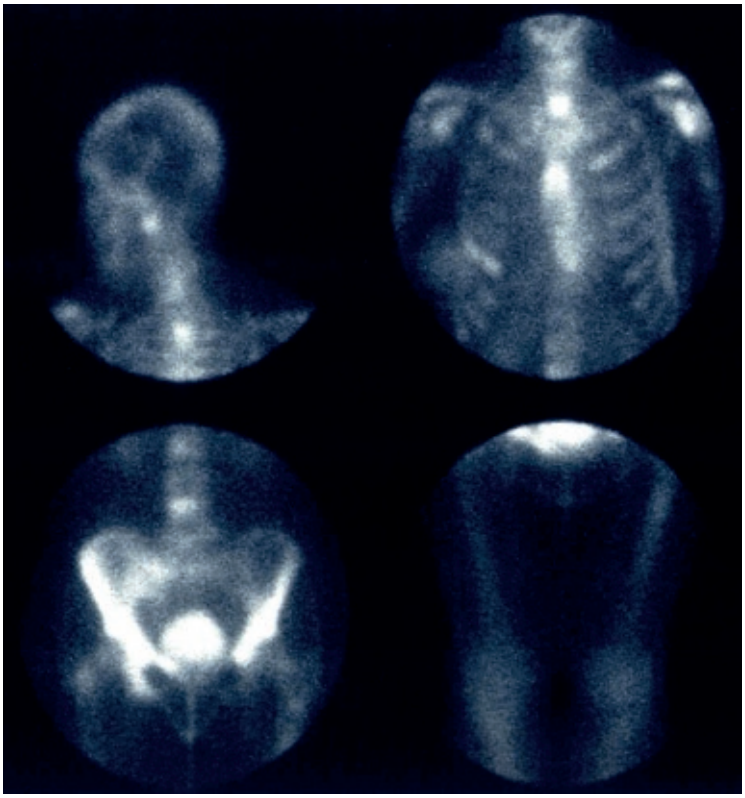
ISSUES TO CONSIDER

A significant decrease in retained activity for normal tissue has been observed between tracer and high treatment amounts of ^{153}Sm-EDTMP (12). Saturating effects should be evaluated, and taken into account for individual treatment planning.

Care should be taken with regard to target definitions, as uptake occurs at sites of increased osteoblastic activity.

NEED FOR INVESTIGATION

For $^{89}SrCl_2$, there is a need to develop reliable dosimetric methodology for the treatment. For the rest of the treatments, further investigations of dose-effect relationships should be conducted.



Sm-153 EDTA scan 9 hours after administration

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^{223}Ra dichloride for the treatment of bone metastases from castration resistant prostate cancer

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

^{223}Ra dichloride is marketed under the tradename of Xofigo® (formerly Alpharadin®) and approved for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. Radium is a natural bone seeker that in the form of $^{223}RaCl_2$ is used for targeting of skeletal metastases. Being an analogue to calcium, cationic radium is taken up by areas of increased osteoblastic activity. In 2005 results from the first clinical study of $^{223}RaCl_2$ were reported (1). This was a single dosage study including patients with metastases from prostate or breast cancer. No dose-limiting toxicity was observed and a fractionated administration regimen was then investigated. A fractionated approach is now routinely used for the delivery of this treatment; patients are given 6 injections of 55 kBq/kg body weight with a 4 week interval (2).

EFFECTIVENESS

The ALSYMPCA phase III study of patients with progressive castration-resistant metastatic prostate cancer and pain showed that $^{223}RaCl_2$ improved overall survival relative to placebo (3). In addition, the time to first symptomatic skeletal event, and the time to increases in alkaline phosphatase and prostate-specific antigen levels were prolonged.

IMAGING

The low yield of photons, combined with the low amount of activity administered, makes quantitative imaging of ^{223}Ra challenging. However, it has been demonstrated that prolonged gamma camera imaging is feasible (4) and that activity can be quantified to within 20% - 50%, depending on the volume imaged. Medium energy general purpose collimators and energy windows centred at 82 keV, and possibly 154 keV and 270 keV are recommended.

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

The absorbed dose to normal tissues has been estimated with the ICRP model for radium (5). Bone endosteum, red bone marrow, liver, colon and intestines were reported to receive the highest absorbed doses. In an imaging-based biodistribution study, $^{223}RaCl_2$ was confirmed to rapidly clear from the blood and the main route of excretion was found to be via the small bowel (6). A study of normal tissue dosimetry based on sequential quantitative imaging, external counting and urine and faecal collection for 6 patients treated twice with 100 kBq/kg of $^{223}RaCl_2$ showed that absorbed doses delivered to normal organs vary by an order of magnitude (7). Bone surfaces received from 2.3 - 13.1 Gy/MBq, and the wholebody from 14 - 66 mGy/MBq. Red marrow absorbed doses ranged from 0.2 – 1.9 Gy from a single administration of 50 kBq/kg. The short range of the alpha particles (<100µm) emitted from $^{223}RaCl_2$ distributed on trabecular bone surfaces probably contributes to a heterogeneous dose profile in the marrow space, explaining the low haematological toxicity.

TUMOUR DOSIMETRY

To date, a single study has investigated absorbed doses to metastases using gamma camera imaging. A range of 0.2 Gy – 1.9 Gy was demonstrated. Uptake of $^{223}RaCl_2$ was seen to correlate with that of ^{99m}Tc MDP (8).

ABSORBED DOSE-EFFECT

There is no evidence as yet of correlations between the absorbed doses delivered and effect.

DOSIMETRY-BASED TREATMENT PLANNING

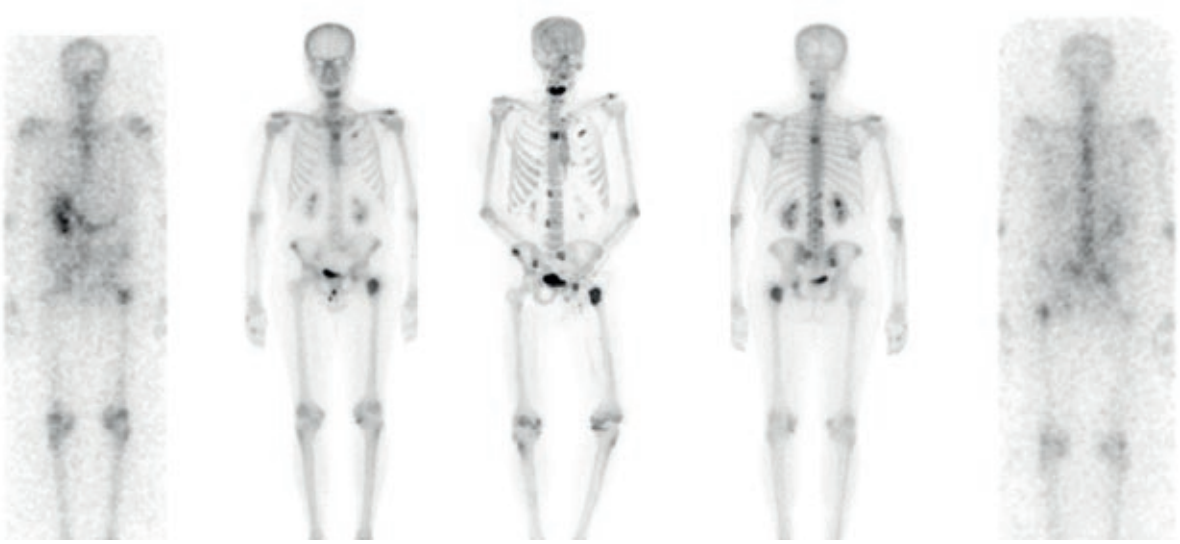
There is currently no indication for dosimetry in the treatment planning of $^{223}RaCl_2$. The potential for treatment planning is demonstrated by the ability to quantitatively image $^{223}RaCl_2$ and the correlation of uptake with pre-therapy ^{99m}Tc MDP. The range of delivered absorbed doses demonstrated from initial studies and the lack of reported toxicity indicate the feasibility to administer higher activities on a personalised basis. There is a potential use for dosimetry to predict toxicity or response in the treatment planning of $^{223}RaCl_2$. The fractionated regimen allows 'adaptive planning', whereby sequential administrations (the activity per fraction, or the number of fractions) are based on the dosimetric results from the preceding administration.

ISSUES TO CONSIDER

^{223}Ra is an alpha emitter with a half-life of 11.4 days which decays to stable lead via a chain of five daughters, and most of the energy is emitted through 4 alpha particle emissions (5.6-7.4 MeV). As the third daughter (^{211}Pb) has a half-life of 36 minutes, there is therefore a possibility that subsequent disintegrations may occur elsewhere. However, no redistribution of radioactive daughters has yet been reported.

NEED FOR INVESTIGATION

Given the challenges associated with estimating patient-specific absorbed doses for ^{223}Ra the first priority should be to develop reliable dosimetric methodology for this treatment and to conduct clinical trials to evaluate response in relation to the absorbed dose. The short range of the alpha emissions necessitates an investigation of small scale dosimetry and microdosimetry, both for bone and tumour tissue. The sparse data available on absorbed doses delivered to tumours indicates that these may be low in comparison with beta emitters. Alpha emissions incur a relative biological effect that has been quoted as ranging from 3 – 5. Accumulation of dosimetry and response data will enable the Relative Biological Effect (RBE) to be determined.



Imaging during Ra-223 treatment. Anterior Ra-223, anterior Tc-99 MDP, F-18 Fluoride, posterior Tc-99m MDP, posterior Ra-223

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^{177}Lu-PSMA ligands for the treatment of metastatic castration-resistant prostate cancer

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

PSMA (prostate-specific membrane antigen) is a glutamate carboxypeptidase II overexpressed in prostate cancer. Different radiolabelled ligands targeting PSMA have been developed for treatment of patients with advanced prostate cancer, including the small molecule inhibitors ^{177}Lu-DKFZ-PSMA-617 and ^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE), and the monoclonal antibody based ^{177}Lu-DOTA-J591. Investigations of ^{131}I or ^{90}Y based ligands have also been performed, however, the current focus is on ^{177}Lu radiolabelled ligands and especially the small-molecule inhibitors. As the radiotherapeutics are still in clinical trials, no standard treatment regimens have developed. The most common way to deliver ^{177}Lu-PSMA small-molecule inhibitors seems to be in a fractioned approach of 2-9 GBq in each cycle (1-3). For antibodies the regimen is restricted to a single administration, and 2.59 GBq/m^2 BSA was given in a phase II trial of ^{177}Lu-DOTA-J591 (4). Commonly, the treatment is preceded by a diagnostic assessment using an analogue ligand with a PET (or SPECT) radionuclide.

EFFECTIVENESS

While the survival benefits of these treatments are yet to be reported in randomised trials, efficacy can be evaluated by biochemical response defined by decline in prostate-specific antigen (PSA), response assessed by PET/CT imaging, radiologic response, pain relief or quality of life. In a German multi-centre study 45 % of patients had a 50 % decline in PSA after 1-4 therapy cycles of ^{177}Lu-PSMA-617 (5). Several other trials have also demonstrated high efficacy for small-molecule inhibitors in patients with metastatic castration-resistant prostate cancer (2, 6, 7).

IMAGING

Imaging can be performed essentially as described for ^{177}Lu-DOTATATE, however, as lower amounts of radioactivity are given, there may be a need for prolonged acquisitions. Multiple SPECT/CT scanning is recommended using with medium energy general purpose collimators and energy window centred at 208 keV (8).

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

In studies of SPECT/CT based dosimetry for ^{177}Lu-PSMA-617, the organs with the highest absorbed doses were the salivary/parotid glands and kidneys, receiving mean absorbed doses of approximately 1.2-1.4 and 0.6-1.0 Gy/GBq, respectively (9-11). The mean absorbed doses to red marrow were reported between 12 and 48 mGy/GBq. Lacrimal glands may also represent a dose-limiting organ (12). For ^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE) similar absorbed doses are observed; of 1.3 Gy/GBq, 0.8 Gy/GBq and 14 mGy/GBq for parotid glands, kidneys and red marrow, respectively (2). The absorbed doses to normal tissue are likely higher for the antibody-based ^{177}Lu-DOTA-J591 (13).

TUMOUR DOSIMETRY

One study has investigated absorbed doses to metastases for ^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE), demonstrating a range from 0.03 to 78 Gy/GBq and a mean value of 3.3 Gy/GBq (2). For ^{177}Lu-DOTA-J591, absorbed doses for tumour lesions ranged between 1.2 and 47.5 Gy (mean 13.1 Gy/GBq) (9).

ABSORBED DOSE-EFFECT

There is as yet no study that has reported on absorbed doses compared to response or toxicity of the treatments.

DOSIMETRY-BASED TREATMENT PLANNING

For therapy with ^{177}Lu-PSMA small-molecule inhibitors dosimetry driven treatment planning has a potential for both easy implementation and providing large benefits for the patients. Absorbed doses to risk organs may be significant over the treatment cycles, and prospective absorbed dose measures may prove valuable to determine the acceptable number of cycles. Administrations of tracer amounts of ^{177}Lu-PSMA-617 and pre-therapeutic dosimetry have been investigated, and the authors concluded that the substantial individual variance seems to make patient dosimetry mandatory (10). A more practical approach may be to perform treatment planning based on quantitative imaging from the previous treatment cycle or the pre-therapeutic diagnostic assessment with a surrogate ligand.

ISSUES TO CONSIDER

While the normal tissue absorbed doses have been reported relative invariable between therapy cycles (9), it should be investigated in a larger patient material whether Gy/GBq values from the first cycle can be used directly for treatment planning of the next cycles. Prospective imaging with positron-emitting surrogate markers may deviate from the actual biodistribution.

NEED FOR INVESTIGATION

The primary dose-limiting organs are thought to be salivary and lacrimal glands for the small-molecule inhibitors. However, this should be further investigated as clinical side effects more often include haematotoxicity than xerostomia. The dose-effect curves, with tolerance limits for normal tissue and the desirable absorbed dose to tumours, will likely need to be empirically determined. The experience from other molecular radiotherapies demonstrates that the common assumption of identical tolerance limits for MRT as for EBRT can often lead to an under-dosage of radiopharmaceuticals – as the tolerance limits are actually higher. This may be explained by different dose-rates, energies, or the short range of the beta emissions which necessitates an investigation of small scale dosimetry.

Further possibilities for development include combination treatments. An alpha-emitting radiopharmaceutical, ^{225}Ac-PSMA-617, is currently under investigation, and the complementary role of the beta- and alpha-emitting ligands should be explored.

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10

Radioembolisation with 90Y microspheres for the treatment of primary and metastatic liver cancer

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

Intra-arterial locoregional liver therapies have their rationale in the fact that liver lesions are fed mainly by the arterial stream, while normal parenchyma is supplied by portal vein blood flow. As seen in the survey, at present two products are mainly used, ^{90}Y glass microspheres and ^{90}Y resin microspheres, both licensed by the US Food and Drug Administration (FDA) as medical devices to treat liver primary hepatocarcinoma (HCC) and liver metastases (1). A product using ^{166}Ho is in development (2).

EFFECTIVENESS AND TOXICITY

Many studies already have demonstrated a competitive outcome of radioembolisation (TARE) with respect to conventional treatment modalities, both in intermediate and advanced HCC stages (3) and metastases (4).

IMAGING

Simulation scanning is performed with ^{99m}Tc-albumin macro aggregate (MAA) administered under angiographic guidance for quantitative imaging and pre-treatment dosimetry (1). The permanent trapping into liver capillaries of the ^{99m}Tc MAA and of therapeutic particles (^{90}Y microspheres) allows dosimetry to be performed from only one scan (5). This procedure can also be used to evaluate the fraction of activity that is shunted to the lung where this occurs. Post therapy quantitative imaging can be performed by ^{90}Y bremsstrahlung SPECT or ^{90}Y PET with suitable corrections (6). Reproducible activity quantitation across different PET systems has been demonstrated (7).

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

Toxicity is of particular importance, as patient death from radioembolisation-induced liver disease leading to liver failure can be a consequence of a standard treatment (5). Dosimetry for normal liver is performed from quantitative ^{99m}Tc, ^{90}Y bremsstrahlung or ^{90}Y PET imaging. Lung dosimetry is also of importance as this can cause severe toxicity and may also be performed with imaging, with suitable corrections for photon attenuation (5).

TUMOUR DOSIMETRY

Tumour absorbed doses can vary widely and have been reported as high as 1000 Gy (8). Dosimetry is simplified by the assumption that the microspheres are trapped so that only physical decay occurs.

ABSORBED DOSE-EFFECT

Correlations between the absorbed doses delivered and toxicity and response have been reported both for hepatocellular carcinoma (9-11) and colorectal metastases (12, 13).

DOSIMETRY-BASED TREATMENT PLANNING

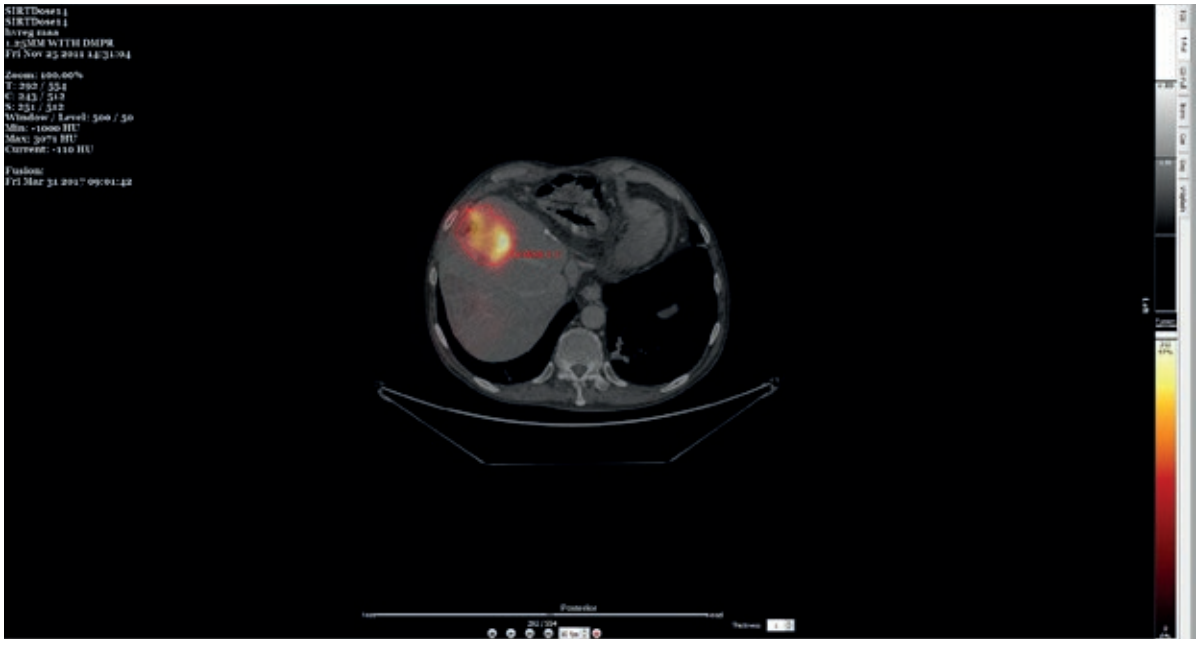
With current recommendations dosimetry is often used as a basis for treatment planning, although methods for dose prescription vary.

ISSUES TO CONSIDER

The low positron abundance enables quantitative imaging with PET although with prolonged acquisition times. The response threshold appears to be strongly dependent upon lesion size, indicating that target lesion dosimetry may be modified to account for this.

NEED FOR INVESTIGATION

The accuracy with which a pre-therapy ^{99m}Tc MAA study can predict the absorbed doses delivered at therapy has been reported with conflicting results. Standardisation of PET and SPECT imaging, particularly for bremsstrahlung, is needed as is standardisation of dosimetry procedures to facilitate direct comparisons of results obtained from different centres. The promising indications of absorbed dose effect relationships imply that a multicentre study would produce the evidence for personalised treatments. A potential for treatment planning would be to focus on delivering the maximum tolerable dose to healthy tissue (14).



Absorbed dose map fused with CT. The maximum lesion absorbed dose is 75 Gy

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90Y-ibritumomab tiuxetan for radioimmunotherapy of non-Hodgkin lymphoma

INTRODUCTION.

Radioimmunotherapy (RIT) with ^{90}Y-ibritumomab tiuxetan (marketed under the tradename of Zevalin®) is approved for the treatment of non-Hodgkin, CD20-positive indolent or transformed lymphoma, in the setting of relapse after rituximab-containing treatments or as a consolidation after first line therapy (1-3). The ibritumomab antibody targets CD20 antigen found on the surface of normal and malignant B cells.

The radioactivity to be administered takes into account patient weight and platelet blood count only, and no optimisation based on pre-therapeutic dosimetry is routinely prescribed. Usually 11 MBq or 14 MBq are administered per kg of body weight. Treatment administration is preceded by two infusions of unlabelled rituximab (Mabthera®) 250 mg/m^2, given one week apart in order to optimise RIT delivery by saturating non-tumoural CD20-positive sites (4).

EFFECTIVENESS

A randomised controlled trial of ^{90}Y-ibritumomab tiuxetan versus rituximab in relapsed or refractory low-grade or transformed B-cell NHL has shown an overall response rate (ORR) of 80% and complete response (CR) of 30 % for the ^{90}Y-ibritumomab tiuxetan group (3). In follicular lymphoma, a single RIT infusion as first line treatment shows ORR of 87% and median progression-free survival (PFS) of 26 months (5). RIT with ^{90}Y-ibritumomab tiuxetan has been fractionated in two administrations showing an ORR of 94.4% with 58.3% CR. At a median follow-up of 3.1 years, estimated 3-year PFS is 58%, and overall survival 95%. (6).

IMAGING.

As ^{90}Y is an almost pure β- emitter, the labelling of ibritumomab with a γ-emitting surrogate, such as ^{111}In, is required for pre-therapeutic dosimetry. Both final products, namely ^{90}Y-ibritumomab and ^{111}In-ibritumomab, can be assumed to have the same biodistribution in the human body (7, 8). The physical half-lives of ^{90}Y (64 hours) and ^{111}In (68 hr) are closely matched. To determine the slow antibody kinetics, the biodistribution of the labelled molecule has to be followed for several days in order to build a reliable time-activity curve. A trace amount of 185 MBq ^{111}In-ibritumomab is usually injected one week before the planned therapeutic infusion. Three to five imaging time points are needed for reliable curve fitting: 1-4 h, 24-48 h, 72 and 96-120 h. Suggested camera settings (9, 10) should be validated in-house.

VERIFICATION OF PLANNED RADIATION DELIVERY.

Bremsstrahlung radiation is emitted from the patient body after a treatment with ^{90}Y-ibritumomab tiuxetan, and gamma camera imaging of such emission is possible though of limited sensitivity and resolution (7). Although ^{90}Y has a small branch of position emission, at the standard ^{90}Y-ibritumomab tiuxetan administered activities this is not sufficient and not focal enough to allow direct PET imaging as in the case of hepatic radioembolisation.

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY.

Normal organ dosimetry for ^{90}Y-ibritumomab tiuxetan has been the subject of a MIRD dose estimate report (10). Median absorbed dose values calculated (in mGy/MBq) included Red Marrow 2.73 (± 0.90), Liver 3.64 (± 1.38), Kidneys 2.44 (± 0.61), Spleen 4.65 (± 2.32), Lungs 0.76 (± 0.48) and Whole body 0.58 (± 0.10). This report showed that the dosimetry approach, assumptions, and choice of parameters can substantially affect the calculated doses (10). Using a full SPECT/CT protocol instead of planar imaging, systematically lower absorbed doses have been found for the liver and spleen (11). A separate study determined that image-based bone marrow dosimetry models are better predictors of myelotoxicity than methods based on blood samplings (12).

TUMOUR DOSIMETRY

According to the experience of external beam radiotherapy, a total dose of 30-36 Gy is needed to eradicate lymphoma lesions. However, reduced-intensity protocols of 2 x 2 Gy are successfully used in selected cases of indolent lymphomas. When explored, the tumour absorbed dose range delivered by RIT was wide (range: 5.8 – 67 Gy) (13).

ABSORBED DOSE-EFFECT

No clear dose-response correlation has been shown (13). However, these first studies used a two-dimensional approach, so that no refined radiobiological models could be taken into account. When this has been done in similar types of treatments, as in the case of RIT with the anti CD20 ^{131}I-tositumomab (Bexxar®), an improved dose-response correlation was demonstrated (14). A three dimensional, voxel-based approach to RIT with ^{90}Y-ibritumomab tiuxetan is still to be optimised (9).

Transient and generally manageable myelotoxicity is the most common side effect of RIT. Pilot studies have shown that, when given as standard, non myeloablative activities, only exceptionally would administration of ^{90}Y-ibritumomab tiuxetan be contraindicated because of excessive absorbed doses to organs at risk (OARs) (15). However, concerns regarding the absorbed dose delivered to organs at risk may arise in case of severely ill and heavily pre-treated patients as well as if additional external beam radiotherapy is planned in the treatment course.

DOSIMETRY-BASED TREATMENT PLANNING

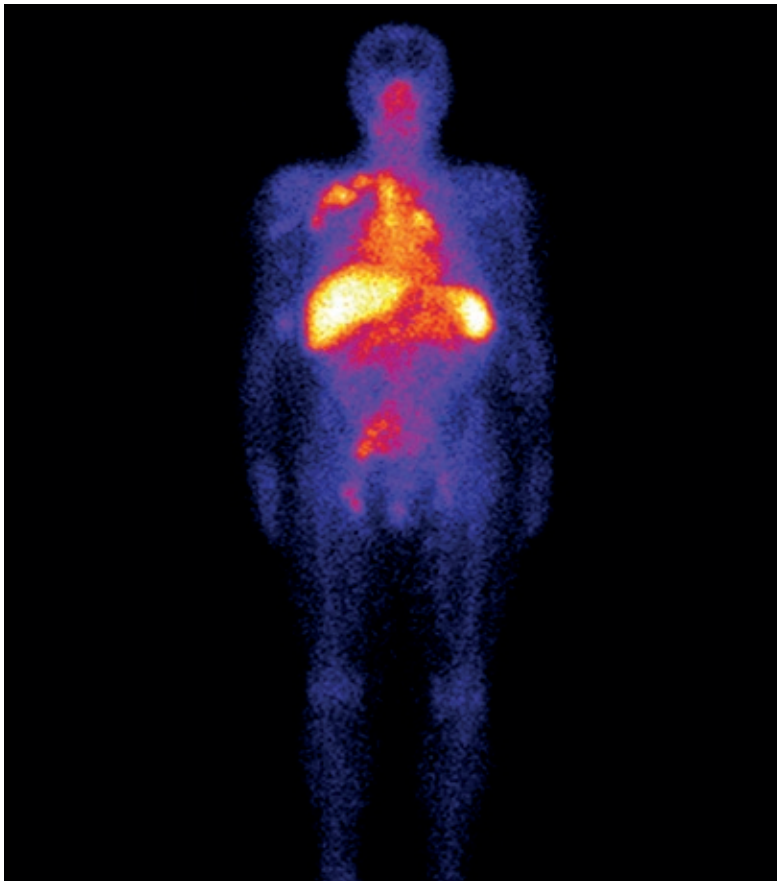
The strongest rationale for pre-therapeutic dosimetry is the prevention of unexpected toxicities in the disease course of fragile patients or when a deviation from the standard administration protocol is foreseen, as in the frame of myeloablative protocols. The pre-therapeutic imaging with ^{111}In-ibritumomab tiuxetan can be used for treatment planning, which can also take into account the planned delivered dose to lesions. Studies on fractionated therapies have determined that median organ absorbed doses were equivalent between fractions except for the spleen (12). Clinical studies employing myeloablative activities would always require an adequate planning as the risk of non-haematological toxicities may not be negligible (16).

ISSUES TO CONSIDER

Radiolabelled antibodies have a slow kinetic, therefore requiring pre-therapeutic dosimetry protocols lasting for several days. The use of a surrogate isotope (^{111}In) might imply minimal kinetic differences with the final therapeutic product. As ibritumomab is a murine antibody, there are concerns regarding the development of human anti mouse antibodies (HAMA) for repeated administrations. Verification of the actual delivered dose is challenging.

NEED FOR INVESTIGATION

- Extended indications for the use of ^{90}Y-ibritumomab tiuxetan
- Therapy fractionation
- Re-treatment strategies
- Myeloablative strategies
- The role of patient organ and tumour dosimetry with newer camera technologies and refined radiobiological models.



In-111 Zevalin: Anterior scan of a patient with Follicular Lymphoma, acquired 96 hours after injection. Multiple mediastinal, right axillary and bilateral inguinal lymph-nodes are seen, as well as small subcutaneous disease implants in the right arm.

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12

Radiosynovectomy

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

Radiosynovectomy (synoviorthesis or synoviolisis) (RSO) is an intra-articular injection of small radioactive particles (0.05 - 2 µm) to treat a synovitis. The aim of treatment is to improve mobility and to maximally decrease soreness, discomfort and bleeding into the joint. It is most commonly used to treat rheumatoid arthritis (RA), poly-arthritis and haemophilic arthritis (1-3). Further indications may be osteoarthritis and the articular effusion after joint replacement (4). ^{90}Y and ^{32}P colloid are used for larger joints such as the knee, while ^{186}Re colloid is frequently used for smaller joints including elbows and ankle. ^{169}Er citrate is administered for metatarsalphalangio (4).

EFFECTIVENESS

The response to treatment differs significantly based on the grade of synovitis, the previous stage of arthritis, and the degree of preceding cartilage destruction. For rheumatoid arthrosis response depends on systemic inflammatory level. In general RSO is considered to be effective, tolerable and safe (5).

ADMINISTRATION AND IMAGING

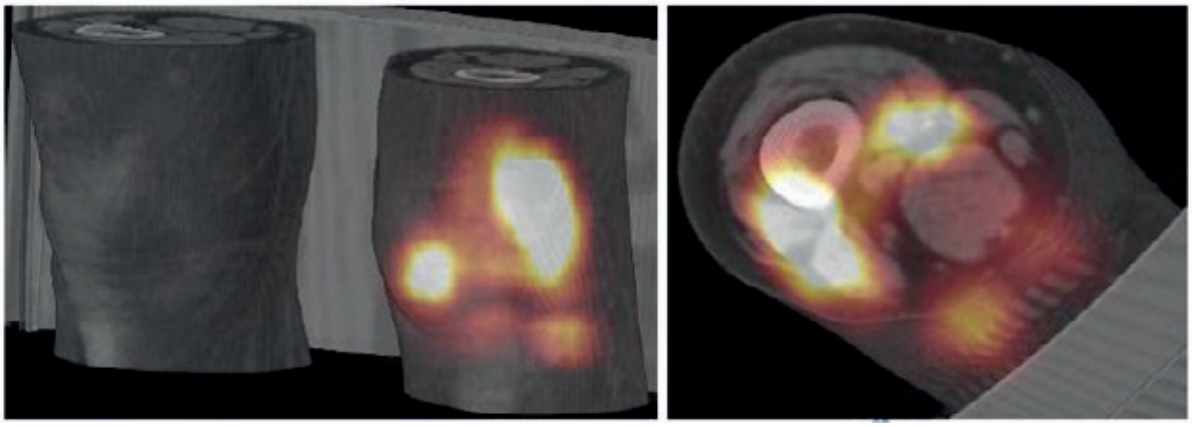
RSO can be preceded by two-phase bone scintigraphy (^{99m}Tc MDP/HDP/HEDP) and/or ^{99m}Tc-HIG scintigraphy of affected joints. Puncture of joints other than knee is recommended under fluoroscopic or ultrasound guidance (6). Intra-articular distribution may be verified by bremsstrahlung imaging to identify possible lymph nodes and leakage for further radiation burden estimation.

DOSIMETRY

Image based dosimetry is not performed due to a lack of adequate photon emissions at the activities administered. For most of the used radionuclides blood dosimetry using dicentric chromosome counting was performed in a limited number of patients to prove the overall safety of the therapy. In a case of significant leakage of ^{90}Y colloid from a knee joint the biologically assessed dose to whole body was calculated to be 130 mGy. No significant absorbed dose to the whole body was reported for ^{169}Er citrate or ^{186}Re sulphide radiosynoviorthesis using the same methodology (7). An absorbed dose of around 130 Gy to synovium was reported, based on commonly administered activities (5). An absorbed dose of 100 Gy is reported to achieve a similar treatment result as a surgical synovectomy (4).

ISSUES TO CONSIDER AND INVESTIGATE

RSO represents a minor low-cost intervention and the potential to simultaneously treat multiple joints in short intervals. Nevertheless treatment prediction is challenging. Treatment can be modulated by choosing higher energy beta-emitters for large joints and low-energy beta for small joints. The potential for individualised dosimetry remains an open question.



Example of intra-articular distribution of Y-90 citrate after injection into a knee of a patient presenting with therapy refractory gonarthritis. No extra-articular activity is visualized, excluding radiopharmaceutical leakage after injection.

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RESOURCE REQUIREMENTS

Implementation of dosimetry for therapy, particularly on a routine basis, has implications for infrastructure resourcing. The level of resources required will depend on the complexity of the dosimetry procedure and will vary according to local and national protocols and guidelines. Each procedure will have resource implications for both an initial set up of a dosimetry service and for ongoing support.

Resources fall into categories of equipment and staff. Whole-body dosimetry may be performed with an externally mounted compensated Geiger counter which enables multiple measurements to be made by either staff or, if necessary, by comforters and carers. A portable Geiger counter may also be used and, not uncommonly, a patient may be imaged although for high levels of ^{131}I deadtime effects must be accounted for. Blood dosimetry may be derived from samples measured in a well counter.

Image-based dosimetry requires a gamma camera that has been set up for the radionuclide under investigation at activity levels relevant to the procedure. In addition to routine quality control procedures, this entails determination of calibration factors for image quantification and characterisation of camera deadtime. PET systems, if used for dosimetry, must also be set up for quantitative imaging for each radionuclide imaged. Volume estimation may be acquired from CT or, in the case of radioiodine treatment of benign thyroid disease, from ultrasound scanning as well as from the SPECT and PET data.

As a multidisciplinary area, a range of trained staff are necessary to provide a comprehensive service. These include medical physicists for image quantification and absorbed dose calculations, nuclear medicine technologists and radiographers with experience in high activity imaging, nurses for blood sampling, physicians and radiologists for volume outlining and possibly paediatric specialists to help with imaging.

CONCLUSION

The treatment of cancer with radiopharmaceuticals is undergoing a significant expansion. Many new radiotherapeutics are being introduced into the clinic at costs in line with those for conventional chemotherapeutics and an increasing number of patients are being treated for common as well as rare cancers. This will have a significant effect on healthcare funding, patient management, and on the logistical and scientific challenges faced by nuclear medicine departments. As medicine in general begins to focus on personalised cancer, and as molecular imaging continues to attract increased attention (and funding), this growth in radiotherapeutics offers unprecedented opportunities for recognition, support and scientific and clinical advance. As can be seen in this report, the groundwork for dosimetry-based individualisation of treatment has been laid. Further development will surely follow as dosimetry is introduced into the clinic.

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