CHAPTER 19

RADIONUCLIDE THERAPY

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19.1. INTRODUCTION

Cancer has been treated with radiopharmaceuticals since the 1940s. The radionuclides originally used, including ^{131}I and ^{32}P, are still in use. The role of the physicist in radionuclide therapy encompasses radiation protection, imaging and dosimetry. Radiation protection is of particular importance given the high activities of the unsealed sources that are often administered, and must take into account medical staff, comforters and carers, and, as patients are discharged while still retaining activity, members of the public. Regulations concerning acceptable levels of exposure vary from country to country. If the administered radiopharmaceutical is a γ emitter, then imaging can be performed which may be either qualitative or quantitative. While a regular system of quality control must be in place to prevent misinterpretation of image data, qualitative imaging does not usually rely on the image corrections necessary to determine the absolute levels of activity that are localized in the patient. Accurate quantitative imaging is dependent on these corrections and can permit the distribution of absorbed doses delivered to the patient to be determined with sufficient accuracy to be clinically beneficial.

Historically, the majority of radionuclide therapies have entailed the administration of activities that are either fixed, or may be based on patient weight or body surface area. This follows methods of administration necessarily adopted for chemotherapy. However, given that in vivo imaging is possible for many radiopharmaceuticals and that the mechanism of therapy is the delivery of a radiation absorbed dose, the principles of external beam radiation therapy apply equally to radionuclide therapies. These are summarized in European Directive 97/43:

> "For all medical exposure of individuals for radiotherapeutic purposes exposures of target volumes shall be individually planned; taking into account that doses of non-target volumes and tissues shall be as low as

reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure".

In this directive, the term 'radiotherapeutic' specifically includes nuclear medicine for therapy.

Radionuclide therapy is a rapidly expanding cancer treatment modality, both in terms of the number and range of procedures given, and many new radiopharmaceuticals are now entering the market. At present, there is a paucity of guidelines governing levels of activity to administer and these vary widely according to local protocols. The application of internal dosimetry to therapeutic procedures will allow the data to be collected on which to establish the evidence necessary to optimize treatment protocols.

For many therapy procedures, dosimetry studies have been conducted. These have demonstrated that a wide range of absorbed doses are delivered both to target tissues and to normal tissues from the administration of fixed activities due to variations in uptake and retention of a radiopharmaceutical. It is likely that, in conjunction with patient variations in radiosensitivity, this accounts for the variable response seen with radionuclide therapy.

Recent advances in the quantification of single photon emission computed tomography and positron emission tomography data, and increased research into patient specific rather than model based dosimetry, have led to the possibility of personalizing patient treatments according to individual biokinetics.

19.2. THYROID THERAPIES

19.2.1. Benign thyroid disease

Benign thyroid disease (typically hyperthyroidism or thyrotoxicosis) is most commonly caused by Graves' disease, an autoimmune disease affecting the whole thyroid gland and causing it to swell. Thyroid toxic nodules, consisting of abnormal thyroid tissue, are also responsible for overactive thyroid glands. Iodine-131 NaI (radioiodine) has been used since the 1940s to treat hyperthyroidism successfully.

There is a long standing wide acceptance of radioiodine as a treatment for hyperthyroidism, particularly for patients with solitary toxic adenoma, although treatment protocols vary, and there is limited evidence to compare long term results from surgery, anti-thyroid drugs or radioiodine. Guidelines are available from the European Association of Nuclear Medicine (EANM) and the American Thyroid Association, as well as from individual countries including Germany and the United Kingdom.

19.2.1.1. Treatment specific issues

Standard administrations can vary from 200 to 800 MBq, depending on the patient situation and local practice. While persistence of symptoms will result from inadequate treatment, entailing further administrations, it can be argued that patients should not receive more activity than is necessary to render them euthyroid. Therefore, in common with other radionuclide therapies, a major issue is that of personalized treatment based on patient specific dosimetry. This necessitates determination of the thyroid volume and calculation of the activity required to administer a fixed absorbed dose based on a tracer study. A range of methods have been followed to determine the thyroid volume, using, for example, ultrasound, ^{123}I-NaI or ^{124}I-NaI, and there is some discrepancy in the reported absorbed doses required to achieve euthyroidism. Further research work would certainly benefit patients.

Radiation protection advice must be given to a patient undergoing radioiodine treatment although standard treatments can usually be conducted on an out-patient basis.

19.2.2. Thyroid cancer

Thyroid cancer accounts for less than 0.5% of all cancers and there are 28 000 new cases diagnosed each year in Europe and the United States of America. Papillary and follicular thyroid cancer account for 80–90% of cases, with the remainder being anaplastic carcinomas, medullary carcinomas, lymphomas and rare tumours. Increased risk is associated with benign thyroid disease, radiation therapy to the neck and poor diet. As with benign thyroid disease, thyroid cancer has also been treated with radioiodine for over sixty years and in conjunction with total or near total thyroidectomy is widely used for an initial ablation of residual thyroid tissue. Up to 20% of cases may present with metastatic disease, usually to the lungs or bones although also to liver and brain. Treatment for distant metastases usually involves further and often higher administrations of radioiodine. This treatment is the most common application of radionuclides for therapy and is very successful, with complete response rates of 80–90%. Nevertheless, the disease can prove fatal in a higher proportion of patients that are most at risk, which include the young and the elderly.

19.2.2.1. Treatment specific issues

There are a number of controversies concerning the treatment of thyroid cancer with radioiodine. These include the extent of a low iodine diet prior to administration, levels of activity to administer for ablation or for therapy, and the

time interval between ablation and the determination of success, which itself is subject to debate. The issue that most affects the physicist is that of standardized versus personalized treatments, which has been debated since the early 1960s. Fixed activities given for ablation can vary from 1100 to 4500 MBq, and those given for subsequent therapy procedures can be in excess of 9000 MBq. Published guidelines report the variation in fixed activities but do not make recommendations concerning these levels.

It has been conclusively demonstrated in a number of dosimetry studies that patients administered fixed activities of radioiodine receive absorbed doses to remnant tissue, residual disease and to normal organs that can vary by several orders of magnitude. This potentially has important consequences, as it implies that, in many cases, patients may be receiving less absorbed dose than is required for a successful ablation or therapy, while in other cases patients will receive absorbed doses to malignant and normal tissues that are excessively higher than necessary. Undertreatment will result in further administrations of radioiodine with the risk of dedifferentiation over time, so that tumours become less iodine avid. Overtreatment can result in unnecessary toxicity which can take the form of sialadenitis and pancytopenia. Radiation pneumonitis and pulmonary fibrosis have been seen in patients with diffuse lung metastases, and there is a risk of leukaemia in patients receiving high cumulative activities. Personalized treatments were first explored in the 1960s with patients administered activities required to deliver a 2 Gy absorbed dose to the blood and constraints regarding radioactive uptake levels at 48 h. Further approaches have been taken, based on whole body absorbed doses, which can be considered a surrogate for absorbed doses to the red marrow.

Dosimetry for thyroid ablations presents a different set of challenges to that performed for therapies. In the former case, the small volume of remnant tissue can render delineation inaccurate, which subsequently impinges on the accuracy of the dose calculation. Therapies of metastatic disease can involve larger volumes, although heterogeneous uptake is frequently encountered and lung metastases in particular require careful image registration and attenuation correction (Fig. 19.1).

A current issue is that of ‘stunning’, whereby a tracer level of activity may mitigate further uptake for an ablation or therapy. This phenomenon would have consequences for individualized treatment planning, although at present its extent and indeed its existence is being contested. However, it is not infrequent that a greater extent of uptake may be seen from a larger therapy administration than from a tracer administration (Fig. 19.1).

While subject to national regulations, patients receiving radioiodine treatment frequently require in-patient monitoring until retention of activity falls to levels acceptable to allow contact with family members and the public. It is,

therefore, necessary for the physicist to give strict advice on radiation protection, taking into account the patient's home circumstances.

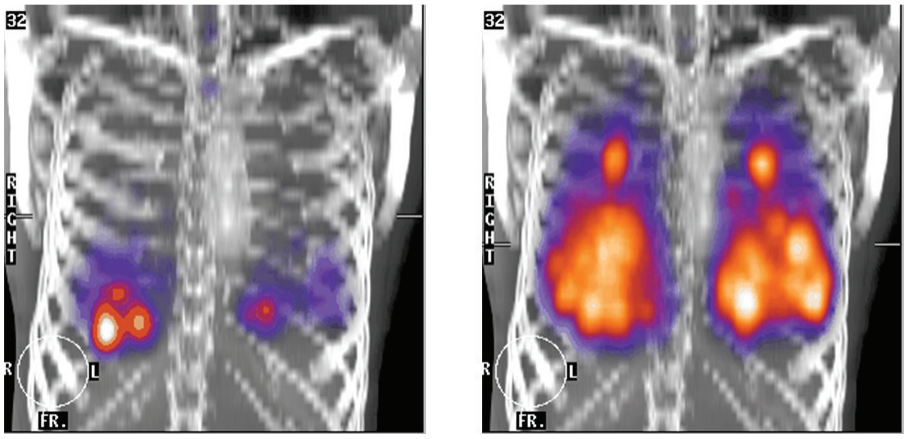

FIG. 19.1. Absorbed dose maps resulting from a tracer administration of 118 MBq ^{131}I-NaI (left) and, subsequently, 8193 MBq ^{131}I-NaI (right) for therapy (maximum absorbed dose: 90 Gy). The absorbed doses were calculated using 3-D dosimetry on a voxel by voxel basis.

19.3. PALLIATION OF BONE PAIN

Bony metastases arise predominantly from prostate and breast cancer. Bone pain is experienced by up to 90% of patients with castration resistant prostate cancer in the later phases of their disease. Radiopharmaceuticals have been established as an effective agent for bone pain palliation for almost 70 years, with ^{89}Sr first being used in 1942. A wide range of radiopharmaceuticals have been used to treat bone metastases and there are two commercially available products, ^{89}Sr chloride (Metastron) and ^{153}Sm-lexidronam (Quadramet) that have received US Food and Drug Administration (FDA) approval (in 1993 and 1997, respectively). A number of other radiopharmaceuticals have been used, including ^{32}P, ^{186}Re-HEDP, ^{188}Re-HEDP, ^{117m}Sn and ^{177}Lu-EDTMP. More recently, the α emitter ^{223}Ra has undergone evaluation in randomized phase III clinical trials and has also received FDA approval.

In the case of ^{89}Sr and ^{153}Sm, administered activities tend to be standardized according to the manufacturer's guidelines. However, administered activities for other agents vary widely according to local protocols, and published guidelines are largely concerned with procedure. Re-treatments are generally considered to be beneficial, subject to recovery of haematological toxicity, and recommendations for the timing of these have been made by both the EANM

and the IAEA. However, no trials have yet been performed to assess the optimal timing or levels of administration.

19.3.1. Treatment specific issues

The main issue concerning the use of radiopharmaceuticals for the treatment of bone pain is that of determining the ideal treatment protocol, including the optimal radionuclide to use, and whether this should be standardized or could be modified on an individual patient basis. In practice, local logistics and availability will have a strong impact on the radionuclide of choice. It is of particular interest that the radionuclides used vary widely in terms of their β emissions. Arguments can be made to support both approaches, in that the longer range β emitters may be more likely to target all of the disease, while the shorter range β emitters (and particularly an α emitter) will avoid unnecessary toxicity. There is also a wide range of physical half-lives between these radionuclides and there is some evidence to suggest that the longer lived ^{89}Sr can produce a response that takes longer to occur but that is longer lasting.

Dosimetry for bone pain palliation is challenging due to the difficulties of assessing the distribution of uptake in newly formed trabecular bone and its geometrical relation to viable red marrow and to disease. Nevertheless, models have been developed to address this interesting problem and a statistically significant correlation has been demonstrated between whole body absorbed doses and haematological toxicity. Dosimetry for other radionuclides is highly dependent on the imaging properties of these radionuclides, although it could potentially be used to increase administered activities in individual patients.

19.4. HEPATIC CANCER

Hepatocellular carcinoma is a major cause of cancer deaths. In recent years, primary and secondary liver cancers have been treated with a range of radionuclides administered intra-arterially, based on the fact that while the liver has a joint blood supply, tumours are supplied only by the hepatic artery. The advantage of this approach is that treatments can be highly selective and can minimize absorbed doses delivered to normal organs, including healthy liver. This procedure requires interventional radiology as the activity must be administered directly into the common, right or left hepatic artery via an angiographic catheter under radiological control and so is a prime example of the multidisciplinary nature of radionuclide therapy. Prior to administration, a diagnostic level of ^{99m}Tc-macroaggregate of albumin (MAA) is given to

ascertain the likelihood of activity shunting to the lung. This is usually evaluated semi-quantitatively.

To date, two commercial products have received FDA approval, classified as medical devices rather than as drugs. Both use ^{90}Y. Theraspheres comprise ^{90}Y incorporated into small silica beads and SIR-Spheres consist of ^{90}Y incorporated into resin. Lipiodol, a mixture of iodized ethyl esters of the fatty acids of poppy seed oil, has also been explored for intra-arterial administration. Lipiodol has been radiolabelled with both ^{131}I and ^{188}Re, the latter having the benefit of superior imaging properties, a longer β path length and fewer concerns for radiation protection due to the shorter half-life.

19.4.1. Treatment specific issues

As with other therapies, outstanding issues include the optimal activity to administer, which is usually based on patient weight or body surface area, arteriovenous shunting observed prior to treatment and the extent of tumour involvement. However, there have been examples of treatments planned according to estimated absorbed doses delivered to the normal liver and this treatment offers the potential for individualized treatment planning based on potential toxicity. Radiobiological consequences have been considered by conversion of absorbed doses to biologically effective doses and there are tentative conclusions that multiple treatments may deliver higher absorbed doses to tumours while minimizing absorbed doses to normal liver.

A particular issue of this treatment concerning the physicist is that of imaging, due to the need to ascertain lung uptake from the pre-therapy ^{99m}Tc-MAA scan, and the possibility of bremsstrahlung imaging as a basis for calculation of absorbed doses delivered at therapy.

19.5. NEUROENDOCRINE TUMOURS

Neuroendocrine tumours (NETs) arise from cells that are of neural crest origin and usually produce hormones. There are several types of neuroendocrine cancer, including phaeochromocytoma, which originates in the chromaffin cells of the adrenal medulla, and paraganglioma, which develops in extra-adrenal ganglia, often the abdomen. Carcinoid tumours are slow growing and arise mainly in the appendix or small intestine although they can also be found in the lung, kidney and pancreas. Medullary thyroid cancer is a special case of an NET that arises from the parafollicular cells of the thyroid gland, which produce calcitonin. For the purposes of radionuclide therapy, NETs tend to be considered as one malignancy and similar radiopharmaceutical treatments are administered,

although due in part to differences in radiosensitivity and proliferation, response is variable between diseases. NETs are frequently treated with radiopharmaceuticals. The mean age at diagnosis is around 60 years although tumours may present at any age.

There are two main mechanisms by which NETs are targeted with radiopharmaceuticals. NETs have been treated with the noradrenaline analogue ^{131}I-MIBG (metaiodobenzylguanidine) for over twenty years, although this is still largely considered an experimental treatment. Although generally considered to be a palliative treatment, high uptake can be achieved and complete responses have been seen. More recently, a number of peptide analogues of somatostatin have been developed, radiolabelled with ^{90}Y, ^{111}In or ^{177}Lu, that offer a range of treatment options. Guidelines for radionuclide therapy of NETs have been produced by the EANM and the European Neuroendocrine Tumour Society, and focus mainly on procedural aspects. Recommendations are not given for administered activities, and these can vary from 3700 to 30 000 MBq of ^{131}I-MIBG and cumulated activities of 12 000–18 000 MBq of ^{90}Y-DOTATOC. Administrations are often repeated, although there are no standardized protocols for the intervals between therapies.

To date, there have been almost no studies directly comparing the relative merits of the different radiopharmaceuticals available for the treatment of neuroendocrine cancer. Key considerations are largely related to the relative path lengths of the radionuclides used, their imaging properties and toxicity. For example, ^{111}In-octreotide therapy readily lends itself to imaging due to dual emission peaks at 173 and 247 keV, and relies on internalization due to radiation delivered by Auger emissions, whereas ^{90}Y labelled analogues can cause irradiation over 1 cm although they can only be imaged with bremsstrahlung scintigraphy. ^{90}Y labelled analogues and ^{131}I-MIBG can cause myelosuppression, thus the administration of higher activities may require stem cell support. Kidney toxicity can be another activity-limiting factor for the somatostatin analogues.

19.5.1. Treatment specific issues

The range of activities administered and the increasingly available range of radiopharmaceuticals developed for the treatment of NETs is indicative of the main issue facing this treatment, which is to determine the optimal treatment protocol. As with other therapies, the issue of personalized versus standardized treatments is at the forefront of this debate, with administrations based on fixed activities modified according to patient weight or, in some cases, based on absorbed whole body doses. It has been shown that a wide range of absorbed doses are delivered to both tumours and to normal organs from fixed activities. Dosimetry for high activities of ^{131}I-MIBG has been the subject of

extensive research in recent years, and must deal with problems resulting from camera dead time, photon scatter and attenuation. Image based dosimetry of ^{90}Y labelled pharmaceuticals has been performed using low levels of ^{111}In given either prior to therapy or included with the therapy administration. More recently, bremsstrahlung imaging has been developed to enable dosimetry to be performed directly.

19.6. NON-HODGKIN'S LYMPHOMA

Of the malignancies arising from haematological tissues, non-Hodgkin's lymphoma is most commonly targeted with radiopharmaceuticals. Various forms of lymphoma are classified into high grade or low grade, depending on the rate of growth. Lymphomas are inherently radiosensitive, express a number of antigens and can be successfully treated with radioimmunotherapy (RIT) using monoclonal antibodies radiolabelled usually with either ^{131}I or ^{90}Y. A number of radiolabelled monoclonal antibodies have been developed and two, ^{90}Y-Ibritumomab Tiuxitan (Zevalin) and ^{131}I-Tositumomab (Bexxar), have received FDA approval. Both target the B-cell specific CD 20 antigen and have been used successfully in a number of clinical trials. Both agents have demonstrated superior therapeutic efficacy to prior chemotherapies in various clinical settings.

As with chemotherapy, RIT is more successful when administered at an early stage of disease. Clinical trials are ongoing to determine how to more effectively integrate RIT into the current clinical management algorithm in lymphoma patients.

19.6.1. Treatment specific issues

Internal dosimetry has been applied to a number of studies using RIT with varying results and conclusions. Initial dosimetry trials for Zevalin found that while absorbed doses were delivered to tumours and to critical organs that varied by at least tenfold, these did not correlate with toxicity or response, and that at the levels of activity prescribed, the treatment was deemed to be safe, obviating the need for individualized dose calculations, and treatment now tends to be administered based on patient weight. However, FDA approval incorporated the need for biodistribution studies to be performed prior to therapy using the antibody radiolabelled with ^{111}In as a surrogate for ^{90}Y under the assumption that the tracer kinetics would translate into clinical therapy and a number of studies are now concerned with assessing the biodistribution and dosimetry based on bremsstrahlung imaging (Fig. 19.2).

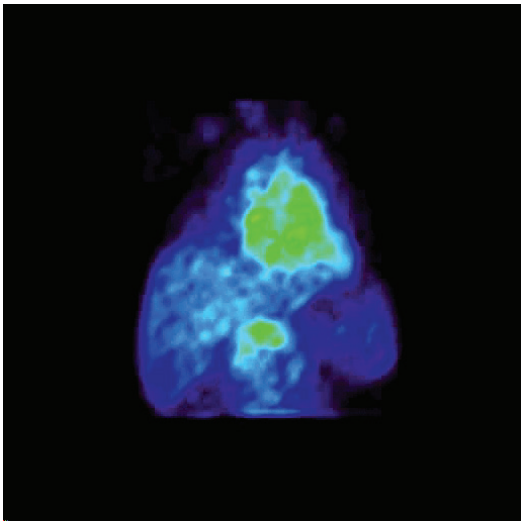

FIG. 19.2. An absorbed dose map (maximum dose: 39 Gy) resulting from 3-D dosimetry of bremsstrahlung data acquired from treatment of non-Hodgkin's lymphoma with ^{90}Y-Ibritumomab Tiuxitan (Zevalin).

In contrast, studies using ^{131}I-Tositumomab (Bexxar) have demonstrated that at least bone marrow toxicity is significantly related to dosimetry. As a result, ^{131}I-Tositumomab is one of the few radionuclide therapies (or indeed radiotherapy procedures) based on individualizing absorbed doses delivered to the critical organ, which in this case is the bone marrow. To this end, the level of administered activity is determined according to a whole body absorbed dose of 0.75 Gy, calculated from a series of three whole body scintigraphy scans.

19.7. PAEDIATRIC MALIGNANCIES

Cancer in children is rare, with an incidence of less than 130 per million and an overall relative survival rate of 57%. Leukaemia and lymphoma account for nearly 50% of cases. Radionuclide therapy for children and young people is correspondingly rare and entails particular scientific and logistical challenges that justify consideration independently of adult treatments. Issues of in-patient care predominantly arise due to the combination of increased nursing requirements and radiation protection considerations. Radiation protection must also play a large role in decisions to allow children to leave hospital, as they frequently have siblings at home.

19.7.1. Thyroid cancer

The ablation and therapy of thyroid cancer with radioiodine is performed for children, who are considered a high risk group. There is commonly a significantly higher incidence of metastatic disease in children than in adults. Fatalities can be as high as 25%, often occurring after many years of repeated radioiodine treatments and consequently high cumulated activities. Thus, potential late toxicity in children from radionuclide therapy needs to be considered.

19.7.2. Neuroblastoma

Neuroblastoma is a malignancy of the neuroendocrine system specific to children and young people. Neuroblastoma is inherently radiosensitive and has been treated with ^{131}I-MIBG since the 1980s, particularly for primary refractory or relapsed patients. Although treatments are generally intended to be palliative, complete responses have been reported. More recently, there has been interest in treating neuroblastoma with radiolabelled peptides, such as ^{177}Lu-Dotatate.

19.7.2.1. Treatment specific issues

While it is generally recognized that protocols for administering radioiodine to children should be modified from those applied to adults, there is little agreement on how such modifications should be determined and, in practice, these can be based on body weight, surface area or age. The EANM guidelines on radioiodine therapy of differentiated thyroid cancer support the principle of individual treatment of thyroid cancer in children and German procedure guidelines advocate administration based partly on the 24 h uptake of a tracer activity prior to ablation.

Despite the small number of centres that have treated children with ^{131}I-MIBG for the treatment of neuroblastoma, there has been a very wide variation in treatment protocols. While many treatments have relied on fixed activities (which have generally ranged from 3700 to 7400 MBq), substantial research and development into quantitative imaging and internal dosimetry of ^{131}I has led to a higher degree of dosimetry based personalized treatments than has been the case for adult therapies. This has led in particular to administered activities being calculated based on whole body absorbed doses which have been shown to correlate with haematological toxicity. Further complications, particularly relating to toxicity and radiation protection, can be caused by an increasing trend towards higher activities, possibly administered with stem cell support and concomitant chemotherapy which can act as a radiosensitizer.

19.8. ROLE OF THE PHYSICIST

The physicist is responsible for a wide range of tasks in nuclear medicine and must perform duties that include the procurement and maintenance of imaging equipment and associated computer systems; responsibility for radiation protection and interpretation; and implementation of national legislation. This comprehensive and challenging role is exemplified in the treatment of cancer and benign disease with radiopharmaceuticals that can entail levels of radioactivity far exceeding those used for diagnostic purposes.

Quality control of scintillation cameras is fundamental to good clinical practice in radionuclide therapy to ensure that the diagnostic information used as a basis for treatment is accurate. This relies on the development of and adherence to a strict procedure of well defined protocols and procedures that must be performed regularly.

Radiation protection pertaining to unsealed sources used for radionuclide therapy entails a greater degree of responsibility than that commonly encountered in diagnostic imaging. Staff are potentially exposed to high levels of radiation of γ, β and α emissions which, therefore, requires careful handling, dispensing and administration of therapeutic radiopharmaceuticals. Therapy procedures can involve staff groups that usually do not encounter high levels of radiation, so that extra precautions are needed. This particularly applies to the care of patients, which may be provided to some extent by family members and carers as well as by nurses, and the scanning of patients following administrations of high activities by radiographers and technicians. Careful monitoring of the involved staff must be performed at all times and the physicist must be aware of national regulations.

There is an increasing opportunity for development of a number of related areas in radionuclide therapy which predominantly involve the physicist. Foremost among these is quantitative imaging. While the clinical viewpoint of radionuclide therapy is focused on the indication and on the treatment, imaging concerns only matters that, to some extent, may be independent of these. Thus, for example, quantitative imaging of ^{131}I uptake in the abdomen will follow the same procedure whether this results from ^{131}I-MIBG treatment of an NET or an ^{131}I-radiolabelled monoclonal antibody for the treatment of lymphoma. Optimization of imaging of bony metastases with a given agent will follow similar procedures whether the metastases arise from prostate or breast cancer. Quantitative imaging is, therefore, predominantly focused on the radionuclide, independently of its formulation, and on the extent and localization of uptake as well as the imaging equipment employed for the purpose. Quantitative imaging must take into account a number of factors that are often of little concern in diagnostic imaging. Scatter is a significant impediment to accurate quantitative

imaging, particularly where high energy emitters such as ^{131}I are used for therapy. Corrections can be applied with relative ease by assessing and subtracting the scatter contribution from one or more energy windows placed adjacent to the peak energy window. Attenuation correction is essential to quantitative imaging and can be performed using a variety of methods. These can range from a straightforward approach that assumes the patient consists entirely of water, to more sophisticated methods that take into account the electron density on a voxel by voxel basis. Dead time corrections are frequently overlooked in the imaging of patients undergoing radionuclide therapy as these seldom require consideration for diagnostic scanning. However, this is an issue of paramount importance that will severely inhibit accurate quantification if ignored. Again, this is a particularly significant factor when using high activities of ^{131}I, and it is essential that each camera is characterized accordingly prior to image processing and analysis.

Accurate image quantification enables further avenues of research and development that have only recently begun to emerge as substantial areas of study. Pharmacokinetic analysis, derived from sequential scanning, can allow inter- and intra-patient variations in uptake and retention to be calculated which can aid understanding and optimization of a radiopharmaceutical. This is particularly relevant for new products. Accurate analysis is dependent on the acquisition of sufficient statistics and data which must include the number and timing of scans. Inherent errors and uncertainties should be considered where possible.

Quantitative imaging and analysis facilitate the accomplishment of accurate internal dosimetry calculations, which are of paramount importance to patient specific treatment planning and which are now becoming mandatory for new products and necessary for the acquisition of the evidence base on which treatments should be performed. Although isolated studies into image based, patient specific dosimetry have been performed for many years, this remains a newly emerging field for which no standardized protocols or guidelines exist. This puts greater responsibility on the physicist whose role must be to advise on image acquisition. This invariably entails balancing scientific requirements with local resource restrictions. As there is only limited software available for dosimetry calculations at present, it may prove necessary to develop software or spreadsheets to perform absorbed dose calculations.

Essentially, the end point of such calculations should lead to a prediction of absorbed doses to the tumour and critical organs from a given administration and confirmation of the absorbed doses delivered after the therapy has been performed. However, interpretation and understanding of the biological relevance of these absorbed doses is not straightforward. Radiobiology for radionuclide therapy has not been developed at the rate seen for external beam radiotherapy (EBRT) but is now attracting more attention. There are both biological and physics aspects

to radiobiology, with the latter largely concerned with constructing models to explain physiological phenomena. To some extent, these models may be adapted from those formulated for EBRT, which are predominantly based on the so-called linear quadratic model. This model is largely predicated on the assumption that cellular radiation damage can be considered separately according to single or double strand DNA (deoxyribonuleic acid) breaks and while this has a validity for radionuclide therapy, a number of confounding factors should be taken into account that can accommodate the relatively low but continuous absorbed dose rates delivered by radioactive uptake and emerging evidence to suggest that DNA is not the only target causing cell death. Radiobiology for radionuclide therapy is likely to become more complicated as radiopharmaceuticals are administered with concomitant chemotherapy or with EBRT and as new factors are discovered, such as the bystander effect, in which unirradiated cells can be killed if they are in proximity to cells that have been irradiated, and hyper-radiosensitivity, which has indicated excessive sensitivity to very low levels of irradiation.

In summary, it is likely that the varied role enjoyed by the physicist will become more complicated as radionuclide therapies are increasingly subject to accountability and as the field expands. Radionuclide therapy is the only cancer treatment modality that allows imaging of the therapeutic drug in situ. It is the duty of the physicist to capitalize on this by providing the information necessary to enable optimal and cost effective treatment.

19.9. EMERGING TECHNOLOGY

In the coming years, a number of factors will affect the development of radionuclide therapy and, in particular, the role of the physicist. New imaging technology has emerged in recent years in the form of hybrid scanners, which will have a significant impact on improving the accuracy of dosimetry from radionuclide therapies.

A range of new radiopharmaceuticals is now emerging and previously used radiopharmaceuticals are being revisited. In particular, there is currently a growing interest in α emitters, although these have been used in some form for many decades. The physical properties of α particles have distinct advantageous and disadvantageous implications for radionuclide therapy. The short range of emissions (10–100 μm in soft tissue) means that uniform uptake of a radiopharmaceutical is critical to a successful treatment as there is little radiation crossfire. However, the high linear energy transfer ensures that radiation damage resulting from uptake in a cell is likely to be lethal and that cells immediately adjacent are also likely to be killed. Examples of alpha therapy to date include ^{211}At for direct infusion into resected gliomas, antibodies radiolabelled with

^{213}Bi or ^{225}Ac for the treatment of leukaemia and ^{223}Ra for the treatment of bone metastases. Dosimetry for α emitters remains largely unexplored and is subject to a number of challenges due to the difficulty of localization and the need to take into account the emissions of daughter products, which may not remain at the initial site of uptake.

The introduction of more stringent regulatory procedures will increase the need for accurate internal dosimetry. The FDA now requires dosimetric evaluation of new radiopharmaceuticals, and it is becoming commonplace for new uses of existing agents to also be the subject of a phase I/II clinical trial to ascertain absorbed doses delivered to critical organs. As brief palliative effects translate into longer lasting survival, critical organ dosimetry will become more important to ensure minimization of unnecessary late toxicity. However, it should be noted that basic dosimetry calculations aimed at estimating critical organ absorbed doses are not necessarily sufficient to ensure an optimal treatment protocol, which must take tumour dosimetry into account.

The increasing trend towards accountability and evidence based medicine will require adherence to strict radiation protection procedures for patients, families and staff, and it may become necessary to assess exposure, particularly to family members, with greater accuracy.

Scientific developments are likely to proceed rapidly, and many are now within the reach of departments that have only basic research facilities, since accurate absorbed dose calculations can be obtained from careful imaging procedures and a relatively simple spreadsheet. Individualization of absorbed dose calculations can then be achieved. Dosimetry based treatment planning will also become an essential element of patient management as options of chemotherapy or EBRT administered concomitantly with radiopharmaceuticals are explored. The practice of internal dosimetry itself continues to evolve and can be divided into categories that require different approaches. In addition to image based dosimetry, these include whole body dosimetry, blood based dosimetry and model based dosimetry. A particular focus at present is on red marrow dosimetry, as this is the absorbed dose limiting organ for many therapies.

Multi-centre prospective data collection is critical to the development of this field, and international networks will be required to accrue a sufficient number of patient statistics to enable the formulation of agreed and standardized treatment protocols.

19.10. CONCLUSIONS

Nuclear medicine physics is playing an increasingly important role in the service and management of radionuclide therapies. In addition to the tasks traditionally associated with nuclear medicine, which primarily involve the maintenance of imaging and associated equipment, radiation protection and administration of national regulations, there is a growing requirement for patient specific treatment planning which requires quantitative imaging, internal dosimetry and radiobiological considerations.

While radionuclide therapy is usually performed within nuclear medicine, it is often to be found within clinical or medical oncology, or within endocrinology. In effect, radionuclide therapy requires a multidisciplinary approach that involves diverse groups of staff. The adoption of treatments based on individualized biokinetics, obtained from imaging and external retention measurements, places the physicist more centrally within this network, as is seen in EBRT.

There is currently the need for increased training in this field, and due to the relatively low numbers of patients treated even at specialist centres, multi-centre networks will facilitate the exchange of expertise and the gathering of prospective data necessary to advance the field. As this hitherto overlooked area of cancer management expands, the scientific opportunities available to the nuclear medicine physicist will also increase.

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