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Exploring drug safety of radiopharmaceuticals

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Nanno Schreuder

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Chapter 1

General introduction and outline of the thesis

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1.1 INTRODUCTION

Nuclear medicine is a medical specialty that uses radiopharmaceuticals for the diagnosis or treatment of patients. A radiopharmaceutical is a radioactive drug that consists of a tracer part linked to a radionuclide. The tracer part is a molecule or particle; it determines where the radiopharmaceutical will localise in the body. The radionuclide is an atom emitting radiation that can be detected by scanners or that delivers a radiation dose to a target area. Nuclear medicine uses the radiation the radionuclide emits to visualise or treat organs where the tracer localises. Radionuclides typically used in nuclear medicine are alpha, beta⁻, beta⁺, and gamma emitters (α , β^- , β^+ , and γ). An alpha-particle is a helium nucleus (${}^4_2\text{He}$); a beta⁻-particle is an electron. Both deliver a high energy over a short distance and are used for therapy in nuclear medicine. A beta⁺-particle, also called a positron which, upon interacting with an electron, is annihilated and gives rise to two photons or gamma rays (γ -rays). Gamma rays are a form of electromagnetic radiation, have a long range in tissue, and can be used in imaging in nuclear medicine^{1, 2}.

Most radiopharmaceuticals are used for diagnostic purposes to enable visualisation of physiological processes using imaging modalities such as planar imaging, single photon emission computed tomography (SPECT), or positron emission tomography (PET). Figure 1.1 shows a schematic presentation of SPECT and PET. Planar imaging acquires a two-dimensional image of the body or body parts. Single photon emission computed tomography uses a gamma camera (with one or two detectors), which rotates around the patient to detect gamma emission from single photon-emitting radionuclides and acquires information from multiple angles to construct a three-dimensional image. Positron emission tomography uses positron emitting radionuclides and employs multiple detectors placed in a ring around the patient to detect coincident photons originating from annihilation of a positron with an electron³.

Fig. 1.1 Schematic presentation of SPECT and PET. (A) The radionuclide emits a photon that is detected by a rotating gamma camera. (B) The radionuclide emits a positron that travels in tissue for a short distance until it interacts with an electron. When an electron and positron annihilate, they produce two gamma photons to be emitted in opposite directions. Multiple gamma detectors positioned in a circle detect these photons. Adapted with permission from Berger et al⁴.

Today, healthcare professionals often combine SPECT and PET with computed tomography (CT), which uses X-rays. These hybrid cameras are then referred to as SPECT/CT or PET/CT and offer better imaging than SPECT or PET alone, because they have the ability to image both processes in the body as well as anatomy, which allows for accurate localization of abnormalities. Over the years, nuclear medicine imaging modalities have become essential in many areas of medicine to detect and monitor diseases^{1, 3, 5}. An example of one of the most-used diagnostic

radiopharmaceuticals is [^{18}F]fludeoxyglucose (FDG)* in combination with PET for diagnosis, staging, restaging, and assessing therapy response in oncology. Other examples of diagnostic radiopharmaceuticals using SPECT are [$^{99\text{m}}\text{Tc}$]Tc-tetrofosmin for myocardial perfusion imaging to detect ischaemia and myocardial infarction, and [^{123}I]ioflupane, used in the diagnosis of Parkinson's disease^{5,8}.

Radiopharmaceuticals are also used in therapy; these typically contain a beta⁻ or alfa particle-emitting radioactive element. These therapeutic radiopharmaceuticals deploy their action by delivering a radiation dose to a specific target in the body in order to damage or eradicate abnormal tissue⁹. An example of a therapeutic radiopharmaceutical is [^{223}Ra]Ra-dichloride for the treatment of bone metastases in castrate-resistant prostate cancer¹⁰.

1.2 DRUG SAFETY

Drug safety is an important aspect of medical practice and has the public's full attention. A tragedy with the drug thalidomide in the early 1960s made everyone aware that taking drugs is not without possible negative consequences. Thalidomide was marketed in the late 1950s as an anti-emetic and used to treat morning sickness in pregnant women. It proved to be a potent teratogen, causing birth defects in thousands of children¹¹. This tragedy led to improvements in drug testing and requirements for safety evaluation. Regulators now conduct extensive safety evaluation on drugs—including radiopharmaceuticals. Drugs must show a favourable benefit-risk profile before manufacturers can market them. However, pre-marketing trials, in general, include a relatively small number of patients, have a limited follow-up time, and usually exclude specific groups of patients—such as, children, elderly, pregnant women or patients with specific underlying disorders, like renal-impairment—who might be at greater risk of adverse events. Often, information about a drug's safety becomes available from its use in larger or specific groups of patients after it is marketed. This phase of the lifecycle of a drug is often where uncommon adverse drug reactions, drug reactions with a long time to onset,

*The names of the radiopharmaceuticals in this thesis were standardised according to the Anatomical Therapeutic Chemical classification system and the International Consensus Radiochemistry Nomenclature Guidelines^{6,7}.

or issues related to the use of the drug—such as treatment failure, poor quality, interactions with other substances, and incorrect use of drugs—may arise. Information regarding use in a clinical setting, as provided by healthcare professionals and patients, is important to understanding more about the safety of a drug and will ultimately aid in improving the safety of a drug^{12, 13}.

In the past decades, radiopharmaceuticals have proven to be very safe^{14, 15}. Nevertheless, safety issues with radiopharmaceuticals may occur. However, radiopharmaceutical drug safety issues differ from other drugs because of some unique aspects of radiopharmaceuticals. One such aspect is that the tracer part in the formulation is usually administered in very low mass quantities, generally in the range of micrograms, and therefore does not have a pharmacological effect¹. For that reason, an adverse drug reaction due to a pharmacological action is unlikely to occur for most radiopharmaceuticals, in contrast to other drugs. However, idiosyncratic adverse reactions, that are not dose-related, may occur with radiopharmaceuticals or with excipients used in the formulation¹⁵. Furthermore, as the purpose, in general, is diagnostic imaging, an individual patient often encounters radiopharmaceuticals only once or a few times¹⁴. Accordingly, drug safety issues that might be seen with long-term use of other drugs are unlikely to occur with radiopharmaceuticals.

Another important aspect of drug safety of radiopharmaceuticals is the distribution in the body, also known as biodistribution. Both biodistribution and localisation of the tracer will determine imaging or therapy outcome. Interactions with other drugs may alter the biodistribution and might ultimately affect diagnostic or therapy outcomes^{16, 17}.

In addition to the aspect of biodistribution, certain groups of patients need additional attention to ensure optimal outcome and avoid safety issues. These patients need extra precautions, such as special preparations or a change in dose. For some groups of patients, such as children and pregnant or breastfeeding women, guidelines are available^{18, 19}.

Finally, radiation exposure to the patients may be a concern with the use of radiopharmaceuticals. Nevertheless, the exposure of patients to radiation from nuclear medicine procedures is not excessive, and the incremental risks are small and outweighed by the benefits, such as providing useful diagnostic information that

cannot be obtained using other methods and is important for determining a course of treatment²⁰.

Even though radiopharmaceuticals have an excellent safety record, information regarding use and possible adverse effects in a clinical setting as provided by healthcare professionals and patients is important to understand more about the safety of radiopharmaceuticals and will ultimately aid in further safety improvement. For this reason, we will address radiopharmaceuticals drug safety issues in this thesis, with the main topics being adverse reactions, interactions with drugs, and considerations in specific patient populations.

1.2.1 Adverse reactions

The World Health Organization (WHO) defines an adverse drug reaction as ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’. The term adverse drug reaction must be distinguished from the term adverse event. An adverse event is not necessarily related to the drug and is defined by the WHO as ‘any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment’^{21, 22}. Adverse drug reactions have a proven causal relationship with a drug, while adverse events do not and can be related to different causes. However, knowledge of adverse events is of interest in drug safety evaluation, as establishing a causal link with a particular drug at the moment the event occurs or is reported may not be possible.

Researchers often use causality methods to determine whether a relation between an adverse event and a drug is present. Important aspects in a causality method are time sequence, response pattern to the suspected pharmaceutical, and rechallenge. Using a causality method, investigators weight these aspects to attribute a category of causality, such as ‘not related’, ‘unlikely’, ‘possible’, ‘probable’, or ‘certain’. Often-used causality methods for radiopharmaceuticals are the Naranjo algorithm²³ and the method Silberstein described¹⁵.

In order to report, analyse, and compare adverse events in drug safety, healthcare professionals commonly use standardised terminology. This enables the researcher

to code the symptoms, as the patient recalls them, into standardised terms. These terms can be categorised into main groups and then used for data representation. An example of standardised terminology is the Medical Dictionary for Regulatory Activities (MedDRA[®]), which the European Union mandates for safety reporting²⁴.

1.2.2 Adverse reactions of radiopharmaceuticals

Researchers assume that adverse reactions with radiopharmaceuticals rarely occur. Studies report a frequency of adverse events of 0.11% in Europe and 0.021% in the United States^{14, 15, 25}, which is low compared to the 1% to 2% reported for ‘regular’ therapeutic drugs^{26, 27} and the 5% to 8% reported for drug reactions in hospitalized patients²⁸. This may be explained by the unique aspects of radiopharmaceuticals, such as the lack of pharmacological effect because of the very low mass quantities administered and the fact that radiopharmaceuticals are often used only once or a few times in an individual patient. However, some authors indicate that another important reason for this low frequency might be that these studies rely on voluntary identification and reporting, and that adverse events of radiopharmaceuticals are underreported^{29, 30}. Such underreporting of adverse events is well known for other drugs³¹. In addition, adverse events of radiopharmaceuticals may be left undetected because follow-up contact seldom occurs between the patient and the nuclear medicine department after the nuclear medicine examination is completed. Furthermore, in current studies, other aspects such as severity, latency time, and outcome are often not studied in detail^{29, 32–35}. There is a clear need to further study and understand the characteristics and frequency of adverse events of radiopharmaceuticals.

1.2.3 Involvement of patients

The view of the patient plays an important role in drug safety. Patients can report adverse events themselves in several countries and provide additional useful information^{36, 37}. Such information can complement the information healthcare professionals provide, as patients report adverse events and aspects that are different from those that healthcare professionals report. Patients provide more detailed

information about the adverse events and may provide important information about novel adverse reactions or new insights on known adverse reactions, as well as aid in identifying adverse reactions in specific populations. Finally, patients can also provide first-hand information about their expectations and experiences, such as the outcome of an adverse event and the impact on their quality of life^{38–41}.

Little research has been done on adverse reactions of radiopharmaceuticals from the patient's perspective. To our knowledge only one small study using one radiopharmaceutical was performed. In this study of 55 patients using [^{99m}Tc]Tc-medronic acid, one patient-reported headache, dizziness, and a dry mouth. However, the researchers did not provide detailed information about the method of recording and analysing the adverse events⁴². Research using patient-reported adverse events of radiopharmaceuticals may well aid in our understanding of the characteristics and true frequency of patients' adverse reactions to radiopharmaceuticals. In addition, patients may provide information about the outcome and the impact on their lives. Patients' perspectives could therefore help healthcare professionals to better inform patients and to be better prepared in detecting and managing radiopharmaceuticals adverse events.

1.2.4 Interactions of radiopharmaceuticals with drugs

Another drug safety aspect of radiopharmaceuticals concerns interaction with other substances that alter biodistribution, which could lead to unusual imaging and might ultimately affect diagnostic or therapeutic outcomes^{43–45}. Understanding these interactions is important, as they may affect a patient's diagnosis or therapy. In the case of interactions with a diagnostic radiopharmaceutical, an interaction might influence the scan—e.g., reduce the uptake in an area of interest or cause abnormal uptake in non-relevant areas—and in that way lead to wrong or incomplete information that could ultimately affect the patient's diagnosis. Amongst the factors associated with altered biodistribution of radiopharmaceuticals are the use of other drugs (including over-the-counter drugs), food, alternative medicines, issues with the preparation of the radiopharmaceutical, adsorption to administration devices, other medical procedures, or unexpected pathophysiology^{16, 43, 45–49}. Researchers

classify the effect of a substance on the biodistribution of radiopharmaceuticals as pharmacologic, pharmacokinetic, toxicologic, pharmaceutical, or unidentified interactions⁴³.

A pharmacologic interaction occurs when a substance directly or indirectly alters the radiopharmaceutical at its site of localisation. One example is interaction with the radiopharmaceutical [¹²³I]ioflupane. Healthcare professionals use this radiopharmaceutical in the diagnosis of Parkinson's disease and other related diseases. It is a cocaine analogue, binds to the presynaptic dopamine active transporter, and allows for the detection of the loss of nerve cells in a part of the brain called the striatum. Several drugs can interact with [¹²³I]ioflupane imaging, such as methylphenidate, which has shown to completely block the physiologic uptake in the striatum⁵⁰.

A pharmacokinetic interaction occurs when a drug alters the plasma concentration of the radiopharmaceutical by assorting an effect on the absorption, distribution, metabolism, or excretion of the drug. One example is the interaction of colchicine with [¹⁸F]fluorocholine, used in PET imaging for diagnosis of prostate cancer and detection of parathyroid adenoma amongst others. Choline is an important component of phospholipids in cell membranes, and its metabolism has an anabolic and catabolic pathway via phosphatidylcholine. In tumours, the anabolic pathway outweighs the catabolic pathway, giving it a higher uptake of [¹⁸F]fluorocholine. It is supposed that colchicine stimulates the catabolic pathway and leads to an impaired uptake of [¹⁸F]fluorocholine⁵¹.

A toxicologic interaction occurs when the dosing of a drug leads to an increased pharmacologic effect or an adverse effect and subsequently changes the biodistribution of the radiopharmaceutical. For example, one case describes a blood brain barrier damaged by methotrexate, resulting in an increased uptake of [^{99m}Tc]Tc-pertechnetate in the cerebral ventricles⁵².

A pharmaceutical interaction occurs when a physicochemical reaction between a drug and the radiopharmaceutical takes place. This interaction can, for example, take place when substances come into contact, precipitating the radiopharmaceutical. For example, the combination of intravenous iron with ^{99m}Tc-diphosphonates can lead to a high blood pool activity⁵³.

For some interactions, the mechanism is unknown. For example, it is known that in patients using metformin—an oral antidiabetic—a high colonic uptake of FDG is often seen. However, the mechanism is still unknown and although several studies have suggested that metformin should be discontinued before the FDG PET scan, the optimal discontinuation period is still unclear^{54–56}.

Nuclear medicine professionals must be aware of interactions that influence or alter the biodistribution of radiopharmaceuticals so they can take necessary precautions, such as informing the patient to stop a certain drug or food. In addition, when interactions do occur, nuclear medicine professionals will be able to explain uncommon findings, and in that way, improve the diagnostic outcome for patients¹⁶. Although many factors interacting with the biodistribution of radiopharmaceuticals are known, well-defined research is still scarce and recommendations for clinical use are mostly lacking. Research in this area may help in providing clear guidance.

1.2.5 Specific patient populations and radiopharmaceuticals

Certain groups of patients need additional attention in order to ensure an optimal outcome and avoid safety issues. Extra precautions, such as special preparations or a change in dose, are needed to ensure a safe use of radiopharmaceuticals in these patients. These patient groups include, for example, pregnant or breastfeeding women, children, elderly patients, and dialysis patients¹⁶. In the patient group of breastfeeding women excretion of radiopharmaceuticals or metabolites in breast milk could potentially expose a child to an undesirable radiation dose. A study in breastfeeding mothers showed that stopping breastfeeding was needed for [¹³¹I]sodium iodine; a temporary 12-hour interruption was needed for [¹²⁵I]iodohippurate, [¹³¹I]iodohippurate, [^{99m}Tc]Tc-pertechnetate, and [^{99m}Tc]Tc-macrosalb; and no interruption was needed for other radiopharmaceuticals¹⁸. In the group of children clinicians must adjust the dose of radiopharmaceuticals for children, as children may have a greater potential risk for developing late effects of radiation exposure. The dosage card used in Europe and the United States bases the dose not only on the weight of the child but also on the specific radiopharmaceutical¹⁹. Another example of a specific group of patients using

radiopharmaceuticals who are at risk for a rare complication are patients with advanced metastatic neuroendocrine tumours. A case report describes a carcinoid crisis after injection of [^{18}F]fluorodihydroxyphenylalanine (DOPA), which is the result of a massive release of neurotransmitters such as serotonin and characterized by flushing, changes in blood pressure, difficulty breathing, and rapid heart rate. Carcinoid crisis can potentially be life-threatening, and it is therefore advised to slowly inject the tracer, and have appropriate drugs available to treat this condition, such as somatostatin analogues and perhaps ketanserin⁵⁷.

For some other specific patient groups, little research has been done and guidelines are not available. For example, clear recommendations for patients with renal insufficiency are not yet available^{58,59}. For patients carrying an acute porphyria gene, which in the case of drug exposure could cause acute attacks with severe symptoms, no assessment of radiopharmaceuticals has been done. The need to investigate the safe use of radiopharmaceuticals in some specific groups of patients is clear.

1.3 OUTLINE OF THE THESIS

Despite the fact that radiopharmaceuticals have an excellent safety profile, relatively little is known about adverse reactions, interactions and use in some specific patient groups. For this reason, we studied drug safety issues in this thesis, with the main topics being adverse reactions, interactions with drugs, and considerations in specific patient populations. The overall purpose of this thesis is to better understand radiopharmaceuticals drug safety. The broader intent is to improve the safe use of radiopharmaceuticals and increase patients' and health care professionals' awareness.

While it is known that radiopharmaceuticals can cause adverse events, information is only available in case reports and databases and may not be readily available to healthcare professionals. In **Chapter 2**, we present a systematic review of the literature with an overview of the most common adverse events of diagnostic radiopharmaceuticals and their characteristics as described in literature, such as

frequency and seriousness, and the proposed mechanism leading to the adverse event. Patients can provide important information about adverse events and provide an important contribution to the detection and understanding of adverse events, as well as healthcare professionals' ability to manage them. In order to investigate possible adverse events of radiopharmaceuticals in patients, we needed a suitable instrument. Therefore, we describe the development, validation, and testing of a questionnaire to be used with patients and present the results in **Chapter 3**. Using this questionnaire, we conducted a prospective cohort study of 1,002 patients in a regional hospital in the Netherlands (Isala). In this study, we not only aimed to assess the characteristics and frequency of patient-reported adverse events of radiopharmaceuticals but also to assess the outcome and follow-up. We present the results of this study in **Chapter 4**. In addition to systematic research, the analysis of an individual case can also contribute to more knowledge about adverse reactions. In **Chapter 5** we describe an example of a patient who developed an anaphylactic reaction to [^{99m}Tc]Tc-macrosalb used for pulmonary scintigraphy. Besides adverse events, important safety issues with radiopharmaceuticals also include unusual imaging outcomes and considerations in specific patient populations. One known unusual imaging outcome is the increased colonic uptake in FDG PET scans with patients using metformin. We analyse in **Chapter 6** whether a metformin discontinuing period of 48 hours or more is sufficient to prevent FDG uptake in the colon. A specific patient population where drug safety is of importance are patients who carry acute porphyria genes. As drug exposure in these patients might lead to potentially fatal acute attacks, knowing whether healthcare professionals can safely use radiopharmaceuticals in these patients is important. In **Chapter 7**, we therefore present an assessment and classification of the porphyrogenicity of radiopharmaceuticals. Another patient population where extra precautions may be needed are patients with renal insufficiency. In these patients, healthcare professionals may need to adjust the dose for optimal outcome and prevention of adverse effects. In **Chapter 8**, we therefore present a systematic review aiming to provide dose recommendations of radiopharmaceuticals in patients with renal insufficiency. In **Chapter 9**, we summarise our findings and discuss future perspectives to further improve drug safety of radiopharmaceuticals.

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Chapter 2

Adverse events of diagnostic radiopharmaceuticals: a systematic review

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ABSTRACT

Diagnostic radiopharmaceuticals used in nuclear medicine can cause adverse events. Information on these adverse events is available in case reports and databases but may not be readily accessible to healthcare professionals. This systematic review provides an overview of adverse events of diagnostical radiopharmaceuticals and their characteristics. A median frequency for adverse events in diagnostical radiopharmaceuticals of 1.63 (interquartile range: 1.09-2.29) per 100,000 is reported. Most common are skin and subcutaneous tissue disorders, and general disorders and administration site conditions. Many adverse events reported are minor in severity, although 6.7% can be classified as important. In rare cases, adverse events are serious and potentially life-threatening. With the introduction of new radiopharmaceuticals and the increasing use of positron emission tomography-computed tomography (PET/CT), previously unknown adverse events may be detected in daily practice. Future work should cover the experience of the patient with adverse events from diagnostic radiopharmaceuticals.

2.1 INTRODUCTION

Radiopharmaceuticals are drugs containing a radioactive isotope used for diagnostic or therapeutic purposes^{1, 2}, with the radioactive isotopes emitting radiation that can be detected with imaging modalities, such as single-photon emission computed tomography (SPECT) or positron emission tomography (PET). Images and data allow for functional processes such as metabolism to be evaluated in the human body. Most diagnostic radiopharmaceuticals are used in very small quantities³—generally in the range of micrograms—and therefore do generally not have a pharmacological effect, although adverse reactions may still occur. These adverse reactions can often not be explained by the known actions of the radiopharmaceutical, and are mostly unpredictable. The World Health Organization defines an adverse drug reaction as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” and an adverse event as “any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment”^{4, 5}. “Adverse drug reaction” excludes events that do not have a proven relationship with a drug, although it may not be possible to establish a causal link at the moment the event occurs or is reported. Therefore, adverse events are still of interest in evaluating drug safety. For this reason, and for uniformity, the more general term “adverse event” is used here.

Assessment is needed to determine if a particular drug caused the adverse event, specifically looking at the probability of causality and including clinical judgment. Many systems have been developed to support this process; for radiopharmaceuticals, often-used causality methods are the Naranjo algorithm⁶ and the method described by Silberstein⁷.

Adverse events related to diagnostic radiopharmaceuticals are considered rare. Detailed information on these adverse events is available in case reports or dedicated databases, although this information might not be readily available to healthcare professionals when a patient experiences an adverse event. Information on these adverse events—including their severity, duration, and frequency—is needed for

healthcare professionals to understand risk and management for patients⁸. For this reason, a comprehensive overview of adverse events related to diagnostic radiopharmaceuticals is essential. Several reviews have been conducted, some providing a narrative summary of adverse reactions^{9–15} and others focusing on a specific topic or combination of topics with preparation errors or product defects¹⁶; one review, published as a letter to the editor, presents data on the prevalence of adverse events for radiopharmaceuticals¹⁷. Additionally, several information databases have been developed to provide information about adverse events related to radiopharmaceuticals, although two are currently inaccessible^{18–20}. However, to our knowledge, a systematic review to describe adverse events related to diagnostic radiopharmaceuticals has not yet been published.

This review aims to provide an overview of the most common adverse events and their characteristics (such as frequency, severity, and proposed mechanism), for diagnostic radiopharmaceuticals as reported in literature.

2.2 METHODS

This review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines²¹, and the review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under number 4201604831.

2.2.1 Search strategy

We performed a systematic search using the databases MEDLINE (PubMed) and Embase, applying no year limits and therefore extending as far back as the late 1940s. For each database, a University Medical Center Groningen staff member and one of the authors (N.S.) developed the search strategy. The search strategy for MEDLINE was: ('Radiopharmaceuticals' (MeSH) OR 'Radiopharmaceutical*' (tiab) OR 'Radioisotopes' (MeSH) OR 'Radioisotope*' (tiab)) combined (AND) with ('adverse effects' (subheading) OR 'adverse reactions' (tiab) OR 'adverse effects' (tiab) OR 'adverse events' (tiab) OR 'side effects' (tiab)). A filter for the

search was applied—NOT (Animals NOT Humans)—to exclude animal-only studies. The search strategy for Embase was: ('Radiopharmaceutical agent'/exp OR 'Radioisotope'/exp OR 'Radiopharmaceutical*':ab,ti OR 'Radioisotope*':ab,ti) combined (AND) with ('adverse reaction'/exp OR 'adverse effect*':ab,ti OR 'adverse reaction*':ab,ti OR 'adverse event*':ab,ti OR 'side effect*':ab,ti); a filter was applied to exclude articles available in MEDLINE, and a filter was applied—NOT (Animals NOT Humans)—to exclude animal-only studies. The articles selected were screened for relevant references, which were included in the selection process. The initial search was completed in September 2016 and updated with recent articles until July 10, 2018.

2.2.2 Study selection

The first author (N.S.) assessed all titles obtained. For potentially relevant articles, the full text was obtained and two reviewers (D.K. and N.S.) assessed them independently for relevance. In cases where the reviewers' opinions differed, a third researcher (E.v.P.) was consulted to reach consensus. Selected articles met the following criteria: described adverse events that are possibly or likely attributed to radiopharmaceuticals as the main outcome parameter; only dealt with diagnostic radiopharmaceuticals; related to radiopharmaceuticals used in humans.

2.2.3 Assessment of articles' methodological quality

Two reviewers (D.K. and N.S.) independently assessed the methodological quality of the included studies using the method described by Murad et al²². For each article, the reviewers scored eight items with leading explanatory questions; scores were added to create an aggregate score and ranked as "low," "moderate," or "good." In cases of differing opinion on a score, a third researcher (E.v.P.) was consulted to reach consensus.

2.2.4 Data collection

For studies meeting the selection criteria, data were extracted using a standardized approach. When available, data were extracted on: (1) study design; (2) name(s) of

radiopharmaceutical(s); (3) verbatim record of each adverse event and standardized term; (4) number of patients with an adverse event per radiopharmaceutical; (5) total number of patients being studied and/or the calculated frequency; (6) the confidence interval given for a calculated frequency; (7) the method of causality assessment used; and (8) corresponding probability of the causality assessment.

2.2.5 Synthesis of results

To compare the results, we handled the data in the following way:

The names of the radiopharmaceutical were standardized and categorized using the Anatomical Therapeutic Chemical (ATC) classification system²³. The ATC system divides active substances into several groups according to the organ or system on which the substance acts and its therapeutic, pharmacological, and chemical properties. Diagnostic radiopharmaceuticals are grouped into a specific group (V09) and subdivided into 10 subgroups depending on the site of action or organ system.

The adverse events were extracted from the articles exactly as written, with the Medical Dictionary for Regulatory Activities (MedDRA) terminology²⁴ used to code the verbatim record of the adverse event or, in cases for which the adverse events were not yet described, according to MedDRA-standardized terminology. MedDRA® is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The standardized terminology contains terms on five hierarchical levels. The highest level is the system organ class, of which there are 26; the lowest is the lowest level term, linked with a preferred term. Whereas lowest level terms may represent synonyms, preferred terms represent a unique medical concept and are therefore favored for data representation. Each preferred term is linked to a system organ class, making system organ class ideal for representing a large dataset with multiple preferred terms. Our study used preferred term and system organ class to present data. Adverse events with an unlikely causality as determined by the author of the particular study were excluded.

Adverse events were screened for important medical events (IMEs) using the IME list drafted by the EudraVigilance Expert Working Group²⁵. This list relates to the MedDRA terms and provides guidance on whether an adverse event could be considered important; serious adverse events are occurrences that result in death, are life-threatening, require hospitalization, result in disability, or are congenital defects, and IMEs are those that might jeopardize the patient or require intervention to prevent a serious adverse event²⁶. Two researchers (D.K. and N.S.) independently conducted extraction, coding, and screening for severity. When the syntheses of the results were not in agreement, a third researcher (E.v.P.) was consulted to resolve discrepancies.

2.3 RESULTS

2.3.1 Search results

The initial search found 18,464 titles, and the second search (until July 10, 2018) found 1,899 titles, for a total of 20,363 titles; another 24 articles were identified through references. Figure 2.1 outlines the selection process, and Table 2.1 provides an overview of the 101 articles meeting the inclusion criteria.

From the included articles, 46 are case reports, 23 prospective studies, 16 retrospective studies, and 16 summaries of case reports collected by registries maintained in a country or continent. Thirty-seven of the articles describe adverse events in a population using various diagnostic radiopharmaceuticals, and the other 64 articles are related to one specific radiopharmaceutical. In one article, the author planned to study the frequency of adverse events in radiopharmaceuticals but found none¹¹⁷; this study was included, as it relates to the frequency of adverse events in radiopharmaceuticals. Some articles mention adverse events related to the non-radioactive pharmaceuticals pyrophosphate and stannous agent, which are used in combination with radiopharmaceutical [^{99m}Tc]Tc-pertechnetate for blood pool scintigraphy; because of their clear use in a diagnostic procedure in nuclear medicine, these two agents were included in the results.

Fig. 2.1 Selection of studies according to the PRISMA statement²¹

Of the studies, 12 (12%) use a described method to determine causality: seven use the method described by Silberstein⁷, two use the algorithm described by Naranjo⁶, two use a method developed for radiopharmaceuticals proposed by Cordova¹²⁷, and one uses a method described by Bégau¹²⁸.

Table 2.1 Overview of included articles reporting adverse events as an outcome of use of diagnostic radiopharmaceuticals

First author (reference)	Year	Study design	Number of patients	Radiopharmaceutical	Number with AE	Causality method
Alderson ²⁷	1973	C	2	[¹¹¹ In]In-pentetic acid	2	ND
Atkins ²⁸	1972	PS	1,107,621*	Various	124	ND
Atkins ²⁹	1986	SC	NA	Various	21 [†]	ND
Aziz Jalali ³⁰	2004	C	1	[²⁰¹ Tl]Tl-chloride	1	ND
Bach-Gansmo ³¹	2016	PS	714	[¹⁸ F]fluciclovine	4	ND
Bagheri ³²	1996	PS	14,794	Various	3	B
Balan ³³	2003	C	1	[^{99m} Tc]Tc-medronic acid	1	ND
Banerji ³⁴	1972	RS	88	[¹³¹ I]I-human albumin	36	ND
Barnes ³⁵	1972	C	5	[¹³¹ I]I-human albumin	5	ND
Bliek ³⁶	1971	C	1	[¹³¹ I]I-human albumin	1	ND
Block ³⁷	1970	C	1	[^{99m} Tc]Tc-sulfur colloid	1	ND
Bohdiewicz ³⁸	1998	PS	1,041	[¹¹¹ In]In-satunomab pendetide	45	ND
Burton ³⁹	2003	C	1	[^{99m} Tc]Tc-nanocolloid	1	ND
Chicken ⁴⁰	2007	C	1	[^{99m} Tc]Tc-nanocolloid	1	ND
Child ⁴¹	1975	C	1	[^{99m} Tc]Tc-macrosalb	1	ND
Codreanu ⁴²	2013	C	1	[¹⁸ F]fludeoxyglucose	1	N
Collins ⁴³	1988	C	1	[^{99m} Tc]Tc-medronic acid	1	C
Commandeur ⁴⁴	1992	C	1	[⁶⁷ Ga]Ga-citrate	1	ND
Cotrina-Monroy ⁴⁵	2010	C	1	[^{99m} Tc]Tc-nanocolloid	1	ND
Deppen ⁴⁶	2016	PS	97	[⁶⁸ Ga]Ga-DOTA-TATE	3	ND
Detmer ⁴⁷	1965	C	1	[¹³¹ I]I-human albumin	1	ND
Doerr ⁴⁸	1991	PS	116	[¹¹¹ In]In-satunomab pendetide	7	ND
Dos Santos Almeida ⁴⁹	2013	PS	55	[^{99m} Tc]Tc-medronic acid	1	ND
Doukaki ⁵⁰	2010	C	1	[^{99m} Tc]Tc-sestamibi	1	ND
Dramov ⁵¹	1971	C	2	[¹³¹ I]I-human albumin	2	ND
Dworkin ⁵²	1966	C	1	[¹³¹ I]I-macrosalb	1	ND
EANM [†] , ⁵³	1994	SC	62	Various	52 [‡]	ND
EANM [†] , ⁵⁴	1995	SC	73	Various	73 [‡]	ND
EANM [†] , ⁵⁵	1996	SC	64	Various	54 [‡]	ND
ENMS [†] , ⁵⁶	1982	SC	51	Various	51	ND
ENMS [†] , ⁵⁷	1984	SC	24	Various	24	ND
ENMS [†] , ⁵⁸	1987	SC	62	Various	62 [‡]	ND
ENMS [†] , ⁵⁹	1987	SC	24	Various	24 [‡]	ND
FDA [†] , ⁶⁰	2005	SC	63	[^{99m} Tc]Tc-fanolesomab	63	ND
Ford ⁶¹	1978	SC	57	Various	57 [‡]	ND
Hart ⁶²	1989	C	1	[^{99m} Tc]Tc-oxidronic acid	1	ND
Hertel ⁶³	1990	PS	800	Various	1	ND
Hesse ⁶⁴	2011	C	1	[^{99m} Tc]Tc-sestamibi	1	ND
Hesslewood [†] , ⁶⁵	2002	SC	62	Various	38 [‡]	S
Hesslewood [†] , ⁶⁶	2003	SC	61	Various	35 [‡]	S
Hesslewood ⁶⁷	1997	PS	71,046	Various	8 [‡]	S
Hirosawa ⁶⁸	1991	PS	981	[¹²³ I]Iobenguane	4	ND
Hurman ⁶⁹	1982	C	1	[^{99m} Tc]Tc-pentetic acid	1	ND
Ishibashi ⁷⁰	2009	C	1	[¹³¹ I]Iobenguane	1	ND
James ⁷¹	1992	PS	115	Various	17	ND
Jayabalan ⁷²	1975	C	3	[¹¹¹ In]In-pentetic acid	3	ND
Johnston ⁷³	2015	PS	60	[^{99m} Tc]Tc-sulfur colloid	11	PA

Table 2.1 (Continued) Overview of included articles reporting adverse events as an outcome of use of diagnostic radiopharmaceuticals

First author (reference)	Year	Study design	Number of patients	Radiopharmaceutical	Number with AE	Causality method
Jonas ⁷⁴	1972	C	1	[¹³¹ I]I-human albumin	1	ND
JSNM ⁷⁵	2003	RS	1,390,843	Various	27	ND
JSNM ⁷⁶	2004	RS	1,395,928	Various	37	ND
JSNM ⁷⁷	2005	RS	1,357,419	Various	21	ND
Kennedy-Dixon ^{†, 78}	2017	SC	191	Various	176	S
Koopmans ⁷⁹	2005	C	1	[¹⁸ F]fluorodihydroxyphenylalanine (DOPA)	1	ND
Kusakabe ⁸⁰	2002	RS	1,401,962	Various	24	ND
Kusakabe ⁸¹	2006	RS	1,277,906	Various	16	ND
Kusakabe ⁸²	2007	RS	1,264,098	Various	19	ND
Kusakabe ⁸³	2008	RS	1,189,127	Various	32	ND
Lai ⁸⁴	2016	PS	85	[^{99m} Tc]Tc-tilmanocept	6	ND
Laroche ^{†, 85}	2015	SC	6,434,988 [¶]	Various	256	ND
Lee ⁸⁶	2013	C	1	[¹⁸ F]fludeoxyglucose	1	N
Line ⁸⁷	2004	PS	30	[^{99m} Tc]Tc-fanolesomab	12	ND
Littenberg ⁸⁸	1975	C	1	[^{99m} Tc]Tc-microspheres	1	ND
Makaryus ⁸⁹	2008	C	1	[^{99m} Tc]Tc-sestamibi	1	ND
Maltby ⁹⁰	2002	C	1	[¹³¹ I]iodomethyl norcholesterol	1	ND
Manoharan ⁹¹	2017	PS	20	[⁶⁸ Ga]Ga-edotreotide (DOTA-TOC)	4	ND
Matsuda ⁹²	2009	RS	1,192,072	Various	11	ND
Matsuda ⁹³	2012	RS	1,046,243	Various	22	ND
Matsuda ⁹⁴	2013	RS	1,068,833	Various	14	ND
Matsuda ⁹⁵	2014	RS	1,060,526	Various	11	ND
Matsuda ⁹⁶	2015	RS	1,056,876	Various	8	ND
Matsuda ⁹⁷	2017	RS	1,056,828	Various	15	ND
Matsuda ⁹⁸	2018	RS	1,052,650	Various	9	ND
Mooser ⁹⁹	1998	C	1	[^{99m} Tc]Tc-medronic acid	1	ND
Mujtaba ¹⁰⁰	2007	C	1	[^{99m} Tc]Tc-sestamibi	1	ND
Nicol ¹⁰¹	1967	C	1	[¹³¹ I]I-human albumin	1	ND
Núñez ¹⁰²	2007	C	1	[¹³¹ I]sodium iodine diagnostic	1	ND
O'Dorisio ¹⁰³	2018	PS	26	[⁶⁸ Ga]Ga-edotreotide (DOTA-TOC)	9	ND
Oldham ¹⁰⁴	1970	C	2	[¹³¹ I]I-human albumin	2	ND
Oosterhuis ¹⁰⁵	1971	PS	83	[¹³¹ I]I-human albumin	3	ND
Peller ¹⁰⁶	1994	C	1	[^{99m} Tc]Tc-mertiatide	1	ND
Pravettoni ¹⁰⁷	2009	C	1	[^{99m} Tc]Tc-sestamibi	1	ND
Ramos-Gabatin ¹⁰⁸	1986	C	1	[^{99m} Tc]Tc-medronic acid	1	ND
Rhodes ¹⁰⁹	1971	C	1	[^{99m} Tc]Tc-microspheres	1	ND
Rhodes ¹¹⁰	1974	PS	30	[¹¹¹ In]In-pentetic acid	6	ND
Rhodes ¹¹¹	1976	C	66	[¹¹¹ In]In-pentetic acid	66	ND
Rhodes ^{†, 112}	1980	SC	8,000,000 [#]	Various	47 [‡]	ND
Roberts ¹¹³	1970	C	1	[¹³¹ I]I-macrosalb	1	ND
Schafer ^{†, 114}	2016	PS	52	[⁶⁸ Ga]Ga-edotreotide (DOTA-TOC)	NA	ND
Schaub ¹¹⁵	1983	C	1	[^{99m} Tc]Tc-sulfur colloid	1	ND
Silberstein ¹¹⁶	2014	PS	1,024,177	Various	21 [‡]	S

Table 2.1 (Continued) Overview of included articles reporting adverse events as an outcome of use of diagnostic radiopharmaceuticals

First author (reference)	Year	Study design	Number of patients	Radiopharmaceutical	Number with AE	Causality method
Silberstein ¹¹⁷	1998	PS	81,801	Various	0	S
Silberstein ⁷	1996	PS	783,525	Various	18 [‡]	S
Smith ^{†, 118}	1967	RS	4,775	[^{99m} Tc]Tc-sulfur colloid	15	ND
Sørensen ¹¹⁹	2013	PS	6	[¹⁸ F]fluciclovine	1	ND
Spicer ¹²⁰	1985	C	1	[^{99m} Tc]Tc-medronic acid	1	CO
Spyridonidis ¹²¹	2008	C	2	[¹³¹ I]iodomethyl norcholesterol	2	ND
Stöckel ¹²²	1983	C	1	[¹³¹ I]iodohippurate	1	ND
Thomson ¹²³	2001	C	1	[^{99m} Tc]Tc-sestamibi	1	ND
Vincent ¹²⁴	1968	C	1	[^{99m} Tc]Tc-macrosalb	1	ND
Williams ¹²⁵	1974	SC	77	Various	77	ND
Williams ¹²⁶	1974	C	1	[^{99m} Tc]Tc-macrosalb	1	ND

[†] Number of patients are totals over three years while number of cases is over four years. [‡] Number of events could not exactly be matched with number of patients. ^{*} Number of patients with AEs also include radiopharmaceuticals with therapeutic use. [¶] Number of patients are totals over eight years while number of cases is over 25 years. [#] Estimation.

Abbreviations: AE, Adverse Event; B, Bégaud; C, Case report; CO, Cordova; N, Naranjo; ND, Not defined; PA, pain scale; PS, Prospective Study; RS, Retrospective Study; S, Silberstein; SC, Summaries of Case reports collected by registers maintained in a country or continent.

2.3.2 Assessed methodological quality of included studies

In terms of methodological quality, 23.0% ($n = 23$) were rated as good, 62.0% ($n = 62$) as moderate, and 15.0% ($n = 15$) as low; this excludes one article that could not be assessed in terms of quality because no adverse events were reported¹¹⁷. Table 2.2 provides a detailed overview of the assessment.

Table 2.2 Methodological quality assessment of studies included

First author (reference)	Q1*	Q2*	Q3*	Q4*	Q5*	Q6*	Q7*	Q8*	Assessment [†]
Alderson ²⁷	yes	yes	yes	yes	no	no	yes	yes	good
Atkins ²⁸	no	yes	no	no	no	no	yes	no	low
Atkins ²⁹	no	yes	yes	no	no	no	yes	no	low
Aziz Jalali ³⁰	no	yes	yes	yes	no	no	yes	yes	moderate
Bach-Gansmo ³¹	yes	yes	yes	no	no	no	yes	no	moderate
Bagheri ³²	yes	yes	yes	no	no	no	yes	no	moderate
Balan ³³	yes	yes	yes	yes	no	no	yes	yes	good
Banerji ³⁴	yes	yes	yes	no	no	no	yes	no	moderate
Barnes ³⁵	yes	yes	yes	yes	no	no	yes	no	moderate
Blik ³⁶	no	yes	yes	yes	no	no	yes	yes	moderate
Block ³⁷	yes	yes	yes	yes	no	no	yes	yes	good
Bohdiewicz ³⁸	yes	yes	yes	no	no	no	yes	no	moderate
Burton ³⁹	yes	yes	yes	yes	no	no	yes	no	moderate
Chicken ⁴⁰	no	yes	yes	yes	no	no	yes	yes	moderate

Table 2.2 (Continued) Methodological quality assessment of studies included

First author (reference)	Q1*	Q2*	Q3*	Q4*	Q5*	Q6*	Q7*	Q8*	Assessment†
Child ⁴¹	no	yes	yes	yes	yes	no	yes	yes	good
Codreanu ⁴²	no	yes	yes	yes	no	no	yes	yes	moderate
Collins ⁴³	no	yes	yes	yes	no	no	yes	no	moderate
Commandeur ⁴⁴	yes	yes	yes	yes	yes	no	yes	no	good
Cotrina-Monroy ⁴⁵	no	yes	yes	yes	no	no	yes	yes	moderate
Deppen ⁴⁶	yes	yes	yes	no	no	no	yes	yes	moderate
Detmer ⁴⁷	yes	yes	yes	no	no	no	yes	no	moderate
Doerr ⁴⁸	yes	yes	yes	no	no	no	yes	yes	moderate
Dos Santos Almeida ⁴⁹	yes	yes	yes	no	no	no	yes	no	moderate
Doukaki ⁵⁰	no	yes	yes	yes	no	no	yes	no	moderate
Dramov ⁵¹	no	yes	yes	no	no	no	yes	yes	moderate
Dworkin ⁵²	yes	yes	yes	yes	no	no	yes	yes	good
EANM ⁵³	no	yes	yes	no	no	no	yes	no	low
EANM ⁵⁴	no	yes	yes	no	no	no	yes	no	low
EANM ⁵⁵	no	yes	yes	no	no	no	yes	no	low
ENMS ⁵⁶	no	yes	yes	no	no	no	yes	no	low
ENMS ⁵⁷	no	yes	yes	no	no	no	yes	no	low
ENMS ⁵⁸	no	yes	yes	no	no	no	yes	no	low
ENMS ⁵⁹	no	yes	yes	no	no	no	yes	no	low
FDA ⁶⁰	yes	yes	yes	yes	no	no	yes	no	moderate
Ford ⁶¹	yes	yes	yes	no	no	no	yes	no	moderate
Hart ⁶²	no	yes	yes	yes	no	no	yes	no	moderate
Hertel ⁶³	yes	yes	yes	no	no	no	yes	yes	moderate
Hesse ⁶⁴	no	yes	yes	yes	no	no	yes	yes	moderate
Hesslewood ⁶⁵	no	yes	yes	no	no	no	yes	no	low
Hesslewood ⁶⁶	no	yes	yes	no	no	no	yes	no	low
Hesslewood ⁶⁷	yes	yes	yes	yes	no	no	yes	no	moderate
Hirosawa ⁶⁸	yes	yes	yes	no	no	no	yes	no	moderate
Hurman ⁶⁹	no	yes	yes	no	no	no	yes	yes	moderate
Ishibashi ⁷⁰	no	yes	yes	yes	no	no	yes	yes	moderate
James ⁷¹	yes	yes	yes	yes	no	no	yes	yes	good
Jayabalan ⁷²	yes	yes	yes	yes	no	no	yes	yes	good
Johnston ⁷³	yes	yes	yes	yes	no	no	yes	yes	good
Jonas ⁷⁴	no	yes	yes	yes	no	no	yes	yes	moderate
JSNM ⁷⁵	yes	yes	yes	no	no	no	yes	no	moderate
JSNM ⁷⁶	yes	yes	yes	no	no	no	yes	no	moderate
JSNM ⁷⁷	yes	yes	yes	no	no	no	yes	no	moderate
Kennedy-Dixon ⁷⁸	yes	yes	yes	yes	no	no	yes	no	moderate
Koopmans ⁷⁹	no	yes	yes	yes	no	no	yes	yes	moderate
Kusakabe ⁸⁰	yes	yes	yes	no	no	no	yes	no	moderate
Kusakabe ⁸¹	yes	yes	yes	no	no	no	yes	no	moderate
Kusakabe ⁸²	yes	yes	yes	no	no	no	yes	no	moderate
Kusakabe ⁸³	yes	yes	yes	no	no	no	yes	no	moderate
Lai ⁸⁴	yes	yes	yes	yes	no	no	yes	no	moderate
Laroche ⁸⁵	yes	yes	yes	no	no	no	yes	no	moderate
Lee ⁸⁶	yes	yes	yes	yes	no	no	yes	yes	good
Line ⁸⁷	yes	yes	yes	no	yes	no	yes	yes	good
Littenberg ⁸⁸	yes	yes	yes	yes	no	no	yes	yes	good
Makaryus ⁸⁹	yes	yes	yes	yes	no	no	yes	yes	good
Maltby ⁹⁰	no	yes	yes	yes	no	no	yes	yes	moderate
Manoharan ⁹¹	yes	yes	yes	yes	no	no	yes	yes	good
Matsuda ⁹²	yes	yes	yes	no	no	no	yes	no	moderate

Table 2.2 (Continued) Methodological quality assessment of studies included

First author (reference)	Q1*	Q2*	Q3*	Q4*	Q5*	Q6*	Q7*	Q8*	Assessment†
Matsuda ⁹³	yes	yes	yes	no	no	no	yes	no	moderate
Matsuda ⁹⁴	yes	yes	yes	no	no	no	yes	no	moderate
Matsuda ⁹⁵	yes	yes	yes	no	no	no	yes	no	moderate
Matsuda ⁹⁶	yes	yes	yes	no	no	no	yes	no	moderate
Matsuda ⁹⁷	yes	yes	yes	no	no	no	yes	no	moderate
Matsuda ⁹⁸	yes	yes	yes	no	no	no	yes	no	moderate
Mooser ⁹⁹	no	yes	yes	yes	yes	yes	yes	yes	good
Mujtaba ¹⁰⁰	yes	yes	yes	yes	no	no	yes	yes	good
Nicol ¹⁰¹	yes	yes	yes	yes	no	no	yes	no	moderate
Núñez ¹⁰²	no	yes	yes	yes	yes	yes	yes	yes	good
O'Dorisio ¹⁰³	yes	yes	yes	no	no	no	yes	yes	moderate
Oldham ¹⁰⁴	yes	yes	yes	yes	yes	no	yes	no	good
Oosterhuis ¹⁰⁵	yes	yes	yes	no	no	no	yes	yes	moderate
Peller ¹⁰⁶	no	yes	yes	no	no	no	yes	yes	moderate
Pravettoni ¹⁰⁷	no	yes	yes	yes	no	no	yes	no	moderate
Ramos-Gabatin ¹⁰⁸	yes	yes	yes	yes	yes	no	yes	yes	good
Rhodes ¹⁰⁹	yes	yes	yes	no	no	no	yes	no	moderate
Rhodes ¹¹⁰	yes	yes	yes	yes	no	no	yes	yes	good
Rhodes ¹¹¹	no	yes	yes	no	no	no	yes	no	low
Rhodes ¹¹²	yes	yes	yes	no	no	no	yes	no	moderate
Roberts ¹¹³	no	yes	yes	yes	no	no	yes	yes	moderate
Schafer ¹¹⁴	yes	yes	yes	no	no	no	yes	no	moderate
Schaub ¹¹⁵	no	yes	yes	no	no	no	yes	no	low
Silberstein ¹¹⁶	yes	yes	yes	yes	no	no	yes	no	moderate
Silberstein ¹¹⁷	No cases were found								
Silberstein ⁷	yes	yes	yes	yes	no	no	yes	no	moderate
Smith ¹¹⁸	yes	yes	yes	no	no	no	yes	no	moderate
Sörensen ¹¹⁹	yes	yes	yes	yes	no	no	yes	yes	good
Spicer ¹²⁰	yes	yes	yes	yes	yes	no	yes	no	good
Spyridonidis ¹²¹	yes	yes	yes	yes	no	no	yes	no	moderate
Stöckel ¹²²	no	yes	yes	yes	no	no	yes	yes	moderate
Thomson ¹²³	no	yes	yes	no	no	no	yes	no	low
Vincent ¹²⁴	no	yes	yes	no	no	no	yes	yes	moderate
Williams ¹²⁵	yes	yes	yes	yes	no	no	yes	yes	good
Williams ¹²⁶	no	yes	yes	no	no	no	yes	no	low
Total score:									good 23 (23%) moderate 62 (62%) low 15 (15%)

* Questions: Q1: Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?, Q2: Was the exposure adequately ascertained?, Q3: Was the outcome adequately ascertained?, Q4: Were other alternative causes that may explain the observation ruled out?, Q5: Was there a challenge/rechallenge phenomenon?, Q6: Was there a doseresponse effect? Q7: Was follow-up long enough for outcomes to occur?, Q8: Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice? †Score: ≤ 3 = low, $> 3 - < 6$ = moderate, ≥ 6 = good

2.3.3 Frequency

Twenty-two studies present the frequency of adverse events for various radiopharmaceuticals in a population. Table 2.3 provides the frequency as reported or estimated by the authors and the method of reporting for each study. A median frequency of 1.63 adverse events per 100,000 administrations (0.0016%) was calculated. In 16 controlled studies, the frequency of adverse events was determined for specific radiopharmaceuticals; the frequency ranged from 0.125% to 40.9% and is discussed in the next subchapter ('Summary of findings').

2.3.4 Summary of findings

In total, 2,447 adverse events were reported in 1,804 patients. We found that 84.4% of the reported adverse events with diagnostic radiopharmaceuticals were related to six system organ classes (Table 2.4), the most common being 'skin and subcutaneous tissue disorders' (26.6%) and 'general disorders and administration site conditions' (24.4%). Other adverse events were related to 'gastrointestinal disorders' (9.8%), 'nervous system disorders' (8.5%), 'investigations (results of tests)' (7.9%), and 'immune system disorders' (7.2%). For 'skin and subcutaneous tissue disorders', the most frequently reported adverse events were rash (248), pruritus (150), erythema (61), urticaria (67), and hyperhidrosis (28).

For 'general disorders and administration site conditions', the adverse events most reported were fever (104), unspecified adverse events (43), and discomfort (35); for 'gastrointestinal disorders', nausea (104) and vomiting (96); and for 'nervous system disorders', dizziness (44), headache (38) and presyncope (32). For 'investigations', the most reported adverse events were related to a change in blood pressure (45), and hypersensitivity (161) was most reported for 'immune system disorders'.

Table 2.3 Study Characteristics relevant for Assessment of frequency of reported AEs

Reference	Year	Country	Duration of study (yr)	number	Reported number with AEs	Frequency per 100,000 administrations	Method of data collection
Atkins	1972	USA	3	1,107,621	111	10.02	Surveys were sent out to institutions to look retrospectively at their data
Bagheri	1996	France	1.5	14,794	3	20.28	Each week a report was sent in by the nuclear medicine department. The pediatric department provided information about AEs in their patients related to radiopharmaceuticals on a weekly basis.
Hesslewood	1997	Europe (8 countries)	1	71,046	8	11.26	Each month a report was sent in by participating institutions. AEs were assessed for causality using Silberstein
JSNM	2003	Japan	1	1,390,843	27	1.94	Based on responses to questionnaires sent to institutions.
JSNM	2004	Japan	1	1,395,928	37	2.65	Based on responses to questionnaires sent to institutions.
JSNM	2005	Japan	1	1,357,419	21	1.55	Based on responses to questionnaires sent to institutions.
Kusakabe	2002	Japan	1	1,401,962	24	1.71	Based on responses to questionnaires sent to institutions.
Kusakabe	2006	Japan	1	1,277,906	16	1.25	Based on responses to questionnaires sent to institutions.
Kusakabe	2007	Japan	1	1,264,098	19	1.50	Based on responses to questionnaires sent to institutions.
Kusakabe	2008	Japan	1	1,189,127	32	2.69	Based on responses to questionnaires sent to institutions.
Laroche	2015	France	8	6,434,988	147	2.28	Search in database of spontaneous reporting. Data of number of diagnoses with SPECT or PET were retrieved from a French health data base.
Matsuda	2009	Japan	1	1,192,072	11	0.92	Based on responses to questionnaires sent to institutions.
Matsuda	2012	Japan	1	1,046,243	22	2.10	Based on responses to questionnaires sent to institutions.

Table 2.3 (Continued) Study Characteristics relevant for Assessment of frequency of reported AEs

Reference	Year	Country	Duration of study (yr)	number	Reported number with AEs	Frequency per 100,000 administrations	Method of data collection
Matsuda	2013	Japan	1	1,068,833	14	1.31	Based on responses to questionnaires sent to institutions.
Matsuda	2014	Japan	1	1,060,526	11	1.04	Based on responses to questionnaires sent to institutions.
Matsuda	2015	Japan	1	1,056,876	8	0.76	Based on responses to questionnaires sent to institutions.
Matsuda	2017	Japan	1	1,056,828	15	1.42	Based on responses to questionnaires sent to institutions.
Matsuda	2018	Japan	1	1,052,650	9	0.85	Based on responses to questionnaires sent to institutions.
Rhodes	1980	USA	1	8,000,000*	47	0.59	Based on forms sent to institutions approximately 3 times a year. Number of administrations is an estimation.
Silberstein	1996	USA	5	783,525	18	2.3	Participants sent in a monthly questionnaire. All AEs were assessed for causality.
Silberstein	1998	USA	4	81,801	0	0	Participation institutions looked retrospectively at their data and provided prospective monthly data. Only PET radiopharmaceuticals were included.
Silberstein	2014	USA	5	1,024,177	21	2.05	Participants sent a quarterly report. All AEs were assessed for causality.
Median and interquartile range (25th–75th percentile)						1.63 (1.09–2.29)	

* Estimation

Table 2.4 Number of reported AEs per SOC for each ATC group of radiopharmaceuticals

	Skin and subcutaneous tissue disorders	General disorders and administration site conditions	Gastrointestinal disorders	Nervous system disorders	Investigations	Immune system disorders	Respiratory, thoracic and mediastinal disorders	Vascular disorders	Cardiac disorders	Musculoskeletal and connective tissue disorders	Psychiatric disorders	Eye disorders	Infections and infestations	Injury, poisoning and procedural complications	Renal and urinary disorders	Blood and lymphatic system disorders	Reproductive system and breast disorders	Hepatobiliary disorders	Endocrine disorders	Psychiatric disorders	Ocular infections, irritations and inflammations	Metabolism and nutrition disorders	Ear and labyrinth disorders	SubTotal
V09A Central nervous system	22	88	10	19	29		3	2	2	8	4	1	6				1							195 (21)
V09B Skeleton	111	90	59	33	16		11	12	4	5	5	5	1		2			1						371 (14)
V09C Renal system	47	34	37	38	8	15	7	9	4	2	5	5		1	1		1					1		215 (5)
V09D Hepatic & reticulo endothelial system	26	90	9	9	6	59	7	6	6		1			10	1									230 (7)
V09E Respiratory system	22	33	5	18	32	31	24	3	13		4				2	1								188 (25)
V09F Thyroid	10	8	4	8	4	9	1	9	1		1		1											56 (2)
V09G Cardiovascular system	70	36	26	32	14	10	10	8	1	1	2	4			1	3				1				219 (13)
V09H Inflammation and infection detection	49	19	9	9	11	3	8	5	6	2	2		3	2				1						129 (10)
V09I Tumour detection	75	53	23	17	9	5	2	8	4	3	3			1		1			1	1				206 (17)
V09X Other diagnostic radiopharmaceuticals	21	146	29	26	65	27	16	20	10	26	10	3	5	2	1								1	408 (51)
Radiopharmaceutical not specified	199	1	30																					230
Subtotal	652 (18)	598 (12)	241	209 (24)	194 (55)	175 (14)	89 (13)	82 (2)	51 (12)	47	37	18	16 (10)	16	8 (3)	5	2	2	1	1	1	1	1	2447 (165)
Percentage of total (%)	26.6	24.4	9.8	8.5	7.9	7.2	3.6	3.4	2.1	1.9	1.5	0.7	0.7	0.7	0.3	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0

Numbers in parentheses represent the number of important medical events

From the reported adverse events, 165 (6.7%) were considered to be an IME. Nine deaths were reported, five occurring with the use of [^{131}I]I-macrosalb or [$^{99\text{m}}\text{Tc}$]Tc-macrosalb for pulmonary scintigraphy in cases of severe reduction in pulmonary capacity^{41, 52, 113, 124, 126}; although these deaths were related to the use of these radiopharmaceuticals, pulmonary vascular pathology was identified as an additional risk factor. Two deaths occurred with the radiopharmaceutical [$^{99\text{m}}\text{Tc}$]Tc-fanolesomab⁶⁰, which was withdrawn from the market, and were attributed to cardiopulmonary failure in diabetic patients; 15 other patients experienced serious events within minutes after injection of the [$^{99\text{m}}\text{Tc}$]Tc-fanolesomab. Two deaths occurred with [^{18}F]fludeoxyglucose⁸⁵; one patient suffered from a convulsive seizure and cardiorespiratory distress, and the other patient suffered from septic shock 24 hours after injection (October 19, 2018 e-mail from Prof. Laroche to N.S.; unreferenced).

A detailed overview of adverse events using standardized terminology for all radiopharmaceuticals and references to the articles can be found in Table 2.5. The following section presents a summary of findings for each commonly used radiopharmaceutical per ATC group. Data presented in this summary are: number of adverse events, characteristics of most reported adverse events, frequency when reported, number of IMEs and their main characteristics, and noteworthy adverse events.

Central nervous system (ATC group V09A)

[^{123}I]ioflupane

For [^{123}I]ioflupane, we found 17 adverse events in seven patients. The most reported were erythema, injection site pain, pruritus, and rash. No IMEs were reported.

[^{111}In]Indium pentetic acid

For [^{111}In]In-pentetic acid (pentetate), we found 133 adverse events in 81 patients. In addition to 67 adverse events not further specified, the most reported adverse events were abnormal cerebrospinal fluid values, fever, and meningitis. From the adverse events reported, 21 were classified as IMEs in five patients, all suffering

from meningitis after the use of [^{111}In]In-pentetic acid (pentetate). Some symptoms in these patients included fever, vomiting, chills, nuchal rigidity, Kernig's sign, Brudzinski's sign, generalized tonic-clonic seizures, and abnormal cerebrospinal fluid values.

[^{111}In]In-pentetic acid is a diagnostic radiopharmaceutical used for cisternography and injected intrathecally, bypassing the blood-brain barrier. A 1974 study investigating patients' febrile response after [^{111}In]In-pentetic acid injection found that 10% of patients had a temperature increase greater than 1°F within eight hours of injection. It is now commonly accepted that pyrogens are involved in the pathogenesis¹¹⁰. Cases of meningitis with [^{111}In]In-pentetic acid were reported between 1973 and 1982^{27, 56, 61, 111}, with no new reports on adverse events after 1982.

[$^{99\text{m}}\text{Tc}$]Technetium exametazime

For [$^{99\text{m}}\text{Tc}$]Tc-exametazime, we found 13 adverse events in seven patients. The most reported adverse event was erythema. No IMEs were reported.

Skeleton (ATC group V09B)

[$^{99\text{m}}\text{Tc}$]Technetium medronic acid

For [$^{99\text{m}}\text{Tc}$]Tc-medronic acid (medronate), we found 104 adverse events in 82 patients. The most reported adverse events were hypersensitivity, nausea, and rash. One study with 55 patients receiving [$^{99\text{m}}\text{Tc}$]Tc-medronic acid found one patient reported an adverse event, for a frequency of adverse events of 1.8%⁴⁹. Three IMEs were reported; one patient had an anaphylactic reaction described by the author as mild⁷, another developed erythema multiforme 48 hours after use¹²⁰, and one involved respiratory distress⁸⁰.

[$^{99\text{m}}\text{Tc}$]Technetium oxidronic acid

For [$^{99\text{m}}\text{Tc}$]Tc-oxidronic acid (oxidronate), we found 200 adverse events in 61 patients. The most reported adverse events were rash, edema, and pruritus. Nine IMEs were reported; one patient suffered from respiratory arrest and lost consciousness two minutes after injection⁷⁶, one lost consciousness one minute after

injection⁷⁶, one suffered from severe respiratory failure⁹⁴, one suffered one minute after injection from convulsions and lost consciousness⁹⁶, one experienced angioedema⁸⁵, and one had an anaphylactic shock and lost consciousness⁹⁷.

Renal system (ATC group V09C)

[^{99m}Tc]Technetium mertiatide

For [^{99m}Tc]Tc-mertiatide, we found 38 adverse events in 23 patients. The most reported adverse events were nausea, dizziness, and rash. No IMEs were reported.

[^{99m}Tc]Technetium pentetic acid

For [^{99m}Tc]Tc-pentetic acid (pentetate), we found 75 adverse events in 50 patients. The most reported adverse events were presyncope, nausea, rash, and vomiting. Three IMEs were reported. One case described paralysis after intrathecal administration; [^{99m}Tc]Tc-pentetic acid is not registered for use intrathecally, and the Committee on Radiopharmaceuticals of the European Association of Nuclear Medicine issued a warning after this case that manufacturers do not specify intrathecal use¹²⁹. Another patient experienced respiratory distress one hour after injection⁶⁹, and one case of seizure was reported¹¹².

[^{99m}Tc]Technetium succimer

For [^{99m}Tc]Tc-succimer, we found 35 adverse events in 32 patients. The most reported adverse events were rash, headache, and nausea. No IMEs were reported.

Hepatic and reticuloendothelial system (ATC group V09D)

[⁷⁵Se]Selenium tauroselcholic acid

For [⁷⁵Se]tauroselcholic acid (SehCAT), we found 18 adverse events in five patients. The most reported adverse events were hypersensitivity, pruritus, and rash. No IMEs were reported.

[^{99m}Tc]Technetium nanocolloid

For [^{99m}Tc]Tc-nanocolloid, we found 12 adverse events in eight patients. The most reported adverse event was urticaria. No IMEs were reported.

[^{99m}Tc]Technetium sulfur colloid

For [^{99m}Tc]Tc-sulfur colloid, we found 135 adverse events in 110 patients. Besides unspecified adverse events, the most reported adverse events were fever, hypersensitivity, and injection site pain. A study investigating different methods of preparation of [^{99m}Tc]Tc-sulfur colloid found a frequency of adverse events of 0.1% to 0.9%¹¹⁸. A study into pain level during [^{99m}Tc]Tc-sulfur colloid use found that 11 (18.3%) of the 60 patients experienced significant pain⁷³. The product's preparation method might cause the injection site pain and is most likely related to the stabilizers used, especially Dextran and Gelatin¹¹⁸. Low pH may be another reason, with Johnston showing that bringing the pH of the [^{99m}Tc]Tc-sulfur colloid solution to the physiological level could reduce pain levels during injection⁷³; Canning used anesthetic cream before injection but was unable to demonstrate a reduction in pain¹³⁰.

Six IMEs were reported. One patient suffered from an adverse reaction of the anaphylactoid type to [^{99m}Tc]Tc-sulfur colloid stabilized with gelatin, diagnosed the next day with acute renal failure; the authors indicated the cause of the acute renal failure is unknown, though the time sequence suggests renal ischemia with resultant acute tubular necrosis³⁷. One case of loss of consciousness was reported¹¹², and one patient experienced an anaphylactic reaction with loss of consciousness¹¹⁵.

Respiratory system (ATC group V09E)[^{99m}Tc]Technetium macrosalb

For [^{99m}Tc]Tc-macrosalb, we found 84 adverse events in 59 patients. In addition to some unspecified adverse events, the most reported adverse events were hypersensitivity, dyspnea, dizziness, and rash. Fourteen IMEs were reported in eight patients: one case of angioedema⁶⁶, two cases of cardiac arrest^{53, 112}, one case in which a patient became unresponsive with bradycardia⁶⁵, one case of respiratory

arrest⁵⁵, and three deaths. The three deaths included two patients who presented with a history of pulmonary hypertension^{41, 126} and one suffering from an advanced pulmonary vascular disease¹²⁴, all three of whom experienced a similar sequence of events (respiratory distress, cyanosis, and hypotension). Similar events are also reported in animal studies when giving a toxic dose of macrosalb particles¹³¹, and the reported events were likely caused by the size and number of particles.

In a person with a normal pulmonary vascular bed, a usual macrosalb dose of 0.1 mg to 4.0 mg with particle sizes of 10 μm to 50 μm will occlude only 0.1% of the cross-section area of the pulmonary vascular bed^{41, 52}. However, when a patient is suffering from a disease in which the number of lung capillaries is seriously decreased, blocking a part of the remainder of the capillary bed could lead to respiratory distress. Additionally, particle size is important to consider, as larger particles are likely to occlude larger vessels, and pulmonary vascular diseases such as pulmonary hypertension or other diffuse lung diseases require particular caution. When a pulmonary perfusion scan is needed in patients with pulmonary vascular disease, the number of particles in the dose to be administered should be calculated, quality control for the size of the particles can be performed with light microscopy, and slow injection of the radiopharmaceutical is advised^{41, 52, 113}. Specifications on particle number and size differ by product. In addition to special considerations for patients with pulmonary vascular diseases, additional care is required for children¹³² since their pulmonary vascular bed is not fully developed. The number of particles may need to be adjusted depending on the age of the child.

[^{99m}Tc]Technetium technegas

For [^{99m}Tc]technegas, we found 16 adverse events in 15 patients. The most reported adverse event was a decrease in oxygen saturation, which was reported in a study evaluating oxygen saturation in patients undergoing lung ventilation scintigraphy using [^{99m}Tc]technegas; that study found that 37% of patients experienced a decrease of more than 10% in oxygen saturation⁷¹. No IMEs were reported.

Thyroid (ATC group V09F)[¹²³I]Sodium iodine

For [¹²³I]sodium iodine, we found six adverse events in five patients. No IMEs were reported. One patient developed a rash after use of an [¹²³I]sodium iodine capsule, with the report's authors determining the excipients of the capsule or the dyes used in the capsule were most likely the cause of this adverse event¹⁰².

[^{99m}Tc]Technetium pertechnetate

For [^{99m}Tc]Tc-pertechnetate, we found 26 adverse events in 17 patients. The most reported adverse events were hypersensitivity, rash, and nausea. Two IMEs were reported: one patient lost consciousness immediately after injection⁸⁰, and another lost consciousness five minutes after injection⁷⁶. Both cases were classified by the author as vasovagal reactions.

Cardiovascular system (ATC group V09G)Pyrophosphate (non-radioactive)

For pyrophosphate, we found nine adverse events in five patients. Two IMEs were reported: one patient who lost consciousness and another who developed an infection at the site of injection the week after administration, eventually leading to necrosis of this site³².

Stannous agent (non-radioactive)

For stannous agent, we found three adverse events in three patients. Two IMEs were reported, both anaphylactic reactions not further specified by the author⁷.

[^{99m}Tc]Technetium sestamibi

For [^{99m}Tc]Tc-sestamibi, we found 66 adverse events in 30 patients. The most reported adverse events were vomiting and malaise. Five IMEs were reported: one patient suffered from an erythroderma affecting more than 90% of his body⁵⁰, one experienced an angioedema⁸⁹, one suffered an anaphylactic reaction with a painless

macroglossia¹⁰⁰, one presented with an exfoliating itching dermatitis¹⁰⁷, and one was diagnosed with erythema multiforme after [^{99m}Tc]Tc-sestamibi administration¹²³.

Three cases of dysgeusia were reported, with the patients describing the taste as being metallic or bitter. The reasons behind this taste disorder after radiopharmaceutical injection is not well understood. Several possible hypotheses have been proposed: high blood levels for the radiopharmaceutical itself⁶⁷, and one of the excipients of the formulation (e.g., the presence of copper ions in some formulations of [¹²³I]iobenguane). The rapid rate of injection may be an additional risk factor. A strange taste can be confusing for the patient, but an explanation can be provided if the nuclear medicine staff are aware of this transient effect.

[^{99m}Tc]Technetium tetrofosmin

For [^{99m}Tc]Tc-tetrofosmin, we found 41 adverse events in 21 patients. The most reported adverse events were rash, nausea, and vomiting. One IME was reported, concerning a patient suffering from an epileptic seizure 24 hours after administration of the radiopharmaceutical; the author specifies the patient also received dipyridamole⁶⁵.

[²⁰¹Tl]Thallium chloride

For [²⁰¹Tl]Tl-chloride, we found 63 adverse events in 25 patients. The most reported adverse events were rash and erythema. Three IMEs were reported: one case of mild anaphylaxis⁵⁵, one patient who experienced bradycardia post-administration after exercise on an ergometer⁷⁷, and one patient who temporarily lost consciousness five minutes after administration of the radiopharmaceutical⁸².

Inflammation and infection detection (ATC group V09H)

[⁶⁷Ga]Gallium citrate

For [⁶⁷Ga]Ga-citrate, we found 82 adverse events in 39 patients. The most reported adverse events were rash, pruritus, and fever. Two IMEs were reported: one patient experienced bradycardia⁷⁶, and another lost consciousness⁸¹. For [⁶⁷Ga]Ga-citrate, 42 skin disorders were reported. It has been suggested that this high number of

adverse events involving the skin is due to the use of a preservative; one report described an adverse event followed by a positive skin test for benzyl alcohol, a preservative used in [^{67}Ga]Ga-citrate⁴⁴.

Radiolabeled leucocytes

For [^{111}In]Indium oxinate-labeled cells, we found five adverse events in three patients. For [$^{99\text{m}}\text{Tc}$]Technetium exametazime-labeled cells, we found seven adverse events in five patients. No IMEs were reported for radiolabeled leucocytes, which are used to image inflammation and infection processes. Steps involving excipients are required to label blood cells. Anticoagulant agents such as acid-citrate-dextrose are used to prevent the blood from clotting, and sedimentation agents such as methylcellulose, dextran, and hydroxyethyl starch are used to accelerate the sedimentation of blood cells¹³³. Although most procedures involve washing the labeled cells, it cannot be excluded that adverse events are related to one of the excipients used.

[$^{99\text{m}}\text{Tc}$]Technetium sulesomab

For [$^{99\text{m}}\text{Tc}$]Tc-sulesomab, we found nine adverse events in three patients. One IME was reported in one patient experiencing pulmonary edema⁵⁴. [$^{99\text{m}}\text{Tc}$]Tc-sulesomab is a radiopharmaceutical based on an antibody, although it is not associated with the development of human anti-mouse antibodies; Fab fragments of IgG antibody lack the Fc-terminal responsible for the immune reactions¹³⁴.

Tumor detection (ATC group V09I)

[^{18}F]Fluciclovine

For [^{18}F]fluciclovine, we found five adverse events in five patients. In a cohort study with 714 patients, 0.6% reported adverse events³¹. In a small study with six patients, one patient experienced one adverse event (frequency of 16.5%)¹¹⁹. No IMEs were reported.

[¹⁸F]Fludeoxyglucose

For [¹⁸F]fludeoxyglucose, we found 80 adverse events in 17 patients. The most reported adverse events were rash, pruritus, and erythema. Eleven IMEs were reported: one anaphylactic reaction⁸⁶, three cases of angioedema, three cases of dermatitis exfoliative, two cases of seizures and two sudden cardiac deaths⁸⁵. One patient with a history of epilepsy suffered 10 minutes after injection from a convulsive seizure and cardiorespiratory distress, and the other patient had a history of lymphoma and suffered from septic shock 24 hours after injection (October 19, 2018 e-mail from Prof. Laroche to N.S.; unreferenced).

[¹⁸F]Fluorodihydroxyphenylalanine

For [¹⁸F]fluorodihydroxyphenylalanine (DOPA), an adverse event classified as an IME was reported in one patient. This IME was a case of a carcinoid crisis, which is the result of a massive release of neurotransmitters such as serotonin and is characterized by flushing, changes in blood pressure, difficulty breathing, and rapid heart rate. Carcinoid crisis can potentially be life-threatening, and the authors advise practitioners to be aware of this rare syndrome, slowly inject the tracer, and have appropriate drugs available to treat this condition, such as somatostatin analogs and perhaps ketanserin⁷⁹.

⁶⁸Gallium-labeled somatostatin analogs ([⁶⁸Ga]Ga-edotreotide (DOTA-TOC),[⁶⁸Ga]Ga-DOTA-TATE, [⁶⁸Ga]Ga-DOTA-NOC)

For the group of ⁶⁸Ga-labeled somatostatin analogs, we found 21 adverse events in 16 patients. A study evaluating safety and comparing [⁶⁸Ga]Ga-DOTA-TATE with [¹¹¹In]In-pentetreotide imaging (conducted with 97 patients) found three adverse events in three patients, for a frequency of 3.09%⁴⁶. In a multicenter trial using [⁶⁸Ga]Ga-edotreotide in 20 patients, four adverse events possibly related to the radiopharmaceutical were found, for a frequency of 20%⁹¹. Another study with [⁶⁸Ga]Ga-edotreotide found nine adverse events in 26 patients (34.6%)¹⁰³. No IMEs were reported.

[¹²³I]Iobenguane

For [¹²³I]iobenguane, we found 41 adverse events in 28 patients. The most reported adverse events were injection site pain, nausea, and vomiting. A multicenter clinical trial involving 981 patients reported a 0.407% frequency of adverse events⁶⁸. No IMEs were reported.

[¹¹¹In]Indium satumomab pendetide

For [¹¹¹In]In-satumomab pendetide, we found 47 adverse events in 53 patients. The most reported adverse events were fever, pruritus, and hypersensitivity. Clinical trials involving 1,041 patients found an adverse event frequency of 3.79%³⁸; a multicenter clinical trial with 116 patients found an adverse event frequency of 6.03%⁴⁸. Four IMEs were found: one study found cases of bradycardia, angioedema, and thrombocytopenia³⁸, and one case of angioedema was reported⁴⁸.

[¹¹¹In]In-satumomab pendetide contains murine monoclonal antibodies. These antibodies might induce an immune response producing human anti-mouse antibodies, which may interfere with murine antibody-based immunoassays, could compromise the efficacy of in vitro or in vivo diagnostic or therapeutic murine antibody-based agents, and may increase the risk of adverse reactions (although the frequency and nature of these reactions are unclear). Several factors known to influence a human anti-mouse antibodies reaction include dose, frequency of dosing, type of immunogenicity of the antibody, and the state of the patient's immune system. When a radiopharmaceutical is only used once, the likelihood of a reaction appears to be low since the immune system needs around 10 days to express IgG and IgM^{63, 87, 135, 136}. For some radiopharmaceuticals containing antibodies, the manufacturer provides additional guidelines for use such as to inquire about possible previous exposure to monoclonal antibodies, conduct a human anti-mouse antibodies test prior to administration, and inform that use could affect future use of murine-based products^{137, 138, 139}.

[^{99m}Tc]Technetium tilmanocept

For [^{99m}Tc]Tc-tilmanocept, we found six adverse events. In a multicenter trial with 85 patients, 36 reported at least one adverse event; the authors indicate that 85% of the reported adverse events were unrelated to [^{99m}Tc]Tc-tilmanocept⁸⁴. No IMEs were reported.

Other diagnostic radiopharmaceuticals (ATC group V09X)[¹³¹I]Iodomethyl norcholesterol diagnostic

For [¹³¹I]iodomethyl norcholesterol for diagnostic use, we found 190 adverse events in 60 patients. The most reported adverse events were nausea, back pain, and flushing. Four IMEs were found in three patients: one case described an anaphylactic shock 15 minutes after injection⁸³, another described a patient with ventricular tachycardia (with the authors believing this patient developed a crisis due to the medical condition)⁹³, and one describing an atypical anaphylactic reaction⁹⁰.

[¹³¹I]Iodomethyl norcholesterol is a norepinephrine analog used for adrenal imaging in primary aldosteronism, such as in pheochromocytoma. Adverse events are most frequently reported in Japan, which might be related to this radiopharmaceutical being used there more frequently⁹⁰. The manufacturer states that no pharmacodynamic effects are expected for doses used in diagnostic imaging¹⁴⁰. However, the reported events suggest involvement of the adrenergic nervous system, as some of the adverse events resemble symptoms also present in pheochromocytoma^{141, 142}. More research would be needed to clarify if the events are possibly connected to pheochromocytoma.

Table 2.5 Overview of AEs per radiopharmaceutical

Central nervous system (ATC group V09A)			
Diagnostical radiopharmaceutical	References	Total number patients	AEs (n when > 1)
[¹²³ I]iofetamine (IMP)	57, 75, 76, 77, 81, 82, 83, 94, 95, 98	13	IME: none reported Other AEs: Erythema (3), Nausea (3), Affective disorder (2), Pruritus (2), Rash (2), Vomiting (2), Adverse reaction, Blood pressure decreased, Blood pressure increased, Chills, Cold sweat, Conjunctival hyperaemia, Dyspnoea, Eczema, Flushing, Headache, Heart rate increased, Pallor, Pyrexia, Respiration abnormal, Urticaria
[¹²³ I]ioflupane	66, 96, 97, 98	7	IME: none reported Other AEs: Erythema (2), Injection site pain (2), Pruritus (2), Rash (2), Abdominal pain, Headache, Heart rate increased, Hyperhidrosis, Influenza, Muscular weakness, Pyrexia, Speech disorder, Urticaria
[¹¹¹ In]In-pentetic acid	27, 56, 61, 72, 78, 110, 111, 112	81	IME: CSF glucose increased (4), CSF protein increased (4), Meningitis aseptic (4), CSF white blood cell count increased (3), CSF cell count increased (2), Generalised tonic-clonic seizure (2), CSF test abnormal, Meningitis
[^{99m} Tc]Tc-exametazime	55, 76, 81, 93, 96	7	Other AEs: Adverse reaction (67), Pyrexia (8), Body temperature increased (6), Headache (4), Nuchal rigidity (4), Vomiting (4), Xanthochromia (3), Musculoskeletal stiffness (3), Chills (2), Kernig's sign (2), Meningeal disorder (2), Myoclonus (2), Brudzinski's sign, Heart rate increased, Hyperreflexia, Irritability, Vaginal haemorrhage
[⁶⁵ Yb]Yb-pentetic acid	56	3	IME: none reported Other AEs: Erythema (2), Anxiety, Blood pressure increased, Chills, Cyanosis, Headache, nasal congestion, Palpitations, Pruritus, Pyrexia, Rash, Vasovagal symptoms
			IME: none reported Other AEs: Adverse reaction (3)

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Skeleton (ATC group V09B)				Total number patients		Total number AEs	
Diagnosical radiopharmaceutical	References	AEs (n when > 1)					
Bisphosphonates (not specified)	53, 54, 55, 61, 65, 66		68			2	41
		IME: Anaphylactoid reaction, Unresponsive to stimuli Other AEs: Dizziness (4), Nausea (3), Rash (3), Vomiting (3), Arthralgia (2), Headache (2), Hyperhidrosis (2), Lethargy (2), Pruritus (2), Pruritus generalized (2), Rash generalised (2), Cyanosis, Dyspnoea, Hypersensitivity, Injection site pain, Limb discomfort, Mouth swelling, Myalgia, Oedema peripheral, Oral mucosal blistering, Pyrexia, Syncope, Throat irritation, Thrombophlebitis, Vision blurred					
[^{99m} Tc]Tc-butadronic acid	55	IME: none reported Other AEs: Adverse reactions not specified	2			-	-
[^{99m} Tc]Tc-medronic acid	7, 29, 33, 43, 49, 55, 56, 57, 58, 59, 75, 76, 80, 82, 83, 92, 93, 96, 97, 98, 99, 108, 112, 116, 120	IME: Anaphylactic reaction, Erythema multiforme, Respiratory distress Other AEs: Hypersensitivity (10), Nausea (7), Nonspecific reaction (7), Rash (7), Presyncope (5), Blood pressure decreased (3), Erythema (3), Headache (3), Pallor (3), Pruritus (4), Rash erythematous (3), Adverse reaction (2), Cardiovascular symptom (2), Chest discomfort (2), Chills (2), Discomfort (2), Local reaction (2), Pruritic rash (2), Pyrexia (2), Vomiting (2), Cold sweat, Conjunctival hyperaemia, Conjunctivitis, Cough, Dizziness, Dry mouth, General symptoms, Hypertension, Hypoaesthesia, Hypotension, Injection site erythema, Injection site pain, Jaundice, Liver function test abnormal, Malaise, Myalgia, nasal congestion, Oedema peripheral, Oliguria, Oropharyngeal pain, Pharynx discomfort, Rash maculo-papular, Renal function test abnormal, Skin reaction, Skin test positive, Swelling face, Tachycardia, Throat irritation	82			3	101

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Skeleton (ATC group V09B)				
Diagnostical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
^{99m} Tc]Tc-oxidronic acid	7, 55, 57, 58, 59, 62, 75, 76, 77, 80, 81, 82, 83, 85, 92, 93, 94, 96, 97, 98, 108, 112	61	IME: Loss of consciousness (4), Anaphylactic shock, Angioedema, Respiratory arrest, Respiratory failure, Seizure Other AEs: Rash (26), Oedema (25), Pruritus (18), Nausea (13), Discomfort (9), Local reaction (9), Not specified (9), Urticaria (8), Vomiting (6), Adverse reaction (4), Erythema (4), Malaise (4), Affective disorder (3), Dermatitis allergic (3), Dizziness (3), Eyelid oedema (3), Hyperhidrosis (3), Hypertension (4), Blood pressure decreased (3), Cold sweat (2), Headache (2), Hot flush (2), Hypersensitivity (2), Rash generalized (2), Abdominal pain, Acute generalised exanthematous pustulosis, Asthenia, Blood creatine phosphokinase increased, Diarrhoea, Dyspnoea, Eczema, Flushing, Incontinence, Injection site erythema, Injection site pain, Lazines, Mood altered, Mouth swelling, Pallor (2), Papule, Presyncope, Pruritus generalized, Rash erythematous, Rash pruritic, Stomatitis, Vasculitis, White blood cell count increased	9
				191
^{99m} Tc]Tc-pyrophosphate	58, 61, 76, 77, 80, 83, 93, 112	18	IME: none reported Other AEs: Adverse drug reaction (7), Adverse reaction, Defaecation urgency, Dizziness, Erythema (2), Flushing, Injection site erythema, Nausea (4), Presyncope, Pruritus, Vomiting (4)	1
				24

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Renal system (ATC group V09C)				
Diagnosical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[⁵¹ Cr]Cr-edetate	54, 56, 59, 78	5	IME: none reported Other AEs: Adverse reaction, Chromaturia, Hypersensitivity, Local reaction, Retching, Testicular swelling	- 6
[¹²³ I]iodohippurate	56, 59	2	IME: none reported	-
[¹³¹ I]iodohippurate	28, 56, 57, 122	18	Other AEs: Local reaction, Presyncope IME: Depressed level of consciousness	2 1
[^{99m} Tc]Tc-ethylenedicysteine	75, 80, 81, 83, 92, 94, 95, 96	10	Other AEs: Hypersensitivity (11), Nonspecific reaction (4), Abdominal pain, Dyspnoea, Flushing, Hypotension, Nausea, Presyncope, Pruritus generalised, Sense of oppression, Tachycardia, Toxicity to various agents IME: Respiratory distress	25 1
[^{99m} Tc]Tc-glucaptate	29, 58, 61, 112	6	Other AEs: Nausea (3), Rash (3), Erythema (2), Pruritus (2), Vomiting (2), Abdominal pain lower, Blood pressure increased, Diarrhoea, Discomfort, Dyspnoea, Flushing, Heart rate increased, Hypertension, Lazinez, Palpitations, Sneezing IME: none reported	23 -
[^{99m} Tc]Tc-meritide	53, 54, 55, 65, 66, 80, 94, 106, 116	23	Other AEs: Presyncope (2), Adverse drug reaction, Chills, Dizziness, Nausea, Nonspecific reaction, Rash, Urticaria IME: none reported Other AEs: Nausea (6), Dizziness (4), Rash (3), Blood pressure decreased (2), Cold sweat (2), Hyperhidrosis (2), Pallor (2), Urticaria (2), Affective disorder, Blister rupture, Cardiovascular symptom, Chest pain, Chills, Discomfort, Eye swelling, Fluid retention, Headache, Malaise, Pruritus generalised, Skin reaction, Somnolence, Syncope, Vomiting	9 - 38

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Renal system (ATC group V09C)				
Diagnostical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
^{99m} Tc]Tc-pentetic acid	7, 28, 29, 53, 54, 55, 56, 58, 59, 61, 65, 69, 76, 77, 80, 81, 82, 112, 125	50	IME: Paralysis, Respiratory distress, Seizure Other AEs: Presyncope (9), Nausea (5), Rash (5), Vomiting (5), Nonspecific reaction (4), Syncope (3), Adverse reaction (2), Chest pain (2), Erythema (2), Hypersensitivity (2), Urticaria (2), Adverse drug reaction, Agitation, Arthralgia, Asthenia, Blood pressure decreased, Blood pressure increased, Conjunctival hyperaemia, Cyanosis, Depressed mood, Dizziness, Dry eye, Dysgeusia, Dyspnoea, Emotional distress, Eye disorder, Flushing, Grunting, Headache, Hypoaesthesia, Malaise, Muscle twitching, Pallor, Pruritus, Rash generalised, Venous pressure jugular increased. For Tc-99m pentetic acid with Fe used in the preparation six AEs were found in one patient, being: adverse drug reaction, dizziness, erythema, hypotension, pruritus, swelling.	3
				72
^{99m} Tc]Tc-succimer	29, 53, 54, 55, 59, 61, 65, 66, 75, 76, 82, 83, 94, 96, 116	32	IME: none reported Other AEs: Rash (7), Headache (4), Nausea (4), Erythema (3), Vomiting (3), Adverse drug reaction (2), Dizziness (2), Discomfort, Erythema of eyelid, Hypersensitivity, Hypoaesthesia oral, Nonspecific reaction, Pallor, Pyrexia, Rash macular, Rash pruritic, Swollen tongue.	-
				35

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Hepatic and reticuloendothelial system (ATC group V09D)

Diagnosical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[¹³¹ I]-rose bengal	61, 112	3	IME: none reported Other AEs: Adverse drug reaction (2), Adverse reaction	-
[^{113m} In]-colloid	28	34	IME: none reported Other AEs: Hypersensitivity (27), Toxicity to various agents (6), Pyrexia	3
[⁷⁵ Se]tauroselcholic acid (SehCAT)	54, 57, 59, 78	5	IME: Anaphylactic reaction Other AEs: Hypersensitivity (3), Pruritus (2), Rash (2), Burning sensation, Dizziness, Dyspepsia, Dyspnoea, Flushing, Local reaction, Nausea, Pain, Swelling, Throat tightness	34
[^{99m} Tc]Tc-albumin colloid	53, 56, 58	6	IME: none reported Other AEs: Hypersensitivity (3), Administration site reaction, Urticaria	1
[^{99m} Tc]Tc-antimony sulfide colloid	56, 57, 59	6	IME: none reported Other AEs: Hypersensitivity (6)	17
[^{99m} Tc]Tc-diethylenetriaminopentaacetic acid-galactosyl human serum albumin (GSA)	76, 80, 83, 94, 96	5	IME: none reported Other AEs: Pruritus (2), Rash (2), Vomiting (2), Blood pressure increased, Cough, Pain, Pyrexia, Sneezing	-
[^{99m} Tc]Tc-nanocolloid	39, 40, 45, 54, 65, 66, 67	8	IME: none reported Other AEs: Urticaria (4), Headache, Hypotension, Mouth swelling, Peripheral swelling, Pruritus, Pruritus generalised, Rash, Rash macular	-
[^{99m} Tc]Tc-phytate	58	2	IME: none reported Other AEs: Adverse reaction (2)	12
[^{99m} Tc]Tc-rheniumsulfide colloid	56	1	IME: none reported Other AEs: Hypersensitivity	-

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Hepatic and reticuloendothelial system (ATC group V09D)

Diagnostic radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[^{99m} Tc]Tc-sulfur colloid	7, 28, 29, 37, 56, 58, 61, 73, 112, 115, 116, 118, 125	110	IME: Loss of consciousness (2), Acute kidney injury, Anaphylactic reaction, Atrial fibrillation, Circulatory collapse Other AEs: Adverse reaction (37), Pyrexia (19), Hypersensitivity (15), Injection site pain (12), Nonspecific reaction (5), Toxicity to various agents (4), Rash (3), Adverse drug reaction (2), Cyanosis (2), Dizziness (2), Erythema (2), Flushing (2), Nausea (2), Pruritus (2), Vomiting (2), Arrhythmia supraventricular, Blood creatinine increased, Blood pressure decreased, Blood urea increased, Bronchospasm, Cardiovascular symptom, Feeling hot, Headache, Hypotension, Not specified, Presyncope, Pulse absent, Respiratory disorder, Swelling, Tachycardia, Urine output decreased, Urticaria, Wheezing IME: none reported	6 129
[^{99m} Tc]Tc-tin colloid	57, 58, 59	3	Other AEs: Hypersensitivity (2), Adverse reaction	- 3

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Respiratory system (ATC group V09E)			
Diagnosical radiopharmaceutical	References	Total number patients	AEs (n when > 1)
¹³¹ I]-macrosalb	28, 36, 52, 113	7	IME: Death (2), Anuria, Haemorrhagic infarction, Hypersensitivity vasculitis, Pulmonary haemorrhage, Skin necrosis
			Other AEs: Body temperature increased (2), Dyspnoea (2), Haemoptysis (2), Heart rate increased (2), Hypersensitivity (2), Nonspecific reaction (2), Agitation, Anaemia, Blood pressure decreased, Blood pressure immeasurable, Blood urea increased, Bundle branch block right, Chest pain, Cough, Cyanosis, Dizziness, Haematuria, Heart rate decreased, Hyperhidrosis, Lung consolidation, Pleuritic pain, PO2 decreased, Rash, Rhinorrhoea, Sinus tachycardia, Tachypnoea, Venous pressure increased
^{99m} Tc]Tc-microspheres	29, 56, 58, 61, 88, 109, 112	48	IME: Anaphylactic shock, Anaphylactoid shock, Choking, Respiratory distress
			Other AEs: Hypersensitivity (16), Adverse drug reaction (7), Presyncope (5), Nonspecific reaction (3), Bronchospasm (2), Cyanosis (2), Flushing (2), Anxiety, Blood pressure immeasurable, Femoral pulse abnormal, Pruritus, Pyrexia, Rash, Urticaria
^{99m} Tc]Tc-macrosalb	7, 28, 41, 53, 54, 55, 57, 58, 61, 65, 66, 71, 76, 80, 83, 112, 124, 125, 126	59	IME: Death (3), Apnoea (2), Cardiac arrest (2), Angioedema, Bradycardia, Loss of consciousness, Respiratory arrest, Right ventricular failure, Unresponsive to stimuli, Ventricular arrhythmia
			Other AEs: Hypersensitivity (11), Adverse reaction (9), Dyspnoea (5), Dizziness (4), Rash (4), Nausea (3), Pruritus (3), Urticaria (3), Cyanosis (2), Erythema (2), Headache (2), Heart rate increased (2), Oxygen saturation decreased (2), Vomiting (2), Adverse drug reaction, Blood pressure immeasurable, Chills, Cold sweat, Dysgeusia, Emotional distress, Face oedema, Local reaction, Mood altered, Oedema, Presyncope, Rash generalised, Respiratory disorder, Syncope, Tachycardia, Wheezing
^{99m} Tc]technegas	71, 78	15	IME: none reported
			Other AEs: Oxygen saturation decreased (15), Paraesthesia
			Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Thyroid (ATC group V09F)				
Diagnostic radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[¹²³ I]sodium iodine	56, 58, 59	3	IME: none reported	-
			Other AEs: Adverse reaction, Hypersensitivity, Presyncope	3
[¹²³ I]sodium iodine (capsule)	76, 102	2	IME: none reported	-
			Other AEs: Pruritus, Rash, Urticaria	3
[¹³¹ I]sodium iodine diagnostic	28, 56, 75, 76	7	IME: none reported	-
			Other AEs: Discomfort (3), Pallor (3), Dizziness (2), Hypersensitivity (2), Hypotension (2), Adverse reaction, Affective disorder, Asthenia, Blood pressure increased, Cold sweat, Cyanosis, Feeling abnormal, Hot flush, Hyperhidrosis, Nausea, Yawning	23
[¹³¹ I]sodium iodine diagnostic (capsule)	102	*	IME: none reported	-
			Other AEs: Urticaria	1
[^{99m} Tc]Tc-pertechnetate	28, 53, 54, 57, 58, 61, 76, 80, 82	17	IME: Loss of consciousness (2)	2
			Other AEs: Hypersensitivity (6), Rash (3), Nausea (2), Adverse reaction, Blood pressure decreased, Dizziness, Flushing, Headache, Heart rate decreased, Hypertension, Pallor, Phlebitis, Presyncope, Sinusitis, Urticaria, Vomiting	24

* AE reported with one patient using both [¹²³I]sodium iodine (capsule) as [¹³¹I] sodium iodine diagnostic (capsule). Abbreviations: AEs, Adverse Events; IME, Important Medical Event.

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Cardiovascular system (ATC group V09G)				
Diagnosical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[⁵¹ Cr]chromate labelled cells and [¹²⁵ I]-human albumin	56	1	IME: none reported Other AEs: Adverse reaction	- 1
[¹²³ I]iodoflucic acid (BMIPP)	57, 81, 83, 95	5	IME: none reported Other AEs: Erythema (2), Rash (2), Blood pressure decreased, Dyspnoea, Headache, Hypersensitivity, Nausea, Rash	- 10
Pyrophosphate (non-radioactive)	29, 32, 116	5	IME: Injection site necrosis, Loss of consciousness Other AEs: Blood pressure immeasurable, Injection site inflammation, Malaise, Neurologic symptom, Nonspecific reaction, Skin reaction, Vomiting	2 7
Stannous agent (non-radioactive)	7	3	IME: Anaphylactic reaction (2) Other AEs: Dizziness	2 1
[^{99m} Tc]Tc-human albumin	57, 61, 95, 112	6	IME: none reported Other AEs: Hypersensitivity (2), Adverse drug reaction, Blood pressure decreased, Flushing, Heart rate increased, Nausea, Pyrexia, Rash, Respiratory disorder	- 10
[^{99m} Tc]Tc-human albumin - DTPA	75, 80, 81, 92	5	IME: none reported Other AEs: Rash (3), Erythema (2), Pruritus (2), Dizziness, Nausea, Oedema peripheral, Pyrexia,	- 11
[^{99m} Tc]Tc-stannous agent labelled cells	29, 58, 59	6	IME: none reported Other AEs: Adverse reaction (2), Hypersensitivity (2), Nonspecific reaction	- 5

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Cardiovascular system (ATC group V09G)				
Diagnostical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
^{99m} Tc]Tc-sestamibi	7, 50, 53, 54, 64, 65, 66, 67, 76, 80, 81, 82, 83, 89, 92, 93, 94, 95, 100, 107, 116, 123	30	IME: Dermatitis exfoliative (2), Anaphylactic reaction, Angioedema, Erythema multiforme Other AEs: Vomiting (5), Malaise (4), Dysgeusia (3), Erythema (3), Hypertension (3), Nausea (3), Pruritus (3), Pruritus generalised, Rash (3), Dizziness (2), Eosinophilia (2), Feeling cold (2), Flushing (2), Swollen tongue (2), Blood pressure increased, Discomfort, Drooling, Dyspnoea, Dysstasia, Eyelids pruritus, Headache, Hyperhidrosis, Injection site pain, Injection site swelling, Neck pain, Neurologic symptom, Oedema, Paraesthesia, Rash generalised, Rash macular, Rash maculo-papular, Skin exfoliation, Skin reaction, Speech disorder, Syncope, Tachypnoea, Wheezing	5
				61
^{99m} Tc]Tc-tetrofosmin	54, 55, 65, 66, 77, 78, 82, 83, 93, 97, 116	21	IME: Epilepsy Other AEs: Rash (6), Nausea (4), Vomiting (3), Dizziness (2), Dysgeusia (2), Injection site erythema (2), Neurologic symptom (2), Pruritus (2), , Burning sensation, Cough, Discomfort, Dyspnoea, Fatigue, Flushing, Hyperhidrosis, Hypertension, Induration, Lacrimation increased, Oropharyngeal pain, Rash generalised, Rhinorrhoea, Slow response to stimuli, Swelling, Thrombophlebitis	1
				40

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Cardiovascular system (ATC group V09G)				
Diagnosical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
²⁰¹ TlTl-chloride	30, 55, 58, 65, 75, 76, 77, 80, 81, 82, 83, 92, 93, 95, 97, 98	25	IME: Anaphylactic reaction, Bradycardia, Loss of consciousness	3
			Other AEs: Rash (10), Erythema (6), Blood pressure decreased (3), Hyperhidrosis (3), Nausea (2), Pruritus (2), Pyrexia (2), Syncope (2), Vomiting (2), Acute generalised exanthematous pustulosis, Adverse reaction, Affective disorder, Amnesia, Asthenia, Chills, Claustrophobia, Conjunctival hyperaemia, Discomfort, Dizziness, Dyspnoea, Eyelid oedema, Feeling hot, Flushing, Hypersensitivity, Hypotension, Incontinence, Leucocytosis , Local reaction, Oral mucosa erosion, Papule, Presyncope, Red blood cell sedimentation rate increased, Respiration rate increased, Skin burning sensation, skin irritation, Urticaria, Vision blurred	60

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Inflammation and infection detection (ATC group V09H)			
Diagnostic radiopharmaceutical	References	Total number patients	AEs (n when > 1)
⁶⁷ Ga[Ga-citrate]	7, 44, 54, 56, 57, 59, 61, 65, 75, 76, 77, 81, 82, 83, 92, 93, 94	39	IME: Altered state of consciousness, Bradycardia
			Other AEs: Rash (15), Pruritus (11), Pyrexia (5), Rash generalized (5), Adverse reaction (3), Erythema (3), Nausea (3), Urticaria (3), Blood pressure decreased (2), Dyspnoea (2), Hyperhidrosis (2), Hypersensitivity (2), Vomiting (2), Affective disorder, Arthralgia, Asthenia, Burning sensation, C-reactive protein increased, Discomfort, Dysgeusia, Feeling cold, Flushing, Generalised erythema, Heart rate increased, Hepatic function abnormal, Local reaction, Palpitations, Paraesthesia, Rash morbiliform, Skin plaque, Sneezing, Syncope, Tachycardia, Thirst, Viral upper respiratory tract infection
[¹¹¹ In]In-oxinate labelled cells	53, 58, 116	3	IME: none reported
^{99m} Tc[Tc-fanolesomab]	60, 87	75	Other AEs: Headache, Hypersensitivity, Myalgia, Nausea, Skin reaction
			IME: Cardiac arrest (2), Cardio-respiratory arrest (2), Sudden cardiac death (2), Hypoxia
^{99m} Tc[Tc-human immunoglobulin (HIG)]	54	1	Other AEs: Human anti-mouse antibody positive (5), Paraesthesia (2), Viral upper respiratory tract infection (2), Ankle sprain, Blood lactate dehydrogenase increased, Contusion, Dyspnoea, Flushing, Hypotension, Malaise, Toothache, Transaminase increased
			IME: none reported
^{99m} Tc[Tc-exametazime labelled cells]	54, 65, 66	5	Other AEs: Nausea
			IME: none reported
^{99m} Tc[Tc-sulesomab]	54, 65	3	Other AEs: Dyspnoea (2), Emotional distress, Flushing, Malaise, Pruritus generalised, Rash pruritic
			IME: Pulmonary oedema
			Other AEs: Blister, Cyanosis, Dizziness, Hyperhidrosis, Hypertension, Nausea, Pruritus, Rash erythematous

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Tumour detection (ATC group V09I)				
Diagnosical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[¹⁸ F]fluciclovine	31, 119	5	IME: none reported Other AEs: Adverse event (4), Injection site erythema	-
[¹⁸ F]fludeoxyglucose	42, 78, 83, 85, 86, 92, 93, 94, 95, 97, 98, 116	17	IME: Angioedema (3), Dermatitis exfoliative (3), Seizure (2), Sudden cardiac death (2), Anaphylactic reaction Other AEs: Rash (13), Pruritus (12), Erythema (9), Urticaria (8) Dysgeusia (3), Nausea (3), Vomiting (3), Hyperhidrosis (2), Local reaction (2), Abdominal pain, Cardiovascular symptom, Chills, Diarrhoea, Discomfort, Head titubation, Heart rate increased, Hypotension, Malaise, Mental status change, Oral pruritus, Papule, Rash generalised, Skin reaction	5 11 69
[¹⁸ F]fluorodihydroxy-phenylalanine (DOPA)	79	1	IME: Carcinoid crisis Other AEs: none reported	1
[⁶⁸ Ga]Ga-DOTA-NOC	78	†	IME: none reported Other AEs: Rash maculo-papular	-
[⁶⁸ Ga]Ga-DOTA-TATE	46	3	IME: none reported Other AEs: Injection site pruritus, Oxygen saturation decreased, Tachycardia	1 - 3
[⁶⁸ Ga]Ga-edotreotide (DOTA-TOC)	91, 103, 114	13	IME: none reported Other AEs: Adverse event (9), Nausea (2), Discomfort, Dysgeusia, Flushing, Headache, Pain, Paraesthesia	17
[¹²³ I]Iobenguane	53, 54, 59, 65, 66, 67, 68, 75, 77, 82, 97, 116	28	IME: none reported Other AEs: Injection site pain (8), Nausea (3), Vomiting (3), Dysgeusia (2), Dyspnoea (2), Adverse reaction, Blood gases abnormal, Blood pressure decreased, Discomfort, Dizziness, Flushing, Heart rate increased, Hypersensitivity, Hypertension, Hypoaesthesia, Hypotension, Palpitations, Persistent depressive disorder, Presyncope, Procedural nausea, Pruritus, Pruritus generalised, Rash, Rash generalised, Skin odour abnormal, Skin reaction, Syncope, Urticaria	- 41

Abbreviations: AEs, Adverse Events; IME, Important Medical Event; † Exact number of patients was not given by author

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Tumour detection (ATC group V09I)				
Diagnosical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[¹³¹ I]Iobenguane diagnostic	70	1	IME: Erythema multiforme	1
[¹¹¹ In]In-satumomab pendetide	38, 48, 53	53	Other AEs: Rash erythematous, Rash pruritic	2
			IME: Angioedema (2), Bradycardia, Thrombocytopenia	4
			Other AEs: Pyrexia (6), Pruritus (4), Hypersensitivity (3), Abdominal pain (2), Flank pain (2), Human anti-mouse antibody positive (2), Hypertension (2), Nausea (2), Rash (2), Arthralgia, Asthenia, Chest pain, Chills, Confusional state, Crying, Diarrhoea, Dizziness, Headache, Hyperhidrosis, Hypotension, Hypothermia, Injection site reaction, Nervousness, Pain, Urticaria, Vasodilatation, Vomiting	43
[^{99m} Tc]Tc-arcitumomab	63	1	IME: none reported	-
[^{99m} Tc]Tc-tilmanocept	84	6	Other AEs: Human anti-mouse antibody positive, Urticaria	2
			IME: none reported	-
			Other AEs: Adverse event (5), Injection site irritation	6

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Other diagnostic radiopharmaceuticals (ATC group V09X)

Diagnostic radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[¹⁹⁸ Au]Au-colloid	28, 56, 57, 125	6	IME: none reported Other AEs: Hypersensitivity (5), Adverse reaction	- 6
[²⁰⁸ Hg]chlormerodrin	28	3	IME: none reported Other AEs: Hypersensitivity (3)	- 3
[¹³¹ I]I-human albumin	28, 34, 35, 47, 51, 56, 58, 74, 101, 104, 105	73	IME: CSF protein increased (11), CSF white blood cell count increased (8), CSF red blood cell count positive (7), CSF pressure increased (6), CSF test abnormal (3), Meningitis aseptic (3), CSF cell count increased (2), CSF glucose increased (2), Meningitis (2), CSF glucose decreased, Neurogenic bladder, Seizure Other AEs: Pyrexia (52), Nonspecific reaction (11), Meningism (6), Nuchal rigidity (6), Body temperature increased (4), Hypersensitivity (4), Confusional state (3), Headache (3), Musculoskeletal stiffness (3), Chills (2), Vomiting (2), Xanthochromia (2), Adverse reaction, Agitation, Atelectasis, Back pain, Chest discomfort, Hyperreflexia, Lethargy, Nausea, Presyncope, Somnolence, Toxicity to various agents, IME: Anaphylactic shock, Electrocardiogram ST segment depression, Ventricular tachycardia	47 109
[¹³¹ I]Iodomethyl norcholesterol diagnostic	56, 75, 76, 77, 80, 81, 82, 83, 90, 92, 93, 95, 96, 97, 121	60	Other AEs: Nausea (16), Back pain (14), Flushing (14), Discomfort (11), Hypersensitivity (10), Blood pressure increased (8), Dyspnoea (8), Erythema (8), Hyperhidrosis (7), Palpitations (6), Affective disorder (5), Blood pressure decreased (5), Chest pain (5), Dizziness (5), Vomiting (5), Chest discomfort (4), Headache (5), Abdominal discomfort (3), Cough (3), Hypertension (3), Pallor (3), Rash (3), Asthenia (2), Feeling abnormal (2), Hot flush (2), Hypoaesthesia (2), Malaise (2), Pruritus (2), Tachycardia (2), Abdominal pain, Abdominal symptom, Abnormal sensation in eye, Arthralgia, Asthma, Cyanosis, Emotional distress, Eyelid oedema, Feeling hot, Heart rate increased, Hyperventilation, Hypotension, Injection site rash, nasal congestion, Neck pain, Ocular hyperaemia, Pain, Papule, Pulse abnormal, Swelling, Vertigo positional	4 186

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

Table 2.5 (Continued) Overview of AEs per radiopharmaceutical

Diagnostical radiopharmaceutical	References	Total number patients	AEs (n when > 1)	Total number AEs
[¹¹¹ In]In-colloid	57	1	IME: none reported Other AEs: Adverse reaction	-
[¹¹¹ In]In-platelets	57	1	IME: none reported Other AEs: Hypersensitivity	1
[^{113m} In]In-pentetic acid	28	1	IME: none reported Other AEs: Hypersensitivity	-
[^{99m} Tc]Tc-iron hydroxide	28	4	IME: none reported Other AEs: Nonspecific reaction (3), Toxicity to various agents	4
[^{99m} Tc]Tc- or [^{113m} In]In-iron precipitate	125	45	IME: none reported Other AEs: Adverse reaction (45)	-
[^{99m} Tc]Tc-plasmin	56	1	IME: none reported Other AEs: Hypersensitivity	45
Diagnostic radiopharmaceuticals not specified	57	419	IME: none reported Other AEs: Rash (110), Vomiting (30), Urticaria (24), Pruritus (64), Skin reaction, Adverse reaction	-

Abbreviations: AEs, Adverse Events; IME, Important Medical Event

2.4 DISCUSSION

Based on a systematic review of the literature, we selected and analyzed 101 of 20,363 titles and provided an overview of 2,447 adverse events associated with the use of diagnostic radiopharmaceuticals. The majority of the reported adverse events with diagnostic radiopharmaceuticals (84.4%) related to six system organ classes. Most reported adverse events were in the system organ classes ‘skin and subcutaneous tissue disorders’ and ‘general disorders and administration site conditions.’

Some of the reported adverse events can be described as allergic reactions—for example, skin reactions such as rash and urticaria, angioedema leading to swelling of face or tongue and breathing difficulty, and even life-threatening anaphylactic shock. Another portion of the adverse events reported with diagnostic radiopharmaceuticals can be described as vasovagal reactions, which include symptoms such as pallor, feeling warm, sweating, a drop in blood pressure, and fainting.

Since most patients typically receive a diagnostic radiopharmaceutical only once, the precise trigger for the allergic reaction is often unknown. Some modern diagnostical radiopharmaceuticals are used in repeated administration for treatment evaluation and follow-up, which might have consequences when the sensitization risk changes. A limited number of case reports note a positive rechallenge: Spicer reports a case with [^{99m}Tc]Tc-medronic acid in which a patient developed a pruritic erythematous rash after the first use and erythema multiforme with the second use after nine months¹²⁰, and Mooser reports a case of an erythematous, pruritic rash after administration of [^{99m}Tc]Tc-medronic acid, with a rechallenge that ^{99m}Tc was responsible for the rash⁹⁹. Núñez reports a case of rash after the use of [^{123}I] and [^{131}I]sodium iodine capsules, arguing that excipients of the capsules or the dyes used in the capsules were the most likely causes; the patient took an [^{123}I]sodium iodine capsule followed five months later with an [^{131}I]sodium iodine capsule and developed an urticarial skin rash similar in appearance on both occasions¹⁰². Commandeur reports a case of hypersensitivity to [^{67}Ga]Ga-citrate, with skin tests demonstrating that the preservative benzyl alcohol caused the reaction⁴⁴.

Our review found the majority of the reported events were minor in severity and often resolved without sequelae. Nevertheless, 165 (6.7%) of the reported adverse events could be classified as IMEs, and nine deaths were reported: five occurring with the use of [^{131}I]I-macrosalb or [$^{99\text{m}}\text{Tc}$]Tc-macrosalb for pulmonary scintigraphy in cases of a severe reduction in pulmonary capacity, two occurring with [^{18}F]fludeoxyglucose, and two occurring with the radiopharmaceutical [$^{99\text{m}}\text{Tc}$]Tc-fanolesomab, which is no longer available. We found a median reported frequency of adverse events in diagnostic radiopharmaceuticals of 0.0016%, which is low compared to the 1% to 2% reported for therapeutic drugs^{143, 144} and the 5% to 7% reported for drug reactions in hospitalized patients^{145, 146, 147}. This frequency is also lower than the earlier reported frequency range of 0.7% to 3.1% with non-ionic iodinated contrast media used in computed tomography (CT)^{148, 149}. For some individual radiopharmaceuticals, we found a frequency ranging from 0.125% to 40.9%, with the higher frequencies including products no longer in use such as [^{131}I]I-human serum albumin and [$^{99\text{m}}\text{Tc}$]Tc-fanolesomab.

The low reported frequency with some diagnostic radiopharmaceuticals can be explained by a low dose, lack of pharmacological effect, and low frequency of administration (often only once); another important reason might be that all of the studies reporting on the frequency of adverse events for various radiopharmaceuticals relied on voluntary identification and reporting. The following aspects might also influence the reporting or publication of case reports of adverse events: (1) Some procedures in nuclear medicine departments sometimes use non-radioactive drugs to conduct an examination, such as stress agents in myocardial perfusion imaging or diuretics in renal imaging. Some adverse reactions may result from these non-radioactive drugs and be inadvertently linked to the radiopharmaceutical, and some adverse events might be missed because physicians assume they result from the investigation procedure itself, such as dyspnea during myocardial perfusion imaging; (2) not every institution maintains good records of its adverse events; (3) physicians might not report adverse events considered to be minor; (4) the level of awareness on adverse events might not be consistent across institutions due to different perceptions on the need to report these events; and (5)

the nuclear department may not be informed about an adverse event, as the patient left after examination^{15, 65}.

Our data regarding frequency are in line with findings from a previous literature review by Salvatori, which included seven studies and found a pooled prevalence rate of 1.9 per 100,000 administrations¹⁷. Salvatori's review does not include an overview of the most common adverse events and their characteristics. In our review we use a systematic approach following the PRISMA guidelines, focusing on a transparent and complete reporting. Furthermore, it covers all diagnostic radiopharmaceuticals and the search was not restricted to a specific time period. Although 85.0% of the articles had a moderate or good methodological quality, they consist primarily of uncontrolled clinical observations that might be prone to bias.

The studies in our review were checked for a double presentation of the data, which can occur, for example, when an event is included in a case report and in a spontaneous reporting summary. We determined double reporting occurred in one article¹⁵⁰, and therefore did not include the paper in this review. However, when an article did not contain a reference to a previously reported case, we were not able to assess double reporting. For 14 articles, the number of events presented could not exact be matched with the number of patients. In these cases, the reported adverse events were counted as one, although the correct number might have been higher; this may have led to some underreporting of adverse events in this review.

Differences in pre-set definitions and study set-up were found. For example, Silberstein introduced a strict definition of 'adverse events'⁷ excluding any vasovagal reactions because these are thought to be so common in a clinical setting that it is extremely difficult to determine their relationship with the injected radiopharmaceutical. However, other researchers such as Hesslewood include vasovagal reactions to ensure all events are captured; Hesslewood notes that excluding vasovagal reactions also excludes the possibility of carefully evaluating the event⁶⁷.

It should be noted that the radiopharmaceuticals were divided into several groups, using the ATC classification system. Because a radiopharmaceutical is included in only one group, classification does not specify each indication of that individual radiopharmaceutical. This did not influence our data, but it does require

readers to be aware of this classification system when looking for information; for example, [^{99m}Tc]Tc-pertechnetate is included in the ATC group ‘V09F Thyroid’ but may also be used to measure the cardiac ejection fraction. Furthermore, this review provides a general overview and therefore does not consider variations in products or procedures that might differ from country to country.

Additionally, some nuclear medicine procedures involve the use of interventional agents to mimic a physiological effect or for preventative use. For example, myocardial perfusion scans often involve the radiopharmaceutical being combined with a pharmacologic stress agent such as adenosine, dipyridamole, or dobutamine, and dynamic renal studies might use furosemide or captopril. For iodinated radiopharmaceuticals, the thyroid might need to be blocked using Lugol’s solution or potassium iodine tablets. In addition to these interventional agents, the relatively recent introduction of combined modalities like PET/CT and SPECT/CT sometimes requires the use of contrast media. In the events reported, it may not always have been possible to decide which of the administered agents was responsible for the adverse event.

2.5 FUTURE PERSPECTIVES

A possible reason for the low frequency of adverse events associated with diagnostic radiopharmaceuticals might be that not all cases are reported or published, and prospective studies describing the experiences of patients with diagnostic radiopharmaceuticals could provide more information.

Several new PET tracers have recently been marketed for use. Our study found 107 adverse events reported with PET tracers ([^{18}F]fludeoxyglucose, [^{18}F]fluciclovine, [^{18}F]fluorodihydroxyphenylalanine (DOPA), and ^{68}Ga -labeled somatostatin analogs). The majority are attributed to [^{18}F]fludeoxyglucose, probably because this agent is mostly used. The number of adverse events we found for PET tracers is far below what has been reported with the conventional gamma tracers. Silberstein also saw this in his 1998 study, finding no adverse events for PET tracers among 81,801 patients¹¹⁷. Possible reasons might be that PET tracers are used in

even smaller doses (micrograms) than the conventional gamma tracers and are labeled molecules that are normally found in the human body (or are analogs of these). Another reason can be that PET tracers are relatively new. With an increasing number of patients exposed to these new tracers, the number of reported adverse events may increase, providing insight into new adverse events. Reporting of adverse events to the relevant regulatory authorities or marketing authorization holder could detect hitherto unknown adverse events.

Finally, the increasing use of combined modalities like PET/CT and SPECT/CT might further increase the reported frequency of adverse events in nuclear medicine examinations because of the use of contrast media¹⁵¹.

2.6 CONCLUSION

This review shows that adverse events can definitely occur with diagnostic radiopharmaceuticals, although the frequency is quite low compared to other types of drugs. The most common adverse events are skin and subcutaneous tissue disorders, and general disorders and administration site conditions. In rare cases, the adverse events can be serious and even life-threatening, but most resolve without sequelae. We recommend nuclear medicine departments be prepared to manage these situations. Furthermore, with the introduction of new radiopharmaceuticals and the increasing use of PET/CT, the nuclear medicine community should remain vigilant in terms of new adverse events. Further research should cover the patient's experience with adverse events resulting from diagnostic radiopharmaceuticals.

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Chapter 3

Patient-reported adverse events of radiopharmaceuticals: development and validation of a questionnaire

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ABSTRACT

Introduction: Radiopharmaceuticals may cause adverse events. Knowledge about adverse events from a patient's perspective could help healthcare professionals to detect, understand, and manage adverse events more efficiently when using radiopharmaceuticals. Researchers need a validated questionnaire that can be used in patients to assess adverse events with radiopharmaceuticals.

Objective: The aim of this study was to develop, validate the content, and perform initial testing of a questionnaire assessing patient-reported adverse events of radiopharmaceuticals.

Methods: Based on existing literature, six professionals drafted and evaluated a first version of the questionnaire. Further content validation was performed using cognitive interviews with six patients undergoing a nuclear medicine examination. After adaptations, the questionnaire was developed into a web-based questionnaire. One hundred patients undergoing nuclear examination tested this version, and the results were used to assess its acceptability and evaluate reported adverse events.

Results: Questions and answer options were revised in the initial questionnaire to improve clarity. In addition, some questions were removed. The final version consisted of 18 questions. In the test phase, the acceptability of the questionnaire was demonstrated (e.g., 79% of the patients who received the questionnaire completed it, the median time to complete the questionnaire was 12 minutes for patients who reported an adverse event). Of the 100 patients (53% men, median age 64 years), 12 reported a total of 22 adverse events. One of these adverse events had a high causal association.

Conclusion: After validation and testing, the developed questionnaire to study patient-reported adverse events of radiopharmaceuticals is a suitable and valid instrument which can be used in future research.

3.1 INTRODUCTION

Radiopharmaceuticals are used in nuclear medicine for diagnosis and therapy¹⁻². While it is known that radiopharmaceuticals can cause adverse events, it is assumed that the frequency of adverse events in diagnostic radiopharmaceuticals is relatively low compared to events caused by other types of drugs³⁻⁸. This can be explained by the low dose of the tracer with a subsequent absence of pharmacological effect, and the limited use of the tracer in an individual patient—usually only once^{3,4}. However, underreporting of adverse events—also described for other types of drugs—is likely to play a role in this low frequency⁹⁻¹¹. In addition, adverse events of radiopharmaceuticals may be left undetected, as follow-up contact seldom occurs between the patient and the nuclear medicine department after the examination is completed.

In order to investigate the frequency of adverse events and partially overcome the issues of underreporting, information provided by the patients themselves can be useful. Such information may shed a different light on the frequency of the adverse events, and more detailed information aids in assessing the causal relationship between the radiopharmaceutical and the reported event. Furthermore, information that patients provide may differ from information that healthcare professionals provide. Physicians generally focus more on serious, often rare adverse events, while patients report milder but more frequent adverse events such as tiredness¹². Patients can also provide information about the impact of adverse events on their quality of life^{13,14}. More knowledge about the frequency of adverse events and the perspective of patients could help healthcare professionals to inform patients and to better prepare them in managing any adverse event that may arise.

Previous research has shown that questionnaires can be useful instruments in obtaining information from patients about adverse events and about, for instance, the time course, severity, and outcome of the adverse events^{15,16}. Even though researchers have developed several questionnaires in the past¹⁵⁻¹⁷, they were developed for other types of drugs and are not suitable for radiopharmaceuticals because of aspects that are unique to the use of these products in nuclear medicine departments. Examples are the specific preparation of the patient before the nuclear

medicine examination or additional steps during the procedure such as physical exercise or the concomitant administration of interventional agents, like agents that induce stress in the case of the assessment of myocardial perfusion. Information about these aspects will be essential when assessing reported adverse events. Furthermore, the use of radiological contrast agents in the case of combined techniques, such as positron emission tomography/computed tomography (PET/CT), and the fact that the nuclear medicine department usually has no follow-up contact with the patient after the examination is completed requires questions to be asked about the experience of patients at several specific moments. To our knowledge, only one study about radiopharmaceuticals assessed adverse events from the perspective of patients. In this study researchers developed and validated a questionnaire, which 55 patients using [^{99m}Tc]Tc-medronic acid completed. However, this study involved one specific radiopharmaceutical and the researchers did not specify detailed information about the method of validation¹⁸.

Therefore, we aimed to develop and validate a questionnaire dedicated to assessing adverse events with radiopharmaceuticals from the patient's perspective, which can be used in future research. This paper describes the development, content validation, and initial testing of the questionnaire.

3.2 METHODS

This study consisted of three phases: (1) the development of a questionnaire in the Dutch language, assessing adverse events from the perspective of patients undergoing an examination using radiopharmaceuticals, (2) the validation of its content, and (3) initial testing of the questionnaire (Figure 3.1). We obtained ethical exemption in writing from the Medical Ethics Committee of the Isala Hospital, in Zwolle in The Netherlands (Reference number 16.08138), as this study did not require formal approval, according to Dutch law.

Fig. 3.1 Process of development and validation of the questionnaire. Adapted with permission from de Vries et al. (2013)¹⁵

3.2.1 Phase 1: Questionnaire development

Based on existing literature^{3-7, 19, 20}, two researchers (Q.d.H., N.S.) drafted a first version of the questionnaire containing the main questions in the following sections: (1) patient characteristics, (2) health status, (3) past nuclear medicine examinations and occurrence of adverse events, (4) preparation by the patient before a nuclear medicine examination, (5) administration of the radiopharmaceutical and occurrence of adverse events, (6) the period after the nuclear medicine examination and occurrence of adverse events, and (7) any further comments by the patient.

In section one, we obtained demographic data using closed-ended questions (i.e., assessing gender, education—grouped according to International Standard Classification of Education (ISCED) 2011²¹—and use of over-the-counter medicines) and open-ended questions (i.e., assessing age, weight, and height). Subsequently in section two, we measured the patient's health status with the EuroQol-5-dimensions-3 levels (EQ-5D-3L) questionnaire²². The EQ-5D-3L is a qualified instrument to measure quality of life, including a descriptive system and a visual analogue score (EQ-VAS)²³. Permission for its use was obtained. Sections three, five, and six contained open-ended and closed-ended questions about adverse events experienced during past nuclear medicine examinations, those associated with the administration of the radiopharmaceutical in the current nuclear medicine examination, and those experienced in the period after the examination, respectively. Section four contained closed-ended (both single-answer and multiple-answer) questions about the preparation by the patient before the nuclear medicine examination. In section seven, the patient could provide additional remarks about both the questionnaire and the nuclear medicine examination.

When patients indicated in the questionnaire that they experienced one or more adverse events, we asked additional closed-ended and open-ended questions, including aspects such as experienced symptoms, status of recovery, whether patients contacted a healthcare professional, and the type of professional (i.e., general practitioner, hospital staff, nuclear physician, nurse, pharmacist, and referring physician hospital). The additional questions also contained items to perform a causality assessment. This concerned the time of onset of the adverse event, previous experiences with nuclear medicine examinations, administration of

interventional agents, or, in the case of combined techniques such as PET/CT, the use of contrast agents and other possible causes of the adverse event. We based these questions on the Naranjo algorithm²⁴, which is commonly used for causality assessment in pharmacovigilance, and the Silberstein algorithm⁷, which specifically focuses on causality assessment of adverse events with radiopharmaceuticals.

A separate section in the questionnaire was meant only for the researchers to provide additional information obtained from the medical records, such as the name of the radiopharmaceutical, its dose (in megabecquerel), type of examination, renal function, co-medication, and indications for use.

3.2.2 Phase 2: Content validation

Previously, it has been determined that five experts are the minimum requirement for content validation. Moreover, it has been suggested that these experts are from all relevant disciplines to cover the content domain being assessed²⁵. We selected six experts with expertise in the field of questionnaire development ($n = 1$), pharmacovigilance ($n = 2$), and nuclear medicine ($n = 3$) to form the expert panel in this study. Members of the expert panel independently reviewed the first paper-based version of the questionnaire. Two researchers (Q.d.H., N.S.) identified issues, which were used to draft a second version.

We subjected the second version of the questionnaire to cognitive interviewing in order to get insight into the way patients understand the questions and how they interpret the answer options, highlighting any ambiguities²⁶. Six patients undergoing a nuclear medicine examination at the Isala Hospital in Zwolle participated in this part of the study. We selected consecutive patients willing to participate on the day of their nuclear medicine examination until we reached six participants. They were 18 years old or older and were able to read and speak the Dutch language. One researcher (Q.d.H.) conducted the interviews and audio-recorded them, with approval of the interviewees. In the interview, the researcher used a set of proactive and reactive so-called ‘probes’, while the patients were completing the questionnaire. Probes are questions specifically designed to obtain detailed information that the interviewee may not otherwise share²⁷. Examples include: ‘How

did you come to an answer?’, ‘Can you repeat the question in your own words?’, and ‘How sure are you of the answer given?’. We transcribed the interviews using transcription software (Atlas.ti v7.5.12) and analysed the transcripts (Q.d.H.) to identify issues where the interviewee had difficulties answering the question. The identified issues were coded according to a dedicated system containing the following five categories: Comprehension/Communication, Recall-based, Bias/Sensitivity, Response categories, and Logical/Structural problems²⁸. Two researchers (Q.d.H., NS) discussed the identified issues, which led to a third and enhanced version of the questionnaire.

Because the questionnaire is to be sent out to patients after a certain time interval after patients have left the nuclear medicine department and is to be used in a larger group of patients, we converted the paper-based questionnaire into a web-based questionnaire. This enabled the automation of sending the questionnaire after a time interval of seven days after the nuclear medicine examination and allowed digital and faster processing of the data. Additionally, web-based questionnaires have shown some advantages in the past, such as a lower number of unanswered questions and more detailed answers to open questions²⁹. The web-based version of the questionnaire was created using an online data manager (De Researchmanager®)³⁰. The expert panel tested the web-based questionnaire on user friendliness and comprehensiveness. This led to revisions of the web-based version.

3.2.3 Phase 3: Testing of the questionnaire

We then tested the revised web-based version of the questionnaire in a larger population of 100 patients to evaluate its acceptability and record adverse events. This is the number of patients recommended in literature³¹. Patients undergoing nuclear examination at Isala hospital were invited to participate in this test phase until we reached 100 participants who completed the questionnaire. Prior to the nuclear examination they received an invitation letter with a participation form. Patients were excluded when data were missing on the participation form that were required to initiate the web-based questionnaire, such as e-mail address or signature. We obtained written permission of patients willing to participate. Those patients

received a link to the web-based questionnaire seven days after their nuclear medicine examination. A reminder was sent after another seven days when patients had not completed the questionnaire, but access to the questionnaire was limited to 21 days after the nuclear medicine examination. These timespans were chosen for two reasons. First, we would expect possible adverse events to occur within a few days after the nuclear medicine examination⁸. Second, longer recall periods may introduce bias due to patients forgetting information or patients bringing up information from other sequential doctor visits or examinations^{32–34}.

To assess acceptability in patients, we evaluated three characteristics: the percentage of patients completing the questionnaire, the time in which they completed the questionnaire, and their ability to answer all questions. We recorded the number of patients completing the questionnaire and the time in which they completed it. To assess the ability to answer all questions, we added—only during the test phase—at the end of each section a question asking whether there were any issues with answering the questions or with the wording, and, if so, what those issues were.

We evaluated reported adverse events and the time course. Reported adverse events were coded according to a Preferred Term of the Medical Dictionary for Regulatory Activities (MedDRA®) terminology. MedDRA is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)³⁵. Furthermore, we performed a causality assessment on all reported cases using the Naranjo²⁴ and Silberstein⁷ algorithms. For the causality assessment, we used data obtained with the questionnaire on the time of onset of the adverse event, adverse events during previous nuclear medicine examinations, the recovery status of the patient, other possible causes of the adverse event such as administration of interventional agents, or as indicated by the patient. To determine if there are previous conclusive reports on this reaction or if it is known response pattern, we used data from the literature⁸ and the summary of product characteristics of the products. Two researchers (Q.d.H., N.S.) independently conducted the coding and assessed the causality. When results syntheses were not in agreement, the results were discussed with a third researcher (E.v.P.) to resolve discrepancies. After

inclusion of the targeted 100 patients, we analysed the results descriptively using Excel version 1808 (Microsoft) and discussed the analysis to come to a final questionnaire (Q.d.H., N.S.).

3.3 RESULTS

3.3.1 Phase 1: Questionnaire development

The first draft of the questionnaire contained 30 main questions distributed over seven sections and additional questions about adverse events, which were posed when patients indicated they experienced an adverse event.

3.3.2 Phase 2: Content validation

The expert panel provided feedback on the content of the first version of the questionnaire. Most of the comments related to clarity and wording. Of the 30 questions in the first version, we removed six questions, added one question, changed four questions, and left 20 questions unchanged. Of the six removed questions, five were related to the waiting period for the patient before and after the examination, which we deemed irrelevant. The sixth question that was removed was about the changes the patients experienced during the examination and was found to be repetitive. This resulted in a revised, second version of the questionnaire (Figure 3.1) with 25 main questions.

Thereafter, six patients participated in the cognitive interviews. The patients were between 51 years old and 76 years old and had varying levels of education. One patient had trouble reading the questions due to partial visual impairment. As the interviewer read the questions out loud for this patient, the patient was still able to participate. Patients mentioned a total of 67 issues, mostly related to the categories Comprehension/Communication (52%) and Response (22%) (Table 3.1).

Table 3.1 *Number and examples of issues identified during the cognitive interviews with patients per category*

Category	Number (%)	Examples of issues mentioned by patients
Comprehension/ Communication	35 (52.3)	Q: "Do you know what contact allergy means?" A: "Ehmm, that you are afraid to touch people?" (patient 1) Q: "Do you know what a radioactive agent is?" A: "I am not sure what it is." (patient 4)
Recall-based	9 (13.4)	Q: "you mentioned your height quite quickly, how certain are you?" A: "I am not completely sure about my current height, because I think that I shrunk a little over the years, so I am not quite sure." (patient 4)
Bias/Sensitivity	3 (4.5)	Q: "What do you think by reading this question?" A: "Oh dear, I have to think about this, and I don't have that time. So, then I will respond very quickly." (patient 1)
Response categories	15 (22.4)	Q: "Can you explain recovering and recovered with sequelae?" A: "Recovering is the tingling in my hand that decreases, recovered with sequelae is that I still have a headache." (patient 1) Q: "But doesn't that mean that you are not recovered at all?" A: "Oh my, I actually read to fast, when I read it again, I will give a different answer." (patient 1)
Logical/Structural	5 (7.5)	Q: "Do the examples cover the definition of a medical professional?" A: "About the examination, uh, no because on Friday I arrived in the hospital and I went here unprepared." (patient 1)

Q = Question by the interviewer, A = Answer by the interviewee

Of the second version, with 25 main questions, we left eleven unchanged, removed eight questions (because they were difficult to interpret by patients and on closer inspection were not considered necessary), revised five questions or answer options to improve clarity, combined one question with another, and added two new questions. The results of the cognitive interviews resulted in a third version of the questionnaire (Figure 3.1) with a total of 18 questions. We converted this third version of the questionnaire to a web-based questionnaire.

Next, five of the six members of the expert panel evaluated the web-based version of the questionnaire and made 66 comments. The most mentioned points were aspects about spelling, layout, or accompanying texts. One term was simplified (i.e., 'medical professional' to 'caregiver') and we changed the wording of two questions. The final questionnaire (Figure 3.1) contained 18 main questions in seven sections and twelve additional questions (Supplementary material 1), and the expert panel considered it suitable for further testing in patients. An English translation of the questions in this questionnaire is presented in table 3.2. All questions removed

during the content validation as well as an English translation can be found in supplementary material 2.

Table 3.2 *Questions of the questionnaire*

Part	Section	No.	Questions
Main questions	Patient characteristics	1	What is your gender?
		2	What is your date of birth?
		3	What is your weight (kg)?
		4	What is your height (cm)?
		5	What is your highest level of education?
		6	Do you use drugs from the drugstore or self-care products?
	Health status	7	Questions about current health status (EQ-5D-3L)
	Past nuclear examinations	8	Have you previously undergone a nuclear medical examination?
			I. What type of nuclear examination has previously been performed on you?
			II. Have you experienced one or more side effects or physical changes that you relate to the nuclear examination immediately or within 7 days after this examination?
	Preparation for nuclear examination	9	What did you think of the patient information you received prior to the examination?
		10	Before the examination did you have to perform one or more of the preparatory actions mentioned?
	Administration of the radiopharmaceutical	11	What type of nuclear examination has been performed on you?
		12	Did you receive a radioactive substance during the examination?
			I. Did you notice a possible side effect or physical change shortly after administration of the radioactive substance?
		13	Did you receive an X-ray contrast agent during the study?
			I. Did you notice a possible side effect or physical change shortly after administration of the X-ray contrast agent?
		14	In your opinion, did unusual things happen during the investigation?
	Time after nuclear examination	15	Did you perform certain actions at home after the examination that were indicated from the hospital?
		16	Did you experience one or more side effects or physical changes within 7 days after the examination that you relate to the nuclear examination?
	Other comments	17	Do you have any comments on the complete nuclear examination?
		18	Do you have any further remarks?

Table 3.2 (Continued) Questions of the questionnaire

Part	Section	No.	Questions
Additional questions		a	With what type of nuclear examination did you notice a possible side effect or physical change? [*]
		b	On what date did the examination take place? [*]
		c	Can you briefly describe what happened? [†]
		d	How much time was there between administration of the drug and adverse event or change? [†]
		e	Have you informed your treating doctor/doctor or other healthcare provider? [‡]
		f	Did you report this adverse event or change to hospital staff? [¶]
		g	Was the adverse event or change treated? [†]
		h	Have you done something yourself to treat possible side effects or changes? [*]
		i	How are the possible side effects or changes at the moment? [†]
		j	Did you experience an adverse event before with an X-ray contrast agent? [#]
		k	Did the adverse event or change lead to: hospitalisation, a life-threatening situation, persistent work disability, or congenital defect? [*]
		l	In your opinion, are there other circumstances or causes that could have caused or worsened this potential side effect? [†]

^{*} Additional question when 8II answered confirmative. [†] Additional question when 8II, 12I, 13I, or 16 answered confirmative. [‡] Additional question when 8II or 16 answered confirmative. [¶] Additional question when 12I or 13I answered confirmative. [#] Additional question when 13I answered confirmative.

3.3.3 Phase 3: Testing of the questionnaire

During two months 650 patients received an invitation letter. Of those, 127 patients provided a valid written permission to participate in the test phase of the web-based questionnaire (Figure 3.2). Of these 127 patients receiving the questionnaire, 100 completed it (79%). This test population consisted of 53% men and 46% women. One patient (1%) indicated a different gender or did not want to specify gender. The median (interquartile range [IQR]) age was 64 (56–71) years old (Table 3.3). Radiopharmaceuticals most used were [^{99m}Tc]Tc-oxidronic acid, [^{99m}Tc]Tc-tetrofosmin, and [¹⁸F]fludeoxyglucose. Of the test population 88% of the patients reported no adverse events, and 12% reported one or more adverse events. Patients reporting no adverse event completed the questionnaire in a median time of 8 minutes (IQR 6–12), and patients who reported an adverse event needed 12 minutes

(IQR 9–16). In respect to the ability to answer the questions, two patients made two comments about the web-based questionnaire. One patient commented that she did not know her exact weight and made an estimation. Another patient indicated that she was not sure if a radiopharmaceutical was administered. All other patients stated they had no problem in answering the questions and understood all words.

Fig. 3.2 Inclusion process of patients in the test phase

Table 3.3 Characteristics of patients in the test phase

Characteristic	Patients (n = 100)
Gender	
Women, n	46 (46%)
Men, n	53 (53%)
Different/does not want to say, n	1 (1%)
Age (years), median (25 th –75 th percentile)	64 (56–71)
Weight (kg), median (25 th –75 th percentile)	80 (68–91)
Height (cm), median (25 th –75 th percentile)	176 (168–187)
Education*	
Early childhood education, n	2 (2%)
Primary education, n	5 (5%)
Lower secondary education, n	18 (18%)
Upper secondary education, n	9 (9%)
Post-secondary non-tertiary education, n	29 (29%)
Bachelor's degree or equivalent level, n	31 (31%)
Master's degree or equivalent level, n	6 (6%)
Patients using over-the-counter medicines, n	66 (66%)
EQ-5D (% of patients indicating a problem)	
Mobility	38%
Self-care	11%
Usual activities	50%
Pain/discomfort	68%
Anxiety/depression	24%
EQ-5D index value, median (25 th –75 th percentile)	0.81 (0.73–0.92) [†]
EQ-VAS, median (25 th –75 th percentile)	65 (50–80) [*]
First injection with radiopharmaceutical, n	64 (64%)
Radiopharmaceutical	
[^{99m} Tc]Tc-oxidronic acid	30 (30%)
[^{99m} Tc]Tc-tetrofosmin	25 (25%)
[¹⁸ F]fludeoxyglucose	24 (24%)
[¹⁸ F]fluorocholine	4 (4%)
[^{99m} Tc]Tc-nanocolloid	4 (4%)
[¹²³ I]sodium iodine capsule	2 (2%)
[^{99m} Tc]Tc-pertechnetate	2 (2%)
Other	9 (9%)
Patients reporting at least one adverse event	12 (12%)
Time to complete questionnaire (min), median (25 th –75 th percentile)	
For patients reporting no adverse events	8 (6–12)
For patients reporting adverse events	12 (9–16)

* According to International Standard Classification of Education (ISCED) 2011²¹. [†] Based on the Dutch algorithm for the EuroQol (EQ5D) scores; utility scores range from 0 (death) to 1 (full health). ^{*} Two patients indicated 0 and might not have been able to move the scale correctly. Abbreviation: VAS, Visual Analogue Scale.

In total, twelve patients reported 22 adverse events. Adverse events reported were: fatigue ($n = 7$), nausea ($n = 3$), abdominal discomfort ($n = 2$), chest discomfort ($n = 2$), feeling hot ($n = 2$), back pain ($n = 1$), dyspnoea ($n = 1$), limb discomfort ($n = 1$), pain in extremity ($n = 1$), paraesthesia ($n = 1$), and sense of oppression ($n = 1$). Patients reported fifteen adverse events to have occurred within one hour after administration of the radiopharmaceutical and reported the other seven adverse events to have occurred within seven days after leaving the nuclear department. Patients reported eight adverse events with [^{99m}Tc]Tc-tetrofosmin, two with [^{18}F]fludeoxyglucose, and other adverse events with [^{223}Ra]Ra-dichloride, [^{99m}Tc]Tc-exametazime-labelled cells, and [^{99m}Tc]Tc-oxidronic acid. We found one adverse event—backpain with [^{223}Ra]Ra-dichloride after 7 days—to be probable (Naranjo) and possible (Silberstein) causally related. The other 21 adverse events were possible (Naranjo) or unlikely (Silberstein) to be causally related. More detail on the adverse events of the radiopharmaceutical, and the causality assessment of the adverse events can be found in supplementary material 3.

3.4 DISCUSSION

In this study, a questionnaire to assess adverse events of radiopharmaceuticals from the perspective of the patient was developed, its content was validated, and initial testing was conducted. During the test phase, the questionnaire had good acceptability in patients. We found that the majority of the patients completed the questionnaire, that respondents completed the questionnaire in a reasonable time of 8 minutes for those not reporting an adverse event and 12 minutes for those reporting an adverse event, and that a vast majority of the patients indicated they had no problem in answering the questions and understood all words.

In the content validation part of our study, the expert panel and the cognitive interviews with patients identified several issues. This shows the importance of involving patients in the development of a questionnaire, as has been noted previously³⁶. During the content validation, we found that the difference between the radiopharmaceutical, the interventional drug, and contrast media is not always clear to patients. After improving the questionnaire by clarifying the questions and putting

the questions in a clear order, this issue did not occur again. However, this aspect might not be completely elucidated, and further research could reveal more detail about the reasons why patients do not always know the difference between the different pharmaceuticals and whether specific information to the patients could improve this understanding.

In the test phase of our study 12% of the patients reported an adverse event of radiopharmaceuticals—with only one adverse event assessed to have a higher causal relationship. This frequency seems to be higher than the number observed in a previous study about radiopharmaceuticals in which one out of 55 patients (1.8%) reported three adverse reactions¹⁸. However, that study involved only one specific radiopharmaceutical which was not used in our study. Further research in a larger group of patients is needed to establish more insight into the frequency and types of adverse effects in nuclear medicine.

We performed a causality assessment using two algorithms and found that the categories of the two algorithms differ. For example: we found one adverse event to be probable (Naranjo) and possible (Silberstein) causally related. This difference is inherent to the setup of each of the algorithms. Naranjo's algorithm uses ten questions with a scoring system assigning causality on the basis of a total score in categories 'definite', 'probable', 'possible', or 'doubtful'. Whereas Silberstein's algorithm uses categories 'not related', 'unlikely', 'possible', or 'probable' with specific conditions to be met for each category. Also, Naranjo's algorithm includes questions on aspects such as re-challenge, reappearance of the reaction with placebo, drug detection in toxic concentrations, and response after dose adjustment which are less relevant for radiopharmaceuticals, and which are not included in Silberstein's algorithm. It might be worthwhile to compare both algorithms and examine the agreement and correlation of both methods in future research. In general, it should be noted that establishing a causal relationship between suspected drug and adverse event is difficult and that despite the fact that algorithms are often used in pharmacovigilance this cannot replace a thorough medical examination for an individual case.

Our questionnaire is a useful addition to the already existing questionnaires assessing adverse events for other types of drugs^{15–17} since it focuses on adverse

events of radiopharmaceuticals and includes aspects that are unique to the nuclear medicine examination. The questionnaire not only asks the patient about adverse events shortly after the examination but also has the possibility to ask about adverse events that occur later. The questionnaire includes relevant questions to support causality assessment. Although the design and validation of this questionnaire was done with a Dutch population with its specific cultural characteristics and in the Dutch language, we expect that the questionnaire is also useful in other populations or languages. However, validation of a translated version is required. Also, validation of the Dutch version has not ended, as it is a continuous process with, for instance, the possibility of changes in the interpretation of questions over time³⁷.

The strength of our study is the systematic development and validation of the questionnaire and the testing in a large number of patients. However, we must acknowledge several limitations of our study. One limitation is that we interviewed a limited number of six patients during the content validation. Although research indicates that a small group will reveal most critical problems³⁸, we cannot dismiss the possibility that a larger number of patients might have revealed additional issues. Another limitation is that data obtained in the test phase might be prone to bias³⁹. Of the patients initially invited, 15% completed the questionnaire, and we did not ask patients the reasons for not participating. Furthermore, the education of the population in the test phase seems somewhat higher (37% having a bachelor's degree, master's degree, or equivalent level) in comparison with the general population (30% having a bachelor's degree, master's degree, or equivalent level⁴⁰). Because of the choice to use a web-based questionnaire, some patients may not have been able to participate. On the other hand, Internet access is rapidly increasing, which will enable more and more patients to participate in web-based questionnaires⁴¹.

3.5 CONCLUSION

We developed a questionnaire to be used for studies to assess adverse events of radiopharmaceuticals from the perspective of the patient. After extensive validation and testing by experts and patients, this questionnaire proved to be suitable and valid. Researchers could use the questionnaire in further studies to learn more about adverse events of radiopharmaceuticals in a larger population and this could be helpful for identifying potential adverse events of new radiopharmaceuticals.

3

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Chapter 4

Patient-reported adverse events of radiopharmaceuticals: a prospective study of 1,002 patients

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ABSTRACT

Introduction: Adverse events of radiopharmaceuticals may be underreported or remain undetected. Patients can provide information about these adverse events to enable health care professionals to detect, understand, and manage them more efficiently.

Objective: In this study, we aimed to (a) determine the type, causality, and frequency of patient-reported adverse events of radiopharmaceuticals and to (b) assess the onset, outcome, and follow-up of these adverse events from the patient's perspective.

Methods: We performed a prospective cohort study of 1,002 patients who underwent a nuclear medicine examination. Using a validated questionnaire, we collected patient-reported information on adverse events that occurred immediately after administration of the radiopharmaceutical as well as those that occurred later. Adverse events were analysed, coded and assessed for causality by two independent researchers.

Results: A total of 187 (18.7%) patients reported 379 adverse events. Most patient-reported adverse events of radiopharmaceuticals belonged to the 'general disorder and administration site conditions' (42.0%) and 'nervous system disorders' (16.9%) system organ classes. Of the patient-reported adverse events, 43.0% were possibly or probably causally related to radiopharmaceuticals. We found the frequency of patient-reported adverse drug reactions to diagnostic radiopharmaceuticals to be 2.8%. No important medical events were related to the administrations of diagnostic radiopharmaceuticals. Most adverse events (80.0%) occurred shortly after administration of the radiopharmaceutical and were resolved within a few hours. Some events (20.0%) emerged after patients had left the nuclear medicine department, took longer to resolve, and sometimes prompted the patient to consult a health care professional.

Conclusion: Adverse reactions to diagnostic radiopharmaceuticals can occur, and the frequency reported by patients was found to be 2.8%, which is higher than reported in the existing literature. We hope that the results of this study increase awareness of these adverse reactions among patients and health care professionals.

4.1 INTRODUCTION

Radiopharmaceuticals are essential for medical imaging and therapy in nuclear medicine. Adverse events with the use of radiopharmaceuticals can occur, although it is assumed in literature that they are rare in comparison with other pharmaceuticals. This can be attributed to a low dose—mostly in the order of micrograms—and the absence of pharmacologic effects for most radiopharmaceuticals. Furthermore, radiopharmaceuticals are used infrequently in individual patients with a short duration of use, often only being administered once or a small number of times in a lifetime^{1–3}. Several studies have been performed to determine the frequency of adverse events in radiopharmaceuticals. Recently, in a systematic review, we reported a median frequency of 1.63 adverse events per 100,000 administrations based on 22 studies of diagnostic radiopharmaceuticals⁴. However, most of these studies retrieved their data from voluntary reports of adverse events from hospitals or pharmacovigilance centres.

Due to underreporting, which is inherent to voluntary reporting, an underestimation of the true frequency of adverse events in radiopharmaceuticals may occur^{4–6}. Reasons for the underreporting of adverse events have been well-described for other drugs and include aspects such as the reporter's lack of time, unclear causal relationships with the drug, uncertainty about the way to report, and inadequate awareness of the benefits of reporting^{7,8}. Adverse events that occur after the use of radiopharmaceuticals may also remain undetected because such events may occur after the patient has left the nuclear medicine department and there is usually no follow-up contact between this department and the patient.

Besides reports by health care professionals, patients themselves are a valuable source of information and there is a growing interest in patient-reported data concerning adverse events^{9,10}. In comparison to health care professionals, patients tend to report different adverse events, including those that were previously unknown, and they also provide detailed accounts of known adverse events, including adverse changes in quality of life^{11–15}. Furthermore, patients are able to disclose adverse events that occur with a later onset, which is useful to detect adverse events that occur after the patient has left the nuclear medicine department.

Nevertheless, studies on the adverse events of radiopharmaceuticals from the perspective of the patient are scarce. To the best of our knowledge, only one study has assessed adverse events in radiopharmaceuticals from the perspective of the patient and described one patient who reported mild adverse events among 55 patients who received [^{99m}Tc]Tc-medronic acid¹⁶.

Knowledge about the true frequency of the occurrence of adverse events associated with the use of radiopharmaceuticals is limited but is needed to enable health care professionals to detect, understand, and manage the adverse events of radiopharmaceuticals efficiently. The current way of collecting safety data may provide us with information on possible safety signals but cannot provide more detailed knowledge of the frequency and impact on the patient of the adverse events of radiopharmaceuticals. For this reason, we recently developed, validated, and tested a questionnaire specifically designed to assess the adverse events of radiopharmaceuticals from the perspective of the patient¹⁷. This validated questionnaire was used to perform a study on a large group of patients who underwent a nuclear medicine examination, focusing especially on adverse events from the perspective of the patients.

The aim of this study was to (a) determine the type, causality, and frequency of patient-reported adverse events of radiopharmaceuticals and to (b) assess the onset, outcome, and follow-up of these adverse events from the patient's perspective. Additionally, we compared the characteristics of the group that did not report adverse events with the group that did.

4.2 METHODS

4.2.1 Study design

We performed a prospective cohort study in patients undergoing a nuclear medicine examination at the Isala Hospital in Zwolle, a 1,103-bed regional hospital in the Netherlands. Data were collected from November 2016 to November 2018. We obtained ethical exemption in writing from the Medical Ethics Committee of the Isala Hospital in Zwolle in the Netherlands (Reference number 16.08138), as this

study did not require formal approval according to Dutch law. All patients gave their approval for the use of their data for this evaluation in agreement with Dutch privacy laws.

4.2.2 Patients

We invited patients who were scheduled for a nuclear medicine examination at the Isala Hospital to participate in this study. Patients received information by letter about the study two weeks before their visit to the nuclear medicine department. We informed patients in general terms that we intended to study their experience with the nuclear medicine examination, and we did not explicitly state the aim of the questionnaire. This approach will limit a social desirability bias, whereby patients would report adverse events in the direction of the perceived aim of the study. Patients could volunteer to participate on the day of their visit to the nuclear medicine department before their examination, and we did not ask patients about their reasons for not participating to avoid placing an additional burden on patients and staff. There were no non-participating patients who still participated after their examination. Patients who underwent a nuclear medicine examination and gave their signed approval for the use of their data for this study were included. Patients were excluded when data were missing that were required to initiate the web-based questionnaire, such as email address or date of birth, or when no radiopharmaceutical was used.

4.2.3 Data collection

We used the questionnaire that we had developed, validated, and tested in our previous work¹⁷. The questionnaire in Dutch and an English translation can be found in supplementary material 1. Participants in the present study received a link to the web-based questionnaire (Researchmanager®; ¹⁸) seven days after their nuclear medicine examination. We sent a reminder after another seven days in case patients had not completed the questionnaire, but access to the questionnaire was limited to 21 days after the nuclear medicine examination. These timespans were chosen for two reasons. First, we would expect possible adverse events to occur within a few

days after the nuclear medicine examination. Second, longer recall periods may introduce bias due to patients forgetting information or patients bringing up information from other sequential doctor visits or examinations^{4,17}. In the questionnaire, we collected data from the patients about several aspects of their characteristics, health status, and occurrence of adverse events at several moments, as well as additional aspects when patients reported an adverse event (Table 4.1). We did not collect specific patient identifiers (such as their name and contact details) and there was also no need to contact patients for further clarification of the data collected. For each patient we added to the data the name of the radiopharmaceutical used and the radioactivity (in megabecquerel) obtained from the medical record system (Eridanos version 7.78, IC2it).

Table 4.1 *Aspects on which data were collected using the questionnaire*

Category	Aspects
Patient characteristics	Gender
	Age
	Weight (kg)
	Height (cm)
	Use of over-the-counter medicines
Health status	Health status using the EuroQol-5-dimensions-3 levels (EQ-5D-3L) questionnaire ^{19, 20}
Occurrence of adverse events	Adverse events during past nuclear examinations
	Adverse events after administration of the radiopharmaceutical
	Adverse events within one week after leaving the nuclear medicine department
Additional data when patients reported adverse events	Symptoms
	Time of onset
	Recovery status of the patient
	Time of recovery
	Contact with a health care professional
	Treatment of the adverse events

4.2.4 Data classification

After obtaining the data with the questionnaire, we standardised the names of the radiopharmaceuticals according to the Anatomical Therapeutic Chemical (ATC) classification system²¹ and applying the International Consensus Radiochemistry Nomenclature Guidelines²². Adverse events reported by patients were manually

coded using terminology from the Medical Dictionary for Regulatory Activities (MedDRA®) version 21.1²³. MedDRA® is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This terminology contains terms on five hierarchical levels: lowest level terms, preferred terms, high-level terms, high-level group terms, and system organ classes. The lowest level terms are connected in meaning to preferred terms, which represent unique medical concepts and can, therefore, be used for data representation. Although the preferred terms can be connected in meaning to multiple system organ classes, a primary system organ class is always allocated to the preferred term in the MedDRA® terminology. In our study, we used both the preferred terms and the corresponding primary system organ classes in our coding. With respect to the type of adverse events, we also screened for important medical events using the important medical event terms list drafted by the EudraVigilance Expert Working Group²⁴. This list contains the preferred terms that are considered to be important by the European Medicines Agency, which comprise occurrences that may result in death, that are life-threatening, require hospitalisation, result in disability, or are congenital defects. In other words, important medical events are those that may jeopardise the patient or require intervention to prevent a serious adverse event²⁵.

To assess the causal relationship between the radiopharmaceuticals and the adverse events, we used the algorithm of Silberstein³, which was specifically developed to determine the likelihood of whether an adverse event is related to a radiopharmaceutical. Silberstein's algorithm comprises four categories of causality: not related, unlikely, possible, and probable. Each category has several criteria based on aspects such as time sequence, response pattern to the suspected test material, and rechallenge. For the causality assessment, we used data obtained through the questionnaire on adverse events' time of onset, the occurrence of adverse events during previous nuclear medicine examinations, the recovery status of the patient, and other possible causes of adverse events, such as the administration of interventional agents or as indicated by the patient. To determine whether previous conclusive reports had been made about the reported event or whether it was a known

response pattern, we used data from our previously published systematic review of the literature⁴ and the summaries of product characteristics (SmPCs).

To ensure clarity, adverse events with a possible or probable proven relationship (as determined with the algorithm of Silberstein) were further defined as adverse drug reactions (ADRs) as specified by the World Health Organization (WHO): ‘a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function’^{26, 27}.

Two researchers (N.J. and N.S.) independently conducted extraction, coding into MedDRA® terms, screening for important medical events, and causality assessment. When the syntheses of the results were not in agreement, the results were discussed with a third researcher (E.v.P.) to resolve discrepancies.

4.2.5 Data analysis

We used SPSS Statistics version 26 (IBM) to compare the characteristics of the group that did not report adverse events with those of the group that did. We determined the normality of the continuous data using the Shapiro-Wilk test in combination with the normal Q-Q plots. When normally distributed, data were compared using the independent t-test, or when they were not normally distributed, the Mann-Whitney U-test was used. For the nominal data of the characteristics, we used the Chi-square test or Fisher’s exact test when the numbers were small. For all analyses, *p*-values of <0.05 were considered to be statistically significant. The other results were analysed descriptively using Microsoft Excel version 1808.

4.3 RESULTS

4.3.1 Patient characteristics

Out of the total 5,497 patients invited, 1,535 (27.9%) patients were considered for inclusion in this study. After excluding patients with no email address (*n* = 74), patients who were not retrieved from the medical record system (*n* = 3), and patients with a missing date of birth (*n* = 1), we sent out questionnaires to 1,457 patients. Of

these patients, 1,147 (78.7%) completed the questionnaire. We excluded 145 patients as they did not use a radiopharmaceutical; some scans at the nuclear medicine department only made use of the computed tomography (CT) modality of the scanning equipment. This resulted in 1,002 patients with questionnaires that were included (Figure 4.1). The median age of the group of patients was 66 years (IQR 57–72), with men (52.7%) and women (47.3%) almost equally represented (Table 4.2). The most commonly used radiopharmaceuticals were [^{99m}Tc]Tc-oxidronic acid ($n = 307$, 30.6%), [^{99m}Tc]Tc-tetrofosmin ($n = 253$, 25.3%), [^{18}F]fludeoxyglucose ($n = 159$, 15.9%) and [^{82}Rb]Rb-chloride ($n = 119$, 11.9%; Table 4.3).

Fig. 4.1 Inclusion process of patients

Table 4.2 Characteristics of patients in the study (n = 1,002)

	Total (n = 1002)	Did not report adverse event (n = 815)	Reported adverse event (n = 187)	p-value
Gender				
Women, n (%)	474 (47.3)	371 (45.5)	103 (55.1)	0.018
Men, n (%)	528 (52.7)	444 (54.5)	84 (44.9)	
Age (years), median (25th–75th percentile)	66 (57–72)	66 (57–72)	62 (53–70)	0.005
Body mass index (kg/m ²), median (25th–75th percentile)	26.6 (24.2–29.8)	26.5 (24.1–29.6)	27.1 (24.7–31.0)	0.042
Use of over-the-counter medicines				
Yes, n (%)	622 (62.1)	502 (61.6)	120 (64.2)	0.513
No, n (%)	380 (37.9)	313 (38.4)	67 (35.8)	
EQ-5D				
EQ-5D index value, median (25th–75th percentile)*	0.811 (0.737–1)	0.811 (0.737–1)	0.811 (0.773–1)	0.839
EQ VAS, median (25th–75th percentile)	70 (50–81)	70 (50–81)	71 (52–80)	0.818
Past nuclear medicine examination				
Yes, n (%)	497 (49.6)	427 (52.4)	70 (37.4)	0.001
No, n (%)	499 (49.8)	382 (46.9)	117 (62.6)	
Do not know, n (%)	6 (0.6)	6 (0.7)	0 (0)	

*Based on the Dutch algorithm for the EuroQol (EQ5D) scores; utility scores range from 0 (death) to 1 (full health)^{19, 20}. Abbreviation: VAS, Visual Analogue Scale.

4.3.2 Patient-reported adverse events

Of the 1,002 patients surveyed, 187 (18.7%) reported 379 adverse events, with an average of 2.0 adverse events per patient. In the group that reported adverse events, there were significantly more women (55.1% versus 45.5%; p -value: 0.018), patients were younger (62 years old versus 66 years old; p -value: 0.005), had a higher BMI (27.1 kg/m² versus 26.5 kg/m²; p -value: 0.042), and indicated more often that they had not had a nuclear medicine examination in the past (62.2% versus 46.9%; p -value: 0.001) than in the group that did not report adverse events. None of the other characteristics of the patients differed between the two groups (Table 4.2).

Of the patients who reported adverse events, 153 reported that 303 (80.0%) adverse events occurred shortly after the administration of the radiopharmaceutical and 51 patients reported that 76 (20.0%) adverse events occurred within one week after leaving the nuclear medicine department. We found that 58.9% of the patient-reported adverse events were related to two system organ classes (Figure 4.2): ‘general disorders and administration site conditions’ (42.0%) and ‘nervous system disorders’ (16.9%). The five most-frequently reported adverse events were a hot feeling ($n = 47$), a sense of oppressed breathing ($n = 26$), chest discomfort ($n = 24$), headache ($n = 20$), and fatigue ($n = 18$).

Of the patient-reported adverse events, 163 (43.0%) in 96 patients were determined to be possibly ($n = 123$; 32.5%) or probably ($n = 40$; 10.6%) causally related and further determined as adverse drug reactions. Another 216 (57.0%) patient-reported adverse events in 91 patients were determined to be unrelated ($n = 177$; 46.7%) or unlikely to be related ($n = 39$; 10.3%; Table 4.3). Of the 163 patient-reported adverse drug reactions, 11 adverse drug reactions in four patients were related to two therapeutic radiopharmaceuticals ([²²³Ra]Ra-dichloride and [¹³¹I]sodium iodine) and 152 adverse drug reactions in 92 patients were related to diagnostic radiopharmaceuticals (Table 4.3). Of patients injected with [^{99m}Tc]Tc-tetrofosmin, 119 adverse drug reactions in 71 patients were attributed to adenosine, which is used as a stressing agent with myocardial perfusion imaging²⁸. Of these 71 patients, seven patients reported both adverse drug reactions mentioned in SmPC of adenosine and those not mentioned in the SmPC of adenosine.

Fig. 4.2 The proportion of adverse events (AEs) of radiopharmaceuticals categorised per MedDRA® system organ class after administration of the radiopharmaceutical and within one week after leaving the nuclear medicine department

Table 4.3 Frequency of adverse drug reactions to radiopharmaceuticals as reported by patients

Diagnostic or therapeutic	Radiopharmaceutical	Dose, median in MBq (range)	Patients, n	Adverse events per Silberstein category, n	Patients with adverse drug reaction, n	Frequency, %	Adverse events per Silberstein category			
							Not related	Unlikely	Possible	Probable
Diagnostic	[^{99m} Tc]Tc-oxidronic acid	700 (189–749)	307	17	6	5	9	12		3.9
	[^{99m} Tc]Tc-tetrofosmin	186 (135–700)	253	72	16	114	13	8*		3.2*
	[¹⁸ F]fluorodeoxyglucose	342 (185–500)	159	10	5	2	2	4		2.5
	[⁸² Rb]Rb-chloride	1480 (1138–1480)	119	65	8	0	0	0		0.0
	[^{99m} Tc]Tc-pertechnetate	800	40	1	0	0	0	0		0.0
	[^{99m} Tc]Tc-meritide	100	26	4	1	0	0	0		0.0
	[¹²³ I]sodium iodine (capsule)	19 (18–22)	22	0	1	0	4	2		9.1
	[^{99m} Tc]Tc-nanocolloid	40 (20–120)	13	0	1	0	0	0		0.0
	[¹²³ I]ioflupane	185 (185–252)	12	0	0	0	0	0		0.0
	[^{99m} Tc]Tc-macrosalb	150	12	0	0	0	0	0		0.0
	[¹⁸ F]fluorocholine	250 (118–250)	9	0	0	0	0	0		0.0
	[⁶⁸ Ga]Ga-edotreotide (DOTA-TOC)	150 (100–150)	8	2	0	0	0	0		0.0
	[^{99m} Tc]Tc-sestamibi	550	4	0	0	0	1	1		25.0
	[¹⁸ F]fluciclovine	307 (242–371)	2	0	0	0	0	0		0.0
	[¹²⁴ I]sodium iodine	74	2	0	1	0	2	1		50.0
	[^{99m} Tc]Tc-exametazime (blood)	500	2	0	0	0	0	0		0.0
	[^{99m} Tc]Tc-succimer	150	1	0	0	0	0	0		0.0
Therapeutic	[¹¹¹ In]In-pentetreotide	200	1	0	0	0	0	0		0.0
	[¹²³ I]Iobenguane	300	1	0	0	0	0	0		0.0
	Subtotal		993	171	39	121	31	28		2.8
Therapeutic	[²²³ Ra]Ra-dichloride	5.0 (4.4–5.8)	7	1	0	2	7	3		42.9
	[¹³¹ I]sodium iodine (capsule)	924 (800–1048)	2	5	0	0	2	1		50.0
Total			1002	177	39	123	40			

* Adverse drug reactions excluding those mentioned in the SmPC of adenosine²⁸.

Table 4.4 Overview of adverse drug reactions coded according to MedDRA® per radiopharmaceutical

Radiopharmaceutical	Total number of patients	Adverse drug reactions (n when > 1)	Total number of ADRs
[¹⁸ F]fludeoxyglucose	4	After administration of the radiopharmaceutical: Discomfort, Dysgeusia Within one week after leaving the nuclear medicine department: Fatigue, Headache	2 2
[¹²³ I]sodium iodine (capsule)	2	After administration of the radiopharmaceutical: Thyroid pain Within one week after leaving the nuclear medicine department: Feeling cold, Malaise, Nausea	1 3
[¹²⁴ I]sodium iodine	1	After administration of the radiopharmaceutical: Salivary gland pain Within one week after leaving the nuclear medicine department: Vomiting	1 1
[¹³¹ I]sodium iodine (capsule)	1	After administration of the radiopharmaceutical: NA	0
[^{99m} Tc]Tc-oxidronic acid	12	Within one week after leaving the nuclear medicine department: Dysgeusia, Scar pain After administration of the radiopharmaceutical: Headache (2), Arthralgia, Chest discomfort, Dysgeusia, Dyspnoea, Feeling cold, Limb discomfort, Nausea, Presyncope, Sense of oppression Within one week after leaving the nuclear medicine department: Headache, Nasal pruritus, Pruritus generalised	2 11 3
[²²³ Ra]Ra-dichloride	3	After administration of the radiopharmaceutical: Arthralgia, Musculoskeletal chest pain, Musculoskeletal pain Within one week after leaving the nuclear medicine department: Fatigue (2), Diarrhoea, Headache, Listless, Musculoskeletal chest pain	3 6
[^{99m} Tc]Tc-sestamibi	1	After administration of the radiopharmaceutical: Rash macular Within one week after leaving the nuclear medicine department: NA	1 0
[^{99m} Tc]Tc-tetrofosmin (not mentioned in SmPC adenosine)	8*	After administration of the radiopharmaceutical: Abdominal pain (2), Abdominal pain upper, Hypoaesthesia, Lip swelling, Pallor, Throat irritation Within one week after leaving the nuclear medicine department: Pruritus	7 1
[^{99m} Tc]Tc-tetrofosmin (mentioned in SmPC adenosine ²⁵)	71*	After administration of the radiopharmaceutical: Feeling hot (29), Chest discomfort (16), Sense of oppression (11), Dyspnoea (8), Headache (8), Chest pain (6), Dizziness (3), Limb discomfort (3), Nausea (3), Flushing (2), Pain (2), Respiratory distress ¹ (2), Tachycardia (2), Vision blurred (2), Anxiety, Asthenia, Cardiac disorder, Dizziness postural, Dysgeusia, Hot flush, Feeling abnormal, Head discomfort, Hypertension, Musculoskeletal discomfort, Palpitations, Stress, Vomiting Within one week after leaving the nuclear medicine department: Headache (2), Chest discomfort, Chest pain, Dizziness, Nausea, Palpitations, Sense of oppression, Urticaria	110 9
TOTAL	96		163

*Seven patients reported both ADRs mentioned in the SmPC of adenosine and ADRs not mentioned in the SmPC of adenosine. The total number of patients who reported an ADR with [^{99m}Tc]Tc-tetrofosmin was 72. ¹Important medical event²⁴.

After excluding patients with adverse drug reactions that were related to adenosine, the frequency of patients with adverse drug reactions related to diagnostic radiopharmaceuticals became 2.8% (28/993; Table 4.3).

The diagnostic radiopharmaceuticals that were most-frequently associated with patient-reported adverse drug reactions were [^{99m}Tc]Tc-tetrofosmin and [^{99m}Tc]Tc-oxidronic acid (Table 4.3). A detailed overview of adverse drug reactions in which standardised terminology according to MedDRA[®] is used for all radiopharmaceuticals can be found in Table 4.4. Two reactions in two patients were considered to be important medical events. These two events were respiratory distress with myocardial perfusion imaging using [^{99m}Tc]Tc-tetrofosmin and adenosine, and were considered to be related to the use of adenosine. Both of these patients reported this to the hospital staff. One of the patients was reassured by the hospital staff and was given instructions for relaxation. He recovered within two minutes. The other patient indicated that she was not treated by the hospital staff and recovered within 10 minutes. When excluding these two patients with an important medical event related to adenosine, no important medical events were related to the administration of diagnostic radiopharmaceuticals (0.0%; 0/993).

4.3.3 Onset, outcome and follow-up of adverse events from the patient's perspective

Among the patients who reported an adverse event that occurred after the administration of the radiopharmaceuticals, 143 patients reported that the onset of the adverse events was shortly after administration with a median time of one minute after administration (interquartile range [IQR]: 0.1–5 minutes). Of the group of patients who reported an adverse event that occurred after the administration of the radiopharmaceuticals, 138 (90.2%) made a full recovery and the median time to recover was 15 minutes (IQR: 2–120 minutes). Twelve patients (7.8%) indicated that they partly recovered and three patients (2.0%) had not yet recovered at the time of the last notification of their status. The adverse events of the patients who reported not to have recovered were found to be unrelated or unlikely to be related to the radiopharmaceutical. The patients reported the adverse events to the hospital staff in

77.1% of cases and indicated that in 8.5% of the cases, they received treatment (Table 4.5).

Table 4.5 Outcome and follow-up of adverse events of radiopharmaceuticals from the perspective of the patient

Time of occurrence	Aspect		Number of patients (%)
After administration of the radiopharmaceutical	Time of onset, median (25th–75th percentile)	1 minute (0.1*–5)	143
		Unknown	10
	Patient status	Fully recovered	138 (90.2)
		Partly recovered	12 (7.8)
		Not yet recovered	3 (2.0)
	Time to recover, median (25th–75th percentile)	15 minutes (2–120)	136
		Unknown	2
	Health care professional contacted	Hospital staff	118 (77.1)
		None	35 (22.9)
Within one week after leaving the nuclear medicine department	Was AE treated?	Yes	13 (8.5)
		No	140 (91.5)
	Time of onset, median (25th–75th percentile)	22 hours (4–39)	48
		Unknown	3
	Status patient	Fully recovered	31 (60.8)
		Partly recovered	12 (23.5)
		Not yet recovered	8 (15.7)
	Time to recover, median (25th–75th percentile)	2 days (1–3)	31
		Unknown	0
	Health care professional contacted [†]	No health care professional	37 (72.5)
		General practitioner	8 (15.7)
		Referring physician hospital	6 (11.8)
		Nurse	4 (7.8)
		Pharmacist	3 (5.9)
		Nuclear medicine department	1 (2.0)
		Unknown	1 (2.0)
	Was AE treated?	Yes	5 (9.8)
		No	46 (90.2)

*Some patients indicated that the adverse event occurred directly or seconds after the injection. [†]Some patients contacted more than one health care professional.

Of the patients who reported an adverse event that occurred within one week after leaving the nuclear medicine department, 48 reported an onset of adverse events at a median time of 22 hours (IQR: 4–39) after administration. Of the group of patients who reported an adverse event that occurred within one week after leaving the nuclear medicine department, 60.8% made a full recovery and the median time to recover was two days (IQR: 1–3 days). Twelve patients (23.5%) indicated that

they had partly recovered and eight patients (15.7%) indicated that they had not yet recovered at the time of the last notification of their status. In four of the eight patients who had not recovered, the adverse events were found to be possibly or probably related to the radiopharmaceutical. One patient indicated at the time of the last notification that he still experienced diarrhoea and fatigue after the administration of [^{223}Ra]Ra-dichloride. One patient still suffered from musculoskeletal chest pain, listlessness, fatigue, and headache after the administration of [^{223}Ra]Ra-dichloride. One patient still had urticaria and pruritus after the administration of [$^{99\text{m}}\text{Tc}$]Tc-tetrofosmin. Finally, one patient still suffered from malaise, nausea, and a cold feeling after the administration of [^{123}I]sodium iodine. Other adverse events in patients who reported to have not recovered were found to be unlikely to be related or unrelated to the radiopharmaceutical. A majority of 72.5% of the patients did not contact a health care professional about the adverse event, and those who did mostly contacted the referring physician of the hospital or their general practitioner. Of all patients reporting an adverse event that occurred within one week after leaving the nuclear medicine department, five patients (9.8%) indicated that they had been treated (Table 4.5).

4.4 DISCUSSION

In this study, we found that most patient-reported adverse events of radiopharmaceuticals belonged to the ‘general disorder and administration site conditions’ and ‘nervous system disorders’ system organ classes. Of the patient-reported adverse events, 43.0% were possibly or probably causally related to the radiopharmaceuticals. We found a frequency of patient-reported adverse drug reactions to diagnostic radiopharmaceuticals of 2.8%. No important medical events related to the administration of diagnostic radiopharmaceuticals were reported. Although two important medical events were attributed to the use of adenosine in myocardial perfusion imaging. Most adverse events (80.0%) of radiopharmaceuticals occurred shortly after the administration of the radiopharmaceutical, and most of these patients recovered (90.2%) quickly with a median time of 15 minutes (interquartile range [IQR]: 2–120 minutes).

We found the frequency of patient-reported adverse drug reactions to diagnostic radiopharmaceuticals to be much higher than the median frequency of 0.0016% that we identified in our literature review⁴, but it seems to correspond with one small study that assessed patient-reported adverse events in 55 patients who received the radiopharmaceutical [^{99m}Tc]Tc-medronic acid, in which a frequency of 1.8% was reported¹⁶. Our findings suggest underreporting of adverse events of radiopharmaceuticals in the literature. Such underreporting of adverse events is well known for other drugs, where a median underreporting rate as high as 94% has been identified⁷. Further research could determine the reasons for the underreporting of adverse events of radiopharmaceuticals and may identify possible areas for improvement in reporting.

The proportion of serious adverse drug reactions that we found in this study was lower than in our previously published systematic review of the literature⁴. Furthermore, there was a difference in the type of adverse events reported. Most of the reported adverse events in our study were ‘general disorders and administration site conditions’ (e.g., a hot feeling, a sense of oppressed breathing, chest discomfort, and fatigue), and ‘nervous system disorders’ (e.g., headache), while in our previously published systematic review of the literature, we found that most reported adverse events were ‘skin and subcutaneous tissue disorders’ (e.g., rash and pruritus), and ‘general disorders and administration site conditions’ (e.g., fever;⁴). From these results, it seems that patients tend to report different adverse events to health care professionals, which is in line with studies of other drugs²⁹.

This study focused on adverse events from the perspective of the patient. We are not aware of other large studies with this focus. Regarding the follow-up of adverse events, patients who experienced an adverse event of a radiopharmaceutical shortly after administration reported this event to the hospital staff in most cases (77.1%). This result is as expected, as patients are under close surveillance by the hospital staff at the nuclear medicine department, such as nuclear medicine technologists. As the hospital staff are likely the first to register an adverse event, they must be aware of this and be prepared to manage such events. Patients who experience an adverse event of a radiopharmaceutical after leaving the nuclear medicine department do not

usually contact the nuclear medicine staff but may report to their family physician or other.

We believe that our study contributes to the area of drug safety of radiopharmaceuticals, in which little research has been conducted. The strengths of our study are that we used a validated and tested questionnaire, as well as a large group of patients. Besides the frequency and type of patient-reported adverse events of radiopharmaceuticals, we studied the outcome and follow-up of these adverse events from the perspective of the patient, which, according to our knowledge, has not been studied before.

A point of attention is that in this study, we focused specifically on adverse events from the perspective of the patient. Although we used a validated and tested questionnaire, one can argue that patients may not be regarded as able to discriminate effectivity between symptoms attributed to the radiopharmaceutical, the disease, or the nuclear medicine examination. Nevertheless, the results of our study are of value to health care professionals, as they illustrate the way that patients experience radiopharmaceuticals. Other studies have shown that patients are interested in their own illnesses and treatment and that both they and health care professionals report adverse events. Importantly, patient-reported adverse events do not replace the information obtained from the health care professional but are a useful complementation^{30–32}. Indeed, the results of our study demonstrate that patients report different adverse events and provide more detail on their experiences with these events in comparison with health care professionals.

A general limitation of studies using a questionnaire is the representativeness of the responders. Even though 1,002 patients participated in this study, this was 18.2% of the 5,497 patients approached. A potential for selection bias may exist and limits the applicability to a larger population. However, the age, gender ratio, and distribution of different types of nuclear medicine procedures of our population corresponds with the Dutch population undergoing a nuclear medicine examination as presented in two older studies^{33, 34}. Furthermore, sending the questionnaire seven days after the nuclear medicine examination may have led to underreporting or overreporting of adverse events or have affected the accuracy of reporting due to possible recall bias. Another limitation of this study is that we could not validate the

exact times of the onset and recovery of the patients. The values presented in table 4.5 are times according to the perception of the patients and might not correspond with actual times. However, these times were adequate to perform the causality assessment. Another study might include a quantitative approach to measure actual times. In addition, although we calculated a frequency, we did not control for confounding. Creating a control group could have been an option but this would have involved difficult practical and ethical aspects.

Using Silberstein's algorithm together with the data that we obtained with the questionnaire, we were able to successfully conduct the causality assessment and establish that 43% of the patient-reported adverse events were possibly or probably related to radiopharmaceuticals. However, the assessment with Silberstein's algorithm has two potential limitations that must be considered. One limitation is that only adverse events with a known response pattern are classified as possibly or probably related, leading to an exclusion of new adverse events. A sub-analysis of our data revealed that the classification would change from unlikely related to possibly or probably related for only five adverse events (paraesthesia with [^{18}F]fludeoxyglucose; chromaturia, thirst, and feeling cold with [$^{99\text{m}}\text{Tc}$]Tc-oxidronic acid; ageusia with [^{123}I]sodium iodine), which we considered to be acceptable. Another limitation is the inability of the algorithm to distinguish between adverse events due to the radiopharmaceutical or interventional drugs, such as adenosine, in our study. Although we overcame this limitation in our study by excluding the adverse drug reactions attributed to adenosine, it may be necessary to update Silberstein's algorithm when using it in future research. In general, one should note that establishing a causal relationship between a suspected drug and an adverse event is difficult and that although algorithms are often used in pharmacovigilance, these cannot replace a thorough medical examination of an individual case.

The findings of this study have several practical implications. Our results imply that adverse events of radiopharmaceuticals as experienced by patients are more common than previously assumed and that nuclear medicine staff are likely to be the first to be informed about a potential adverse event. It is, therefore, important that the nuclear medicine staff are aware of potential adverse events and are prepared to counsel, respond, and manage these events. Furthermore, we suggest that nuclear

medicine staff consistently inform patients about the adverse events of radiopharmaceuticals. It has been supposed that well-informed patients may handle side effects better or may be less concerned about them than uninformed patients³⁵. Patients may be instructed what to do when they experience an adverse event after leaving the nuclear medicine department. One final practical implication is that other health care professionals, such as the referring physician of the hospital or a patient's general practitioner, should be aware that symptoms reported by a patient might be caused by a nuclear medicine examination, as they may be contacted by patients who are experiencing adverse events.

4.5 CONCLUSION

We studied the patient-reported adverse events of radiopharmaceuticals and found that most were 'general disorders and administration site conditions' and 'nervous system disorders'. The reported frequency of patient-reported adverse drug reactions to diagnostic radiopharmaceuticals was 2.8%, which is considerably higher than previously suggested. None of the adverse drug reactions related to the administration of a diagnostic radiopharmaceutical were considered to be an important medical event. Most events occurred shortly after the administration of the radiopharmaceutical and were resolved within a few hours, while 20% of the events occurred later, and these took longer to resolve. This study will hopefully increase awareness of adverse events to radiopharmaceuticals among patients and health care professionals.

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Chapter 5

Anaphylactic reaction to [^{99m}Tc]Tc-macrosalb

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ABSTRACT

A 49-year-old woman developed an anaphylactic reaction to [^{99m}Tc]Tc-macrosalb used for pulmonary scintigraphy. The patient received an intravenous injection of [^{99m}Tc]Tc-macrosalb 120 MBq, containing macroaggregates of human albumin 0.14 mg. Within 1 min she developed itching all over her body, an itching throat and dyspnoea. This was followed by urticaria and facial oedema. She was diagnosed with an anaphylactic shock. The patient received clemastine and prednisone, and fully recovered after release from the hospital. According to the Naranjo assessment algorithm, the relationship between the allergic reaction and the administration of [^{99m}Tc]Tc-macrosalb should be considered as ‘probable’.

5.1 INTRODUCTION

[^{99m}Tc]Tc-macrosalb (macro aggregated albumin; MAASOL®, the Netherlands) is a diagnostic radiopharmaceutical used in lung perfusion scans and venoscintigraphy. The radiopharmaceutical is reconstituted using a kit containing human serum albumin¹. Single or multiple injections with [^{99m}Tc]Tc-macrosalb may be associated with chest pains, rigor and collapse. The frequency of adverse drug reactions in the use of radiopharmaceuticals in general is low, according to the literature. It is generally assumed that the frequency ranges from 2.1 to 6 per 100,000 injections of radiopharmaceuticals^{2, 3}. Although it includes a warning about the possibility of hypersensitivity, according to the Summary of Product Characteristics the frequency of hypersensitivity reactions is not known.

We report a case of a suspected severe [^{99m}Tc]Tc-macrosalb-induced anaphylaxis. We also completed a literature search through PubMed and MEDLINE, without restrictions in language, applying no year limits and therefore extended as far back as the late 1940s. The search terminology included both index terms or free-text words: ‘radiopharmaceutical’ or ‘radioisotope’ combined with ‘adverse effects’, ‘adverse reactions’, ‘adverse events’, or ‘side effects’. A filter for the search was applied to exclude animal-only studies. The search was completed in July 2018.

Only three case reports describing an adverse event following the administration of [^{99m}Tc]Tc-macrosalb were found but did not include an allergic reaction^{4, 5, 6}. To the best of our knowledge, this is the first case report describing an anaphylactic reaction due to a [^{99m}Tc]Tc-macrosalb injection.

5.2 CASE PRESENTATION

A 49-year-old woman was referred for a lung perfusion scan because of a possible chronic thromboembolic pulmonary hypertension as a result of previous pulmonary embolism. The patient has a medical history of heterozygosity for the prothrombin gene, Hemolysis Elevated Liver enzymes and Low Platelet count (HELLP) syndrome, as well as having suffered a stroke during pregnancy, mastitis, melanoma, pneumonia and pulmonary embolism. The concomitant medication used was

rivaroxaban at 20 mg per day with a target international normalized ratio (INR) > 2.5 and oxycodone 5 mg when required for the relief of migraine attacks. As far as we know the patient did not use over-the-counter products at the time of this adverse event.

With an estimated weight of 70 kg and length of 160 cm, the patient received an intravenous injection of 120 MBq of [^{99m}Tc]Tc-macrosalb, containing 0.14 mg macroaggregates of human albumin, according to protocol. Within one minute after the injection she developed itching all over the body, including an itching throat and dyspnoea. Subsequently, within a period of five minutes, urticaria emerged. Fifteen minutes after the administration of [^{99m}Tc]Tc-macrosalb, the patient was transferred to the emergency room. Upon examination the patient had facial oedema, especially around the eyes. The left eye showed some redness and the patient still experienced slight dyspnoea. The emergency doctor diagnosed an anaphylactic reaction, without hemodynamic involvement. The patient was diagnosed with a type I allergic reaction. The patient received 2 mg of clemastine i.v. and 25 mg of prednisone i.v. Approximately two or three hours after administration of [^{99m}Tc]Tc-macrosalb the symptoms improved. The patient was released from the hospital upon recovery and was given 1 mg of clemastine twice daily when required. The patient was contacted a few days later, and a full recovery was confirmed.

The patient had experienced a similar reaction, approximately twenty years ago, to a combination of acetaminophen, propyphenazone and caffeine (Saridon®, the Netherlands), which was used to treat headache. Furthermore, she reported a similar reaction after an injection with a contrast medium used for a CT-scan some years before the reaction to Saridon®.

5.3 DISCUSSION

To establish the frequency of adverse events following [^{99m}Tc]Tc-macrosalb administration, we analyzed the number of doses dispensed (since 2011) at the Zwolle Radiopharmacy versus reported adverse events. Our data showed that this was a single reported case of anaphylaxis in 6778 doses dispensed for administration. This low frequency of adverse events is in line with what is described in the

literature⁷. Furthermore, there are not many studies on this subject. Nevertheless, adverse events with radiopharmaceuticals might be underreported^{7, 8}.

Several mammalian and avian serum albumins (SAs) are known allergens⁹, and a rare case of an allergic reaction to Technetium-Labelled Nanocolloidal Albumin for Sentinel Node Identification has been described¹⁰, but not for [^{99m}Tc]Tc-macrosalb. Although no laboratory tests were sent off for confirmation and a clinical rechallenge was not carried out, it is most likely that the anaphylaxis was induced by [^{99m}Tc]Tc-macrosalb, as the symptoms arose immediately following the injection. For this particular patient we could not determine a prior exposure to [^{99m}Tc]Tc-macrosalb, although this cannot be ruled out. None of the patient's current medication could account for these hypersensitivity symptoms.

The timing between administration of the drug and the start of the symptoms, as well as the fact that this adverse drug reaction is mentioned in the Summary of Product Characteristics (SmPC), is suggestive of a causal relation. We performed a causality assessment using the Naranjo algorithm. The Naranjo algorithm uses ten questions which are scored. The sum of the score gives an indication of probability¹¹. The results—using this causality assessment method—are presented in table 5.1. A Naranjo assessment score of 6 was obtained, indicating that the relationship between the allergic reaction and the administration of [^{99m}Tc]Tc-macrosalb should be considered as 'probable'. The outcome 'probable' was assigned since the allergic reaction reasonable related with time of onset of the reaction, improved after withdrawal of [^{99m}Tc]Tc-macrosalb and could not be ascribed to other characteristics of the patient.

The reaction could be caused by the active ingredient of [^{99m}Tc]Tc-macrosalb, namely macro-aggregates prepared from human serum albumin. Anaphylaxis has been described for human albumin used as volume substitutes^{12–14}. In one study an incidence of 0.011% was determined¹³. However, the amount of human albumin administered as volume substitutes is general much higher (in the order of whole grams) than the amount of [^{99m}Tc]Tc-macrosalb given (a fraction of a milligram). It could also be the case be that the one of the excipients of the formulation caused the reaction. As far as we know, the patient had not previously been exposed to [^{99m}Tc]Tc-macrosalb or to one to its excipients, which would have been required for

any prior sensitisation. Whether or not the anaphylaxis was caused by an allergic reaction or a non-immune mediated reaction is therefore not clear.

Table 5.1 Causality assessment of this case using Naranjo score¹¹

No.	Question	Yes	No	Do not know	Score in this patient
1.	Are there previous conclusive reports on this reaction?	+1	0	0	0
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4.	Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6.	Did the reaction reappear when a placebo was given	-1	+1	0	0
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8.	Was the reaction more severe when the dose was decreased?	+1	0	0	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure	+1	0	0	0
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total score					6

5.4 CONCLUSION

In conclusion, anaphylactoid reactions to [^{99m}Tc]Tc-macrosalb may occur. Although rare, the possibility of such a reaction must be anticipated. Healthcare professionals should check if a patient has had a previous severe reaction to [^{99m}Tc]Tc-macrosalb. Medical personnel should be prepared for these kind of reactions, and suitable protocols for managing and treating anaphylactoid reactions should be readily available.

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Chapter 6

Discontinuation of metformin to prevent metformin-induced high colonic FDG uptake: is 48 hours sufficient?

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ABSTRACT

Objective: In this retrospective, single-centre observational study, we investigated whether discontinuing metformin for at least 48 hours prevents metformin-induced [^{18}F]fludeoxyglucose (FDG) uptake in all segments of the colon.

Methods: Patients with type 2 diabetes who were using metformin before undergoing an FDG PET/CT scan were included. Two groups were created: patients who discontinued metformin for less than 48 hours (<48h group) and patients who discontinued metformin for between 48 and 72 hours ($\geq$ 48h group). A control group comprised non-diabetic patients who were not using metformin before undergoing an FDG PET/CT. We visually scored the uptake of FDG in four segments of the colon—the ascendens, transversum, descendens, and rectosigmoid—using a four-point scale (1–4) and considered scores of 3 or 4 to be clinically significant.

Results: Colonic FDG uptake in the $\geq$ 48h group ($n = 23$) was higher than uptake in the control group ($n = 96$) in the colon descendens (odds ratio [OR]: 14.0; 95% confidence interval [CI]: 4.8–40.9; p -value: 0.001) and rectosigmoid (OR: 11.3; 95% CI: 4.0–31.9; p -value: 0.001), and there was no difference in the colon ascendens and transversum. Colonic FDG uptake in the <48h group ($n = 25$) was higher than uptake in the $\geq$ 48h group ($n = 23$) in the colon transversum (OR: 4.8; 95% CI: 1.3–18.5; p -value: 0.022) and rectosigmoid (p -value: 0.023), and there was no difference in the colon ascendens and descendens.

Conclusions: Discontinuing metformin for 48 hours before undergoing an FDG PET/CT still gives a high uptake in the distal parts of the colon when compared with non-diabetic patients who are not using metformin. Discontinuing metformin for 48 hours seems to be useful for scanning the more proximal segments of the colon.

6.1 INTRODUCTION

[^{18}F]fludeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is used in oncology for diagnosis, staging, restaging, and the assessment of response to therapy¹. Several studies have found an increased FDG uptake—predominantly in the colon—in patients who are using metformin, an oral antidiabetic used in patients with diabetes mellitus type 2^{2–4}. Although FDG PET is not generally performed to study primary colorectal cancer, the increased uptake of FDG in the colon could still obscure lesions and significant findings may be missed. As it is estimated that the number of patients with diabetes mellitus will increase with an averaged annual growth of 2.7%⁵, nuclear medicine physicians will see more patients who are on metformin.

The guidelines of the European Association of Nuclear Medicine (EANM)⁶ recommend that patients continue to take antidiabetics around PET scanning. An exception is when PET scanning is combined with an intravenous contrast agent, in which case, metformin should be discontinued at the time of the procedure and 48 hours thereafter to prevent metformin-associated lactic acidosis. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) does not specify guidelines for PET procedures made in patients on oral antidiabetics⁷. However, several studies have suggested that metformin should be discontinued prior to the FDG PET scan^{2–4} and have recommended feasible and optimal discontinuation periods of metformin^{4, 8, 9} in order to limit the amount of FDG uptake. Even so, the results in these studies are contradictory. Studies by Oh et al. and Hamidizadeh et al. found that discontinuing metformin for 48 hours reduced the intestinal FDG uptake in comparison to the group that continued metformin^{4, 8}. Oh et al. concluded that discontinuing metformin 48 hours before an FDG PET scan is an effective preparation⁴. In contrast, a study performed by Lee et al. demonstrated that FDG uptake in the distal colon remained high even after metformin had been discontinued for over 48 hours⁹.

As there is currently no consensus on the time at which metformin should be discontinued, we aimed to determine whether a metformin discontinuing period of ≥ 48 hours is sufficient to prevent FDG uptake in all segments of the colon when

compared with a control group of non-diabetic patients who are not using metformin. In other words, does discontinuing metformin in patients make their colonic FDG uptake the same as can be expected in patients who are not taking this drug? In addition, we assessed whether colonic FDG uptake differs between patients who have discontinued taking metformin <48 hours before the procedure versus those who have discontinued ≥ 48 hours before.

6.2 METHODS

6.2.1 Study design and patients

We conducted a retrospective, single-center observational study between January 2018 and September 2018 in diabetic patients who had been using metformin before undergoing an FDG PET/CT scan in Isala hospital, Zwolle, a tertiary referral and a 1,103-bed regional hospital in the Netherlands. We compared this data with a control group of non-diabetic patients who had not been using metformin. As metformin is routinely discontinued in patients for 48 hours, we received ethical exemption in writing from the Medical Ethics Committee of the Isala hospital, in Zwolle in the Netherlands (Reference number 190701), as this study did not require formal approval according to Dutch law. However, all patients gave their approval for the use of their data for this evaluation, in agreement with Dutch privacy laws.

Diabetic patients who had been using metformin before undergoing an FDG PET/CT scan and gave approval for using their data for this study were included. We excluded patients with a known colonic malignancy or inflammatory bowel diseases in the medical records, patients who received PET scans that did not cover the abdomen, patients who had discontinued metformin for >72 hours, and cases with incomplete data, such as an unknown metformin discontinuation period or unknown metformin dosage. In patients who had received multiple scans within this period, only the first scan was analyzed. At the Isala hospital, Zwolle, patients who are using metformin are instructed to withhold metformin for 48 hours prior to a PET/CT scan as usual care, but in practice, discontinuation periods may vary. Based on the actual reported time of discontinuing metformin, we created two groups: patients who had

discontinued metformin for <48 hours (<48h group) and patients who had discontinued metformin for ≥ 48 to ≤ 72 hours (≥ 48 h group). Patients in the control group were selected from non-diabetic patients who had not been using metformin and underwent an FDG PET/CT on the same or next day as the metformin patients. For each patient who had been using metformin, we included two consecutive patients in the control group.

For each patient, we recorded the following characteristics: age, sex, body mass index (BMI; kg/m²), blood glucose level (mmol/L), and FDG dose (MBq/kg). In the metformin group, we also asked patients about their daily metformin dose, insulin usage, and their self-reported discontinuation period of metformin (in hours).

6.2.2 Patient preparation

All patients were instructed to fast for at least six hours and—if applicable—to withhold insulin prior to the FDG injection, according to standard protocol. Immediately before the FDG injection, patients' blood glucose levels were measured in capillary blood obtained from a finger-stick with an Accu-Chek glucometer (Roche diagnostics). When the patients' blood glucose reached a level that was higher than 15 mmol/L, the PET/CT scan was cancelled, and the patients were scheduled for another appointment with additional instructions or by emphasizing their adherence to the instructions, depending on the cause of the high blood glucose level prior to PET scanning.

6.2.3 PET/CT acquisition and reconstitution

PET/CT scans were acquired on a Vereos PET/CT (Philips Healthcare) or Ingenuity TF PET/CT (Philips Healthcare). The injected FDG activity (A , MBq) was based on the body weight of the patients (w , kg) and the acquisition time per bed position (t in seconds) using the following quadratic equation: $A = 5.2 w^2/t$ (MBq). Patients were scanned 60 minutes after FDG injection. Images were acquired over 10–16 bed positions—taking 72/144 seconds each—based on a scan from the crown to mid-thigh or the crown to the middle of the lower leg. PET data were reconstructed in a

144 x 144 matrix size with a voxel size of 4x4x4 mm³ (representing a default transaxial field of view of 576 mm), using a default 3D ordered-subset iterative time-of-flight (TOF) reconstruction technique (Vereos PET/CT reconstitution settings: 3 iterations, 15 subsets, and a 3 mm Gaussian post-smoothing filter; Ingenuity TF PET/CT reconstitution settings: 3 iterations, 43 subsets, and a relaxation parameter of 1.0), fulfilling EANM research Ltd (EARL) accreditation specifications¹⁰. A non-contrast CT scan that was used for attenuation correction was obtained using the following parameters: 120 kV, 40–200 mAs rotation time of 0.5 seconds, and 4mm slice thickness.

6.2.4 Data analysis

We randomized and anonymized the obtained PET scans through the use of specific settings of our picture archiving and communication (PACS) system (Sectra IDS7). This ensured that the researchers were blinded to the underlying study group conditions, such as the use of metformin. We visually analyzed the FDG uptake in the colon on dedicated workstations (Sectra IDS7). The following segments of the colon were investigated: the ascendens (from the cecum to the hepatic flexure), transversum (from the hepatic flexure to the splenic flexure), descendens (from the splenic flexure to the sigmoid colon), and rectosigmoid colon (from the sigmoid colon to the anus, excluding the rectal sphincter). The rectosigmoid colon was included because the presence of rectal cancer and thus uptake in the rectum is not unusual¹¹. The uptake in the rectal sphincter was excluded.

Two expert nuclear medicine physicians (B.V., P.J.) and one trained researcher (H.K.), who were blinded to the study group conditions, independently conducted the visual analysis. The four-point scale method of Gontier et al.² was used to score the uptake in the colon, whereby a score of 1 = lower uptake than background hepatic activity, a score of 2 = similar uptake to hepatic activity, 3 = moderately higher uptake than hepatic activity, and 4 = intense and diffuse uptake. A score of 3 or 4 could obscure underlying tumors and was, therefore, assumed to be clinically relevant. When the rating differed, the results were discussed among the three graders to reach a consensus.

6.2.5 Statistical analysis

We analyzed the data using SPSS Statistics version 25 (IBM). The normal distribution of the continuous variables was verified using the Shapiro-Wilk test in combination with the normal Q-Q plots. When normally distributed, data were compared using the independent t-test (two-tailed), or when not normally distributed, the Mann-Whitney U-test (two-tailed) was used. A chi-squared test (two-sided) was performed when appropriate. For the visual analysis, we determined whether there was a significant difference in gradings of 1–2 (low grade) and 3–4 (high grade) between the control group and the ≥ 48 h group and between the < 48 h group and ≥ 48 h group. These dichotomic data were analyzed by calculating the odds ratio (OR) in combination with the 95% confidence intervals (CI). When the number in a group was zero, we used Fisher's exact test. For all analyses, p -values of < 0.05 were considered to be statistically significant.

6.3 RESULTS

6.3.1 Patient characteristics

In the total group of 126 diabetic patients, 80 patients used metformin and were considered for inclusion in this study, 32 of whom were excluded, resulting in the overall inclusion of 48 patients on metformin. Reasons for exclusion were unclear metformin dosage ($n = 11$), patients were suffering from colonic malignancies or inflammatory bowel diseases ($n = 6$), unclear metformin discontinuation period ($n = 5$), incomplete data ($n = 4$), multiple scans of which only the first scan was included ($n = 3$), scans did not include the abdomen ($n = 2$), and technical issues with the scanner ($n = 1$). Of the 48 patients using metformin, 23 reported to have discontinued < 48 hours and 25 had discontinued ≥ 48 hours. A total of 96 patients were included in the non-diabetic control group. Between the three groups, there were no differences in gender, BMI, and injected FDG activity. Between the < 48 h group and ≥ 48 h group, there were no differences in the daily metformin dose, age, blood glucose levels, and insulin use. As expected, patients in the two metformin groups were significantly older and had a higher blood glucose level than those in the control group (Table 6.1).

Table 6.1 Characteristics of the study population

Characteristics	<48h group		≥48h group		Control group		p-value	
	<48h group		≥48h group		Control group		<48h group vs. control group	≥48h group vs. control group
Number of patients	23		25		96		N/A	N/A
Age (years), median (25 th –75 th perc.)	70.0 (63.0–75.0)		69.0 (63.0–77.5)		63.0 (57.0–70.0)		0.001*	0.796
Gender, n (%)	Male: 17 (73.9%) Female: 6 (26.1%)		Male: 13 (52.0%) Female: 12 (48.0%)		Male: 53 (55.2%) Female: 43 (44.8%)		0.156	0.145
BMI (kg/m ²), median (25 th –75 th perc.)	27.7 (24.7–31.8)		26.6 (25.3–30.8)		26.2 (24.0–29.0)		0.214	0.919
Injected FDG activity (MBq/kg), median (25 th –75 th perc.)	3.6 (3.2–4.8)		4.1 (3.3–5.1)		4.0 (3.3–5.0)		0.595	0.683
Blood glucose level (mmol/L), median (25 th –75 th perc.)	9.0 (7.4–11.3)		8.5 (6.5–9.5)		5.3 (5.1–6.0)		0.001*	0.238
Insulin usage, n (%)	Yes: 9 (39.1%) No: 14 (60.9%) Unknown: 0 (-)		Yes: 6 (24.0%) No: 15 (60.0%) Unknown: 4 (16.0%)		N/A		N/A	0.535
Daily dose metformin (mg), median (25 th –75 th perc.)	1,000 (500–2,000)		1,500 (1,000–2,000)		N/A		N/A	0.452

* Statistically significant. Abbreviations: N/A, not applicable; BMI, body mass index; FDG, [¹⁸F]fluorodeoxyglucose.

6.3.2 FDG uptake in the colon

Uptake of FDG in the colon for the four segments varied between the three groups. Overall, high-grade uptake was rarely seen in the control group, but was more common in both metformin groups, despite the patients having discontinued their metformin use. Within the metformin groups, discontinuing for a shorter period led to higher uptake than discontinuing for a longer period. A higher FDG uptake (grades 3–4) was most frequently seen in the <48h group (a total of 60 segments [65.2%]), followed by the $\geq$ 48h group (41 segments [41.0%]), and high uptake was least frequently seen in the control group (52 segments [13.5%]).

The uptake of FDG also varied between the four segments (Table 6.2). A high uptake (grade 3–4) in each group was located in the rectosigmoid (100% in the <48h group, 76.0% in the $\geq$ 48h group, and 21.9% in the control group). Examples of different gradings in four patients are presented in Figure 6.1, while the results of the comparison of the different groups are presented below.

Fig. 6.1 PET/CT images of four patients with different grades of FDG uptake in the colon, from left to right, corresponding to the four-point scale method of Gontier *et al.*²

Table 6.2 Visual analysis of grade uptake 1–2 vs. 3–4 and OR(CI)

Uptake grades	<48h group (n = 23)	≥48h group (n = 25)	Control group (n = 96)	<48h group vs. control group		≥48h group vs. control group		<48h group vs. ≥48h group	
				OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
Ascendens	1–2 15 (65.2%)	21 (84.0%)	79 (82.3%)	2.5 (0.9–6.8)	0.077	0.9 (0.3–2.9)	0.841	2.8 (0.7–11.0)	0.141
	3–4 8 (34.8%)	4 (16.0%)	17 (17.7%)						
Transversum	1–2 12 (52.2%)	21 (84.0%)	90 (93.8%)	13.8* (4.3–44.0)	0.001	2.9 (0.7–11.0)	0.128	4.8* (1.3–18.5)	0.022
	3–4 11 (47.8%)	4 (16.0%)	6 (6.3%)						
Descendens	1–2 5 (21.7%)	11 (44.0%)	88 (91.7%)	39.6* (11.6–135.1)	0.001	14.0* (4.8–40.9)	0.001	2.8 (0.8–10.0)	0.108
	3–4 18 (78.3%)	14 (56.0%)	8 (8.3%)						
Rectosigmoid	1–2 0 (-)	6 (24.0%)	75 (78.1%)	N/A	0.001†	11.3* (4.0–31.9)	0.001	N/A	0.023†
	3–4 23 (100%)	19 (76.0%)	21 (21.9%)						

* Statistically significant. † Statistically significant based on Fischer's exact test. Abbreviations: N/A, not applicable because zero in one group

6.3.3 Metformin discontinuation ≥ 48 hours versus control

Our results demonstrate that even when patients discontinue metformin use for 48 hours, a higher FGD uptake is still seen more frequently than in the control group. A comparison between the group in which metformin had been discontinued for ≥ 48 h and the control group revealed that the colonic FDG uptake in the ≥ 48 h group was significantly higher in the colon descendens (OR: 14.0; 95% CI: 4.8–40.9; *p*-value: 0.001) and rectosigmoid (OR: 11.3; 95% CI: 4.0–31.9; *p*-value: 0.001) and that uptake did not differ in the colon ascendens (OR: 0.9; 95% CI: 0.3–2.9; *p*-value: 0.841) and transversum (OR: 2.9; 95% CI: 0.7–11.0; *p*-value: 0.128) (Table 6.2).

6.3.4 Metformin discontinuation ≥ 48 hours versus metformin discontinuation < 48 hours

Our results show that a higher uptake is seen more frequently in the < 48 h group than in the ≥ 48 h group. A comparison between the group that had discontinued metformin for ≥ 48 h and the group that had discontinued it for < 48 h revealed that the FDG uptake was significantly higher in the < 48 h group in the colon transversum (OR: 4.8; 95% CI: 1.3–18.5; *p*-value: 0.022) and rectosigmoid (*p*-value: 0.023), and there was no difference between both metformin groups in both the colon ascendens (OR: 2.8; 95% CI: 0.7–11.0; *p*-value: 0.141) and descendens (OR: 2.8; 95% CI: 0.8–10.0; *p*-value: 0.108) (Table 6.2).

6.4 DISCUSSION

Our results demonstrate that even when discontinuing metformin for 48 hours before FDG PET scanning, colonic FGD uptake remains high when compared to patients who have not taken metformin at all. In other words, discontinuation periods of 48 to 72 hours still do not normalize colonic FDG uptake to the level observed in patients who have not been using metformin. This increased uptake was observed to be especially high in the distal segments of the colon (descendens and rectosigmoid). In the proximal segments, a discontinuation period of 48 hours normalized colonic

uptake to a level that did not differ to the one observed in non-diabetic patients who had not been using metformin.

Comparing the two metformin groups, we found that patients who had discontinued metformin for at least 48 hours showed high uptake less frequently than patients who had discontinued metformin for less than 48 hours. However, our results are not conclusive for all segments of the colon; FDG uptake in the colon ascendens and descendens did not differ between the two groups, whereas uptake in the transversum and rectosigmoid segments remained higher after the shorter period of metformin discontinuation.

Our results are in line with the results of a study by Lee et al.⁹. Although the total number of patients in the study of Lee et al. was larger ($n = 240$), the number of patients in the 48 to 72 hours discontinuation group of that study was relatively small ($n = 12$). In our study, performed in a European population, we included more patients discontinuing metformin for at least 48 hours ($n = 25$), this contributes evidence to the theory that a metformin discontinuation period of 48 hours is insufficient to prevent FDG uptake in all of the colonic segments. Our results contradict the results found in a study by Hamidizadeh et al. that showed that a discontinuation period of 48 hours lowered the FDG uptake in all of the colonic segments⁸. In our study we used a different control group in comparison with the studies of Lee et al. and Hamidizadeh et al.^{8,9}. The study of Lee et al. compared their results with a diabetic non-metformin control group and the study of Hamidizadeh et al. used a control group of patients who continued metformin. The strength of our study is that we compared our results with a non-diabetic control group that had not been using metformin. This approach enabled us to investigate whether the FDG uptake was comparable to that in a group of patients where we would not expect FDG uptake due to the metformin. Furthermore, in our study, we examined the everyday practice of nuclear medicine and were able to demonstrate the impact of the current policy to discontinue metformin use 48 hours prior to scanning on the actual FDG uptake.

Due to the low number of patients with a high-grade uptake per variable, we were unable to perform logistic modeling and calculate an adjusted OR¹². A larger sample might reveal more about potential confounders. Considering the

characteristics of our study population, the patients who were using metformin were older and generally had a higher blood glucose level in comparison with the patients of the control group. However, we do not expect that these characteristics influenced our results. Previous research has demonstrated that age does not influence the FDG uptake in the intestines¹³. Although a high blood glucose level can lead to increased muscle uptake and competition with FDG for tumor uptake¹⁴, the EANM noted—based on previous research—that fasting hyperglycemia did not influence the clinical value of the interpretation of the scan⁶. Moreover, the above-described mechanisms do not explain an increased colonic FDG uptake in metformin patients.

Although patients were asked to withhold insulin prior to the PET/CT scan, in our study, no exact data were available on when those patients discontinued their insulin use. Although hyperinsulinemia may increase uptake in muscles, there seems to be no known association of colonic FDG uptake with insulin^{3, 13, 15}.

As we were interested in whether discontinuation of metformin would make the colonic FDG uptake as we would expect in patients who had not been taking this drug and similar to the uptake in non-diabetic patients, we did not include a group of patients who had continued the use of metformin, as it is already known that metformin increases FDG uptake. Including such an additional group might have revealed more about the degree of lowering the FDG uptake in patients who had discontinued metformin compared with those who had continued its use.

The mechanism behind the relationship between metformin and FDG uptake in the colon remains unclear. Proposed theories include increased lactate production—and higher glucose usage—in the intestine due to treatment with metformin¹⁶, relocation and increase of apical glucose transporters (GLUT2)^{16–19}, processes related to adenosine monophosphate-activated protein kinase (AMPK) activation^{20, 21}, and the role of increased intestinal microbiome²². A mechanism that involves a long-term effect as a result of exposure to metformin—such as the upregulation of glucose transporters—might explain why FDG uptake remains high for some segments of the colon after the discontinuation of metformin. Additional research may clarify the exact mechanism behind the relationship between metformin and FDG uptake in the colon.

The results of our study raise the question of whether patients should discontinue metformin for even longer than 48 hours before FDG PET procedures. However, longer discontinuation periods may not be feasible for patients and could influence their diabetic control and health, as well as generating logistic problems in patients who require urgent PET scans. As we see a benefit of discontinuing metformin use for 48 hours in the more proximal segments of the colon, we still recommend discontinuing metformin 48 hours before an FDG PET/CT scan. As FDG uptake—especially in the more distal segments of the colon—cannot be completely prevented, lesions might still be obscured and significant findings may still be missed.

6.5 CONCLUSION

Discontinuing metformin for 48 hours in FDG PET/CT results in a high uptake in some parts of the colon when compared with non-diabetic patients who have not been using metformin. Discontinuing metformin for 48 hours seems to be useful for the more proximal segments of the colon, but FDG uptake remains high in the more distal segments of the colon. Discontinuing metformin for 48 hours is preferable to discontinuing for shorter periods. The exact mechanism responsible for the increased FDG uptake in the colon remains unknown.

6.6 ACKNOWLEDGMENTS

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Chapter 7

Radiopharmaceuticals in acute porphyria

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ABSTRACT

Purpose: The acute porphyrias are a group of rare metabolic disorders of the haem biosynthetic pathway. Carriers of the acute porphyria gene are prone to potentially fatal acute attacks, which can be precipitated by drug exposure. It is therefore important to know whether a drug is safe for carriers of acute porphyria genes. In this study radiopharmaceuticals were assessed on their porphyrogenicity (i.e., the potential of a drug to induce an attack).

Methods: The assessment was conducted by classifying the drugs according to the Thunell model.

Findings: From 41 radiopharmaceuticals assessed, [^{131}I]iodomethyl norcholesterol, [$^{99\text{m}}\text{Tc}$]Tc-mebrofenin, [$^{99\text{m}}\text{Tc}$]Tc-phytate, [$^{99\text{m}}\text{Tc}$]Tc-sestamibi and [^{201}Tl]Tl-chloride were classified as possible porphyrogenic.

Implications: [^{131}I]iodomethyl norcholesterol, [$^{99\text{m}}\text{Tc}$]Tc-mebrofenin, [$^{99\text{m}}\text{Tc}$]Tc-phytate, [$^{99\text{m}}\text{Tc}$]Tc-sestamibi and [^{201}Tl]Tl-chloride should not be prescribed for patients experiencing acute porphyria unless an urgent indication is present and no safer alternative is available. In such cases potential users should seek advice from a porphyria expert. Preventive measures may also be required.

7.1 INTRODUCTION

The porphyrias are a group of metabolic disorders caused by abnormal function of the haem biosynthesis pathway that results in a specific accumulation of haem precursors¹. Along this pathway, eight enzymes (cytosolic and mitochondrial) are responsible for the construction of haem (Figure 7.1). There are seven types of porphyria resulting from partial enzyme deficiency; while an additional one is characterized by a gain-of-function mechanism.

Fig. 7.1 A schematic representation of the haem biosynthetic pathway with the mitochondrial and cytosolic enzymes, which are responsible for the transformation of the intermediates. The types of porphyria and related enzyme deficiencies are presented. Adapted from Puy et al.¹

The types of porphyria can be classified into two groups on the basis of the illness they cause (Figure 7.1). The acute porphyria group includes acute intermittent porphyria (AIP), hereditary coproporphyria (HC), variegate porphyria (VP) and a

rare ALA-dehydratase deficiency porphyria (ADP). Patients experiencing one of these types experience sudden neurological symptoms. Variegate porphyria and hereditary coproporphyria can cause either neurological or cutaneous symptoms, or a combination of both. Acute intermittent porphyria (AIP) is the most common type, with an estimated gene prevalence in Europe of 1 per 75,000². The other four types of porphyria (labelled cutaneous porphyria) include the congenital erythropoietic porphyria (CEP), porphyria cutanea tarda (PCT), erythropoietic protoporphyria (EPP) and X-linked dominant erythropoietic protoporphyria (X-LDPP). They are characterized by photosensitivity and mainly affect the skin. Because cutaneous porphyria is not associated with acute neurological symptoms, this report will only discuss the acute porphyrias.

The acute porphyrias cause acute attacks accompanied by typical symptoms such as severe abdominal pain, constipation, nausea, confusion, and seizures. These attacks can be life-threatening¹. An acute attack can last for several days to two weeks. Most of the patients experience one or two acute attacks during their lifetime. A minority will experience repeated attacks, sometimes over numerous years.

There are several risk factors for an acute attack, of which high drug exposure is the most important. Other major risk factors include alcohol use, caloric deprivation, infection, stress, and hormonal changes². The latter phenomenon explains why women are three times more likely to experience an acute attack than men.

Drug exposure is a significant factor in inducing attacks in patients carrying the acute porphyria gene. In the current hypothesis for the pathophysiology of acute porphyria, an inducible enzyme called 5-aminolevulinic acid synthase (ALAS1) has a critical role. In carriers of acute porphyria, the induction of ALAS1 may overload the next catalytic step, controlled by porphobilinogen deaminase (PBGD)³. As a result, porphobilinogen (PBG) and 5-aminolevulinic acid (ALA) may accumulate, of which ALA is believed to be the neurotoxic intermediate causing the neurological symptoms¹. The mechanism by which the transcription of ALAS1 is induced is mediated by nuclear receptors. These nuclear receptors are DNA-binding proteins and are activated by xenobiotics. Two nuclear receptors, the pregnane xenobiotic receptor (PXR) and the constitutively active receptor (CAR), are responsible for most of the drug induced transcriptions^{2, 4}. Each one of these transcription factors

can activate, in parallel, the two genes needed for cytochrome formation (i.e., their apoCYP and ALAS1 target gene) for the biosynthesis of the haem component of the holoenzyme to be formed. The ability of a drug to activate PXR and/or CAR makes the drug a possible porphyrogenic trigger³. The activation of PXR and/or CAR may also be induced by drugs binding to cytochrome P450 (CYP) enzymes and thereby inactivating CYP. This will result in a compensatory haem biosynthesis². The xenobiotic receptors PXR and/or CAR can also be activated by pharmacodynamic actions, physiological actions or side effects. The response or action is largely influenced by the sympatico-adrenal system, hypothalamic-pituitary-adrenal axis, and disturbance of the energy homeostasis³. Another possible mechanism of induction of ALAS1 is reduction of the haem pool by induction of haem oxygenase².

To assess whether a drug is safe to use, we need to determine its porphyrogenicity, or the potential of a drug to induce an acute attack in a patient carrying a gene for acute porphyria². Porphyrogenicity has been determined for a number of substances, and these drugs have been classified and presented in online databases (e.g., <http://www.drugs-porphyria.org>). However, to date, the classification has only been carried out for regular drugs and not for radiopharmaceuticals. Radiopharmaceuticals are drugs containing a radioactive isotope, and are used for diagnostic or therapeutic purposes^{5,6}. In the present study, we assessed the porphyrogenicity of radiopharmaceuticals and classified them according to an algorithm. This algorithm, which was developed by Thunell et al.⁴, presents a technique for predicting the risk that a certain drug may activate the disease in a gene carrier of acute porphyria. The Thunell model was validated by the European porphyria network (EPNet) in an international collaboration project (2007–2010). The EPNet collected 5454 drug reports from eight countries about patients' drug use. The majority of reports were on drugs already classified using the classification algorithm, and clinical outcome agreed with the existing classification in nearly all of these. In a few cases discrepancies were shown between the predicted porphyrinogenicity and clinical experience, in which the drugs had been classified as possibly or probably porphyrogenic, whereas a high number of drug reports of uneventful use were registered. This extensive correlation of prediction with clinical

experience therefore provides reassuring evidence that the predictive method is both robust and safe^{2,7}.

7.2 METHODS

7.2.1 Databases and literature

The 41 radiopharmaceuticals most commonly used in nuclear medicine were selected for study^{5,6}. For these radiopharmaceuticals, the manufacturers' Summaries of Products Characteristics (SmPCs) were consulted. Using the SmPCs, the substance bound to the radioactive element and the additives of the products were determined. A search for relevant general literature was conducted on PubMed using the MeSH terms "porphyrias" with "radiopharmaceuticals". An additional search for each radiopharmaceutical was performed combining the MeSH term "porphyrias" and the individual active substances and additives. In order to determine involvement of CYP, a search was done using the MeSH term "Cytochrome P-450 Enzyme System" as well as active substances and additives. In both searches, the corresponding MeSH term for the active substance and additive was used, when available. No restrictions were applied for language or publication dates.

A search to determine whether the radiopharmaceuticals were already classified was conducted in the following four databases: www.drugs-porphyria.org, www.porphyria-europe.com, www.porphyriafoundation.com, and www.porphyria.uct.ac.za. For these searches, the names of the active substances and the additives were used.

7.2.2 Analysing metabolism of the radiopharmaceuticals and classification using the Thunell model

In cases where the drug was not present in the porphyria databases and no clinical evidence of porphyrogenicity was found in the literature, an analysis of the metabolism of each radiopharmaceutical was performed. The SmPCs of the radiopharmaceuticals were used to obtain data on structure of the drug, metabolism,

and elimination by CYP. The radiopharmaceuticals were classified using the Thunell model.

The potential for porphyrogenicity of a radiopharmaceutical can be excluded when it is not metabolised by CYP, unless the substance is not porphyrogenic through pharmacodynamics, physiological actions or side effects⁴. These radiopharmaceuticals were grouped as not porphyrogenic (NP). For the radiopharmaceuticals that have possible affinity for CYP, a further analysis was performed, using the Thunell model. Using the information on the chemical structure of each radiopharmaceutical, the databases were investigated for analogues of the radiopharmaceuticals. When an analogue was found in one of the databases, but no data indicated CYP affinity, the radiopharmaceutical was classified as probably not porphyrogenic (PNP). The hepatocyte load was determined for the remaining group of radiopharmaceuticals with a possible CYP affinity.

Oral drugs with a daily dose below mg range were considered to be associated with an insignificant hepatocyte load and therefore classified as NP. For the intravenous drugs the hepatocyte load was determined by calculating the plasma concentration, that was derived from a single-compartment model using the formula in figure 7.2, wherein the distribution volume (V_d) was assumed to be equal to the plasma volume (0.05 L/kg body weight)⁸.

$$C = \frac{Q}{V_d}$$

$$Q = \frac{\frac{A}{B} * X}{M}$$

C = Plasma concentration (M)

Q = Quantity of drug (mol)

V_d = Distribution volume (L)

A = Amount labelled substance in the kit (g)

B = Volume radioactive substance (mL)

X = Max. volume radioactive drug ready for administration (mL)

M = Molecular weight labelled substance ($g \text{ mol}^{-1}$)

Fig. 7.2 Equations to calculate the plasma concentration

When the plasma concentration was $<1 \mu\text{M}$ and therefore the hepatocyte load was assumed to be insignificant, the drugs involved were consequently classified as PNP. However, when the plasma concentration was $>1 \mu\text{M}$, the hepatocyte load was considered as probably significant. In this case, the specific CYP3A4 or/and CYP2C9 affinity or the ability to induce ALAS1 transcription, such as activation via PXR and/or CAR of the substance, was determined by obtaining data from the SmPCs. The drug was classified as probably porphyrogenic (PSP) when there was affinity for CYP3A4/CYP2C9 or ability for ALAS1 induction. When information was lacking on the affinity for CYP, or the ability for ALAS1 induction, the drug was classified as possibly porphyrogenic. For drugs with a molecular weight of >50 kDa or blood cells labelled with a radioactive isotope, the passage into the capillary endothelium will be limited and drugs will be confined to the vascular compartment. As a result, the hepatic exposure of these drugs is insufficient to be potentially porphyrogenic.

The SmPCs of the radiopharmaceuticals were used to obtain data on potential porphyrogenicity through inhibition of haem oxygenase, pharmacodynamics, physiological actions or side effects.

7.3 RESULTS

7.3.1 Databases and literature

In the literature search a case report of a false-positive accumulation of [^{131}I]iobenguane with acute intermittent porphyria was found⁹. Because this case was not related to porphyrogenicity of the radiopharmaceutical, it was excluded. No other articles were found using the described keywords. In the four porphyria databases used, the radiopharmaceuticals and the additives were neither identified in the safe nor in the unsafe lists.

7.3.2 Analysing metabolism of the radiopharmaceuticals and classification using the Thunells model

Because the radiopharmaceuticals were not classified in the databases, the metabolism of 41 radiopharmaceuticals were analysed, and the drugs were classified according to the Thunell model. The radiopharmaceuticals that do not have affinity for CYP are shown in table 7.1. They were considered as safe and classified as NP.

Table 7.1 *The radiopharmaceuticals that do not have affinity for CYP and are classified as NOT porphyrogenic.*

Product	Indication*
[⁵¹ Cr]Cr-erythrocytes	measurement of red blood cell volume
[¹⁸ F]fludeoxyglucose	glucose metabolism imaging
[⁶⁷ Ga]Ga-citrate	inflammation and tumour scintigraphy
[¹²³ I]sodium iodine	thyroid scintigraphy
[¹³¹ I]sodium iodine	thyroid therapy
[¹¹¹ In]In-pentetic acid	radionuclide cisternography
[³² P]sodium phosphate	therapy of polycythemia vera
[²²³ Ra]Ra-dichloride	therapy of prostate cancer
[⁸¹ Rb]Rb-krypton gas	pulmonary ventilation scintigraphy
[¹⁸⁶ Re]Re-etidronate	palliative therapy of painful bone metastases
[¹⁵³ Sm]Sm-lexidronam	palliative therapy of painful bone metastases
[⁸⁹ Sr]Sr-chloride	palliative therapy of painful bone metastases
[^{99m} Tc]Tc-bicisate	brain scintigraphy
[^{99m} Tc]Tc-medronic acid	bone scintigraphy
[^{99m} Tc]Tc-mertiatide	dynamic renal scintigraphy
[^{99m} Tc]Tc-oxidronic acid	bone scintigraphy
[^{99m} Tc]Tc-pentetic acid	dynamic renal scintigraphy
[^{99m} Tc]Tc-pertechnetate	thyroid scintigraphy
[^{99m} Tc]Tc-succimer	static renal imaging

* Main indications noted

Table 7.2 presents the drugs that have a possible affinity for CYP. Radiopharmaceuticals [¹²³I]iobenguane, [¹²³I]iolopride and [¹³¹I]iobenguane were determined to be analogues of a drug known in the porphyria databases. [¹²³I]iobenguane and [¹³¹I]iobenguane are norepinephrine analogues. [¹²³I]iolopride is a dopamine analogue. For these analogues, no data indicating CYP affinity were found.

Table 7.2 The radiopharmaceuticals with possible affinity for CYP and their porphyrrogenic classification

Product	Indication*	Information on CYP affinity and ability to induce ALAS1 transcription	Large particle or protein	Plasma concentration	Probable insignificant hepatic load	Drug classification
[¹²³ I]ioberguane	tumour scintigraphy	CYP affinity unlikely	-	-	-	PNP
[¹²³ I]ioflupane	brain scintigraphy	Possible substrate of CYP3A4	-	0.6 nM	Yes	PNP
[¹²³ I]lofopride	dopamine receptor scintigraphy	CYP affinity unlikely	-	-	-	PNP
[¹²⁵ I]l-albumin	measurement of plasma volume	No data	Molecule > 50 kDa	-	Yes	PNP
[¹³¹ I]ioberguane	therapy of neuroblastoma	CYP affinity unlikely	-	-	-	PNP
[¹³¹ I]iodomethyl norcholesterol	adrenal scintigraphy	possible substrate of CYP3A4	-	11.5 µM	No	PSP
[¹¹¹ In]In-oxine leukocytes	inflammation scintigraphy	No data	Blood cell	-	Yes	PNP
[¹¹¹ In]In-pentetreotide	somatostatin receptor scintigraphy	CYP affinity unlikely	-	-	-	PNP
[⁷⁵ Se]tauroselcholic acid	investigation of bile acid malabsorption	CYP affinity unlikely	-	Oral use; daily dose < mg range	Yes	PNP
[^{99m} Tc]Tc-albumin	blood pool imaging	No data	Molecule > 50 kDa	-	Yes	PNP
[^{99m} Tc]Tc-erythrocytes	blood pool imaging	No data	Blood cell	-	Yes	PNP
[^{99m} Tc]Tc-exametazime	brain scintigraphy	No data	-	0.5 µM	Yes	PNP
[^{99m} Tc]Tc-macrosalb	pulmonary perfusion scintigraphy	No data	Molecule > 50 kDa	-	Yes	PNP
[^{99m} Tc]Tc-mebrofenin	hepatobiliary imaging	No data	-	103.34 µM	No	PSP
[^{99m} Tc]Tc-nanocolloid	sentinel node scintigraphy	No data	Molecule > 50 kDa	-	Yes	PNP
[^{99m} Tc]Tc-phytate	liver scintigraphy	No data	-	4.66 µM	No	PSP
[^{99m} Tc]Tc-sestamibi	myocardial perfusion scintigraphy	No data	-	1.57 µM	No	PSP
[^{99m} Tc]Tc-stannous colloid	liver and spleen scintigraphy	No data	-	0.27 µM	Yes	PNP
[^{99m} Tc]Tc-sulesomab	inflammation scintigraphy	No data	Molecule > 50 kDa	-	Yes	PNP
[^{99m} Tc]Tc-tetrofosmin	myocardial perfusion scintigraphy	No data	-	0.07 µM	Yes	PNP
[²⁰¹ Tl]Tl-chloride	myocardial perfusion scintigraphy	No data	-	22.77 µM	No	PSP
[⁹⁰ Y]Y-citrate	radiosynoviorthesis	No data	Molecule > 50 kDa	-	Yes	PNP

* Main indications noted. Abbreviations: ALAS1, 5-aminolevulinic acid synthase; PNP, possibly not porphyrrogenic; PSP, possibly porphyrrogenic.

CYP affinity for the corresponding radiopharmaceuticals seems unlikely and therefore they were classified as PNP¹⁰. [¹¹¹In]In-pentetreotide is an octreotide analogue. Octreotide is a synthetic peptide and was considered to be safe in one reference¹⁰. As a consequence, CYP affinity for [¹¹¹In]In-pentetreotide seems unlikely (i.e., [¹¹¹In]In-pentetreotide was classified as PNP).

In table 7.2, eight radiopharmaceuticals with a molecular size >50 kDa or blood cells labelled with a radioactive isotope were presented and classified as PNP. [⁷⁵Se]tauroselcholic acid is an oral drug with a daily dose below the micromolar range. Hence, it is considered to be associated with an insignificant hepatocyte load and was classified as possibly not PNP. [¹²³I]ioflupane was determined to be an analogue of cocaine and hence a possible substrate of CYP3A4^{11, 12}. Furthermore, [¹³¹I]iodomethyl norcholesterol was determined to be a cholesterol analogue and therefore a possible substrate of CYP3A4¹³.

For the remaining radiopharmaceuticals no data on CYP affinity were found. For the radiopharmaceuticals with a possible affinity for CYP or for which no data on CYP affinity was available, the plasma concentrations were calculated to determine whether these concentrations exceed the estimated porphyrogenic micromolar range (>1 µM). For [¹²³I]ioflupane, [^{99m}Tc]Tc-exametazime, [^{99m}Tc]Tc-stannous colloid and [^{99m}Tc]Tc-tetrofosmin, plasma concentrations below 1 µM were calculated and these agents were subsequently classified as PNP. For [¹³¹I]iodomethyl norcholesterol, [^{99m}Tc]Tc-mebrofenin, [^{99m}Tc]Tc-phytate, [^{99m}Tc]Tc-sestamibi and [²⁰¹Tl]Tl-chloride, plasma concentrations were estimated to be high enough (>1 µM) to trigger a porphyrogenic ALAS1 transcription. Because there was no information available for these drugs regarding the CYP3A4/2C9 affinity and the ability to induce ALAS1 transcription (e.g., such as activation via PXR and/or CAR) they were classified as possibly porphyrogenic.

7.3.3 Potential porphyrogenicity through inhibition of haem oxygenase, pharmacodynamics, physiological actions or side effects

None of the radiopharmaceuticals assessed were found to be inhibitors of haem oxygenase. No data was found in the SmPCs indicating potential porphyrogenicity

through pharmacodynamics, physiological actions or side effects. Because radiopharmaceuticals are administered with low mass doses (i.e., doses in or below the microgram range) pharmacological effects are not expected. Side effects as described in the SmPCs did not relate to responses via the sympathico-adrenal system, hypothalamic-pituitary-adrenal axis, or disturbance of the energy homeostasis.

7.4 DISCUSSION

Our analysis on the porphyrogenicity of 41 radiopharmaceuticals revealed that five radiopharmaceuticals can be classified as possibly porphyrogenic. The assessment was based on information on inhibition of haem oxygenase, metabolism by cytochrome P450 (CYP), CYP affinity, ability to induce ALAS1 transcription, (particle) size and plasma concentration of the drug.

It is important to understand that the outcome of the method used depends on the accuracy of the available pharmacokinetic and pharmacodynamic data. During our study we noticed that these data for radiopharmaceuticals are not always complete. Information on metabolism by CYP and the ability to induce ALAS1 transcription in particular (e.g., such as activation via PXR and/or CAR) is often incomplete or even absent. It is also worth noting that the plasma concentrations that were calculated are very strict. The human body was considered as a single compartment model and the plasma volume was set at 2500 mL, assuming a body weight of 50 kg. For assessing the level of drug exposure the maximum dose given to a patient was used. As a consequence, the plasma concentrations are probably overestimated in order to achieve a safety margin.

The assessment in this study has not taken differences in response of individual patients to radiopharmaceuticals into account. Although individuals might have the same genetic predisposition, responses may be different from what is expected². Other factors may contribute to the increase of the porphyric vulnerability of an individual patient such as the use of other drugs or alcohol, an altered hormone balance, experiencing stress, or suffering from an infection¹⁴. Therefore, an individual assessment that takes all factors into account is important for each patient.

With regard to the five radiopharmaceuticals being classified as possibly porphyrogenic, further information is needed to assess whether they possess a clinically relevant CYP3A4 or CYP2C9 affinity or have the ability to induce ALAS1 transcription. If this is not the case, they can be classified as probably not porphyrogenic. Furthermore, we should be aware of the possible side effects of all radiopharmaceuticals inducing ALAS1 transcription that may provoke an attack.

Most radiopharmaceuticals are used for diagnostic purposes and are commonly administered to patients in a fasted state. It has been suggested that glucose deprivation induces ALAS1 transcription and may well have porphyrogenic consequences¹⁴. It is therefore important to be aware of the risk of fasting associated with diagnostic procedures for carriers of the acute porphyria gene.

A few radiopharmaceuticals are used for therapeutic purposes, sometimes resulting in lasting physiological changes. An example is treatment of the thyroid with [¹³¹I] sodium iodine, resulting in a partial or total thyroid ablation. Physiological changes could potentially alter the susceptibility to porphyrogenic substances of an individual. Therefore, monitoring patients for development of new symptoms after treatment with a therapeutic radiopharmaceutical is required.

Based on the evidence available, classification of these radiopharmaceuticals as PNP or PSP as presented is appropriate. Although it has been shown that the application of the algorithm provides a correct classification in most cases, some examples were found wherein the clinical outcome did not match the algorithm classification^{2,7}. It is for this reason that, clinical confirmation is needed (e.g., listing the number of patients to which the drug has been administered safely by expert physicians). Until then, the radiopharmaceuticals being considered should be used with care as these substances are possibly harmful in acute porphyria patients.

A potentially porphyrogenic drug is not to be prescribed for a carrier of the acute porphyria gene other than upon urgent indication and where safer alternatives are unavailable⁴. When a potentially porphyrogenic radiopharmaceutical must be prescribed, it is best to consult a porphyria expert¹⁶, as preventive measures need to be taken and doctors should be prepared for a potentially acute attack. Preventive measures are adapted to the individual porphyric vulnerability of the patient and the porphyrogenicity of the drug. In general, monitoring for porphyric symptoms can be

recommended, such as red urine, as well as monitoring the concentration of porphobilinogen in the urine. When the patient is probably or highly susceptible, prolonged fasting must be avoided by ensuring the patient is treated early in the morning. They are also advised to seek medical advice in case of any symptoms suggestive of porphyria¹⁵.

7.5 CONCLUSION

From the 41 radiopharmaceuticals assessed, five of them, i.e. [¹³¹I]iodomethyl norcholesterol, [^{99m}Tc]Tc-mebrofenin, [^{99m}Tc]Tc-phytate, [^{99m}Tc]Tc-sestamibi and [²⁰¹Tl]Tl-chloride, are classified as possible porphyrogenic according to the Thunell method and may be unsafe for a carrier of the acute porphyria gene. [¹³¹I]Iodomethyl norcholesterol, [^{99m}Tc]Tc-mebrofenin, [^{99m}Tc]Tc-phytate, [^{99m}Tc]Tc-sestamibi and [²⁰¹Tl]Tl-chloride should not be prescribed for acute porphyria patients unless an urgent indication is present and a safer alternative not available. In such cases potential users should seek advice from a porphyria expert, and preventive measures may be required. The rest of the radiopharmaceuticals are classified as not or probably not porphyrogenic.

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Chapter 8

Lack of consistent dose recommendations for radiopharmaceuticals in patients with renal insufficiency: results of a systematic review

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ABSTRACT

Introduction: Patients with renal insufficiency may need to have their radiopharmaceutical dosage adjusted to prevent adverse effects and poor outcomes, but there are few recommendations on radiopharmaceutical dosing for this group of patients.

Objective: The aim of this study is to provide an overview of the available information on radiopharmaceutical dose recommendations for patients with renal insufficiency and, for those radiopharmaceuticals that are found in the literature to assess the dosing recommendations in this group of patients.

Methods: We performed a systematic literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We conducted a literature search in the MEDLINE (PubMed) and Embase databases and screened potentially relevant studies using inclusion and exclusion criteria. We independently assessed the included observational studies' methodologies and extracted relevant data.

Results: Of the 5,795 studies first identified, 34 were included in this systematic review. These studies described three radiopharmaceuticals: [¹³¹I]sodium iodine, [¹⁸F]fludeoxyglucose, and [¹³¹I]iobenguane. Twenty-nine studies (85.3%) reported data on patients with stage 5 chronic kidney disease (CKD), while only three studies mentioned CKD patients in other stages (8.8%).

Conclusion: We found no consistent recommendations for radiopharmaceutical dosing in patients with renal insufficiency. Although some studies do mention dosing difficulties in patients with insufficient renal function, information is available for only a few radiopharmaceuticals, and recommendations are sometimes contradictory. Further research on radiopharmaceutical dosing in patients with renal function insufficiency is needed to determine whether these patients require specific dosing.

8.1 INTRODUCTION

Nuclear medicine plays an important role in the diagnosis and therapy of diseases, particularly in the field of oncology. The field of nuclear medicine relies on radioactive compounds, so-called radiopharmaceuticals¹. Selecting the right dose of a radiopharmaceutical, expressed in becquerels (Bq) as the activity of the compound's radionuclide, is of high importance. For diagnostic radiopharmaceuticals, the ideal dose will provide accurate, useful diagnostic information while keeping the radiation dose to the patient low^{2,3}. The efficacy will depend on the biodistribution of the diagnostic radiopharmaceutical. Important aspects include localisation in a target organ, localisation in non-target organs, and the mechanisms—such as biological excretion—for removing non-target radioactivity. Advantageous biodistribution will contribute to a good target-to-non-target activity ratio, ensuring optimal image quality which allows a clear diagnostic outcome⁴. For therapeutic radiopharmaceuticals, the ideal dose will deliver the right therapeutic activity without causing adverse effects and with a minimum radiation dose to non-target organs or tissues⁵⁻⁷. The biodistribution of the therapeutic radiopharmaceutical is important because localisation in the target organ will determine the therapeutic response, and non-target organs are at risk of toxicity⁴.

Renal insufficiency is a growing health problem with an estimated prevalence of 11%–13% in the general population and can result from diseases, such as diabetes mellitus and hypertension, or from aging⁸⁻¹⁰. It may reduce the excretion rate of pharmaceuticals and their metabolites, elevating plasma concentrations and requiring the dose to be adjusted^{11,12}. Similarly, for radiopharmaceuticals that are cleared by the kidneys, the biodistribution of the radioactive drug is likely to be altered in patients with renal insufficiency. For diagnostic radiopharmaceuticals, decreased clearance may lead to prolonged blood pool activity and subsequently to a poor target-to-non-target ratio, which may decrease image quality and ultimately affect the diagnostic outcome. For therapeutic radiopharmaceuticals, decreased clearance may lead to increased activity at the target organs or non-target organs, which increases the risk of toxicity. Therefore, it is expected that the

radiopharmaceutical dosage in patients with renal insufficiency will have to be adjusted^{13, 14}.

At present, the dose of a radiopharmaceutical is fixed in most cases, although it is sometimes adjusted for body weight, as in the case of children¹⁵. However, standards for radiopharmaceutical dosing in patients with renal insufficiency are lacking. One review describes treatment with radioiodine for hyperthyroidism and thyroid cancer in end-stage renal disease. The review mentions that the available literature is scarce and that standards, based only on analysis of single case reports, are not coherent¹⁶. Some available nuclear medicine guidelines contain only one paragraph on the use of radiopharmaceuticals in patients with renal insufficiency. Only one nuclear medicine guideline gives a specific dose recommendation for these patients, advising that the administered dose of bone-seeking therapeutic radiopharmaceuticals for palliation of bone pain should be lowered by 50% in patients with creatinine clearance of less than 50 mL/min¹⁷. Other guidelines provide only general, nonspecific comments, such as recommending that renal function should be assessed, that a nephrologist should be consulted, that the administration of the radiopharmaceutical should be carefully planned and managed, or even that patients with renal insufficiency should be excluded^{17–24}. While these effects are particularly relevant in therapeutic applications because a change in biodistribution may affect therapy outcomes or increase the risk of toxicity in these patients, diagnostic radiopharmaceutical guidelines also indicate that scans obtained in renal insufficiency patients may be suboptimal due to a change in biodistribution. Some suggest increasing the time between administration of the radiopharmaceutical and imaging^{19, 25–28}. However, several guidelines for both therapeutic and diagnostic radiopharmaceuticals mention that while dose adjustment may be needed in this group of patients, little is known about this topic^{18, 20, 22, 29–31}.

Therefore, our aim in this systematic review is to provide an overview of the available information on radiopharmaceutical dose recommendations for patients with renal insufficiency and, for those radiopharmaceuticals that are found in the literature, to assess the dose recommendations in this group of patients.

8.2 METHODS

8.2.1 Study design

We conducted this systematic literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement³², and the review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42019136107³³.

8.2.2 Search strategy

We performed a computerised literature search using the databases MEDLINE (PubMed) and Embase. Two researchers (I.d.R. and N.S.) developed a search string for each database (Table 8.1) using keywords for both renal insufficiency and radiopharmaceuticals. No publication year limits were applied. Only studies in the English language were included, and a filter was applied to exclude animal-only studies. An additional filter was applied in Embase to exclude studies available in MEDLINE. We screened the selected studies and review articles to identify additional relevant studies and references. The initial search was completed on 10 May 2019 and updated with recent articles until 7 October 2020.

Table 8.1 Search strategies employed for PubMed and Embase

Database	Search string
PubMed	(((((Radiopharmaceuticals(MeSH) OR radiopharmaceutical*(tiab) OR radioactive drug*(tiab) OR radioiodine(tiab)))) AND ((Kidney Diseases(MeSH) OR kidney disease*(tiab) OR Renal Insufficiency(MeSH) OR renal insufficien*(tiab) OR renal impairment(tiab) OR Glomerular Filtration Rate(Mesh) OR glomerular filtration rate*(tiab) OR eGFR(tiab) OR Metabolic Clearance Rate(MeSH) OR renal clearance(tiab)))) NOT ("Animals"(Mesh) NOT "Humans"(Mesh))) AND English(Language)
Embase	('radiopharmaceutical agent'/exp OR 'radiopharmaceutical agent':ti,ab) AND ('kidney disease'/exp OR 'kidney disease':ti,ab OR 'kidney failure'/exp OR 'kidney failure':ti,ab OR 'renal impairment':ti,ab OR 'glomerulus filtration rate'/exp OR 'glomerular filtration rate':ti,ab OR 'estimated glomerular filtration rate':ti,ab OR 'metabolic clearance'/exp OR 'renal clearance':ti,ab) NOT ('animal'/exp NOT 'human'/exp) AND (english)/lim AND (embase)/lim NOT ((embase)/lim AND (medline)/lim)

8.2.3 Study selection

All titles and abstracts were screened, and we retrieved the full text of potentially relevant studies. Two researchers (I.d.R. and N.S.) independently assessed the full text of each study for relevance. We included studies that met the following inclusion criteria: They described patients diagnosed or treated with a radiopharmaceutical and who suffered from a renal insufficiency, they used a radiopharmaceutical that is (at least partly) cleared renally, and they made recommendations for an adequate dose in these patients or gave additional advice. Studies were excluded if they gave no relevant information on dosing or aspects related to dosing, addressed only the radiation safety of staff, described renal imaging, or were review articles.

8.2.4 Assessment of methodological quality

Two researchers (I.d.R. and N.S.) independently assessed the methodological quality of the included observational studies using the Newcastle-Ottawa Scale (NOS): Quality Assessment Form for Cohort and Case-Control Studies³⁴. For each study, we scored nine items in three domains: selection, comparability, and exposure or outcome. Scores were added to create an aggregate score. The NOS scores were converted to ratings of ‘good’, ‘fair’, or ‘poor’ according to Agency for Healthcare Research and Quality standards³⁵. Studies of good quality were defined as those awarded 3–4 stars in the selection domain *and* 1–2 stars in the comparability domain *and* 2 stars in the exposure or outcome domain. Fair studies were defined as those awarded 2 stars in the selection domain *and* 1–2 stars in the comparability domain *and* 1–2 stars in the exposure or outcome domain. Poor-quality studies were defined as those awarded 0–1 stars in the selection domain *or* 0 in the comparability domain *or* 0 in the exposure or outcome domain. Where opinions on a score differed, we consulted a third reviewer (E.v.P.) to reach consensus.

8.2.5 Data collection

For studies meeting the selection criteria, we extracted data using a standardised approach. Two researchers (I.d.R. and N.S.) independently extracted the following data: (1) author and journal, (2) year of publication, (3) study design, (4) name(s) of radiopharmaceutical(s) and the administered dose(s), (5) indication, (6) number of patients with renal insufficiency, (7) stage of renal insufficiency, (8) where applicable, the type and timing of dialysis after administration of the radiopharmaceutical, (9) recommendation(s) for adjustment of dose, (10) other advice on aspects such as adjustment of dialysis or scintigraphy, (11) reasons for dose adjustment, and (12) study limitations. We standardised the radiopharmaceuticals' names according to the Anatomical Therapeutic Chemical classification system³⁶, and the International Consensus Radiochemistry Nomenclature Guidelines³⁷. Where studies reported the administered dose using the unit curie (Ci), we converted this to the SI derived unit becquerel (Bq) for uniformity of outcome³⁸. Patients with renal insufficiency were classified using the terminology of the chronic kidney disease (CKD) standard (Table 8.2), which includes five stages of kidney damage, from kidney damage with normal kidney function in stage 1 to kidney failure in stage 5^{39,40}. We classified patients on dialysis as stage 5 if they had not been assigned to a specific stage in a study. When the extracted data were not in agreement and consensus could not be reached between the two researchers, a third researcher (E.v.P.) was consulted to resolve discrepancies.

Table 8.2 *Classification of CKD by GFR^{39, 40}*

Stage	Description	GFR, mL/min/1.73 m ²
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	< 15 (or dialysis)

Abbreviations: CKD, chronic kidney diseases; GFR, glomerular filtration rate

8.3 RESULTS

8.3.1 Search results

The literature search identified a total of 5,795 studies in PubMed ($n = 2,684$) and Embase ($n = 3,111$); another 11 studies were identified from references. After removing duplicates ($n = 81$), we screened 5,725 studies by title (and abstract, where necessary), resulting in 65 potentially relevant studies. After a full-text screening we excluded another 31 studies for various reasons: they gave no relevant information on dosing or aspects related to dosing ($n = 18$), they addressed only the radiation safety of staff ($n = 5$), described renal imaging ($n = 5$), or were reviews ($n = 3$). A total of 34 studies remained for inclusion in this systematic review^{41–74}. The selection process is illustrated in a PRISMA flow diagram (Figure 8.1).

Fig. 8.1 Selection of studies according to the PRISMA statement³²

The 34 selected studies included 12 case reports (35.3%), 11 case series (32.4%), five case-control studies (14.7%), two cohort studies (5.9%), three theoretical models (8.8%), and one case report with a theoretical model (2.9%). The radiopharmaceuticals reported in these studies are [^{18}F]fludeoxyglucose (FDG) ($n = 5$; 14.7%), [^{131}I]sodium iodine ($n = 28$; 82.4%), and [^{131}I]iobenguane ($n = 1$; 2.9%). Twenty-nine studies reported data for patients with CKD stage 5 (85.3%), while three studies included patients in other stages (8.8%). In two studies, the CKD stage was not identified, or it was determined in a non-standard fashion (5.9%). Patients in the 29 studies reporting data for CKD stage 5 were on renal replacement therapy. Nineteen studies described patients on haemodialysis (HD) (65.5%), four studies described patients on continuous ambulatory peritoneal dialysis (CAPD) (13.8%), three studies described patients on HD or CAPD (10.3%), one study described patients on HD or intermittent peritoneal dialysis (IPD) (3.4%), one study described patients on continuous haemodialysis (3.4%), and one study did not specify the type of dialysis (3.4%). In these studies, the timing of dialysis varied. For HD, the start of dialysis varied from 15 to 72 hours after administration of the radiopharmaceutical, the number of dialyses varied from one to five times, and the timing intervals varied. For CAPD, the fluid changes varied from four to eight times a day. An overview of the included studies' characteristics is presented in Table 8.3.

8.3.2 Quality of the observational studies

We performed a methodological quality assessment of the included observational studies, namely five case-control studies (Table 8.4) and two cohort studies (Table 8.5). Our assessment yielded one study rated 'good' (14.3%), one study rated 'fair' (14.3%), and five studies rated 'poor' (71.4%).

Table 8.3 Overview of included studies with their characteristics

Reference	Year	Study design	Number of patients	Radiopharmaceutical	Indication	Dose (MBq)	Stage of renal failure (CKD)	Type of dialysis (number of patients)	Timing of dialysis after administration radiopharmaceutical
Akers ⁴¹	2016	COS	58	[¹⁸ F]fluodeoxyglucose	PET/CT	370–555	1–5	NA	NA
Aktaş ⁴²	2008	CCS	10	[¹³¹ I]sodium iodine	TC	1110–3700	5	HD (6); CAPD (4)	24h continued every day for 5d; CAPD increased from 4 to 6–8 times a day
Alevizaki ⁴³	2006	CS	5	[¹³¹ I]sodium iodine	PTC	1110–2590	5	HD (4); IPD (1)	48h, and 2 patients also 96h
Bhat ⁴⁴	2017	CR	1	[¹³¹ I]sodium iodine	PTC	1850	5	HD	15h, 27h, 43h
Courbon ⁴⁵	1997	CR	1	[¹³¹ I]sodium iodine	TC	3700	5	HD	2d, 4d
Courbon ⁴⁶	2006	CS	2	[¹³¹ I]sodium iodine	TC	3700	5	HD	72h, 122h–144h
Culpepper ⁴⁷	1992	CR	1	[¹³¹ I]sodium iodine	FTC	4773	5	HD	24h, 43h, 66h
Daumerie ⁴⁸	1996	CS	3	[¹³¹ I]sodium iodine	PTC	2 treatments of 925	5	HD	2d, 3d
Demko ⁴⁹	1998	CR	1	[¹³¹ I]sodium iodine	TMNG	1045.62	5	HD	24h
Driedger ⁵⁰	2006	CS	3	[¹³¹ I]sodium iodine	PTC	3700; 3700; 2500	5	HD (2); CAPD (1)	NA
El-Zeftawy ⁵¹	2017	CCS	27	[¹³¹ I]sodium iodine	DTC	Mean dose 5550	3 and 4	NA	NA
Foff ⁵²	2013	CS	2	[¹³¹ I]sodium iodine	PTC	1850	5	CHD	24h, 48h
Holst ⁵³	2005	CR and TM	1	[¹³¹ I]sodium iodine	PTC*	3637	5	HD	2d, 3d, 4d
Howard ⁵⁴	1981	CR	1	[¹³¹ I]sodium iodine	PTC	740	5	HD	NA
Jiménez ⁵⁵	2001	CS	3	[¹³¹ I]sodium iodine	PTC	2775; 3219; 4440	5	HD	24h, 48h, 72h, 96h, 144h
Kaptein ⁵⁶	2000	CS	2	[¹³¹ I]sodium iodine	PTC	980; 1110	5	CAPD	3–5 times a day

* Although the study describes hyperthyroidism as well, the reported case was treated with [¹³¹I]sodium iodine for thyroid cancer. † 12 patients were on dialysis, type and timing were not specified. * In this study a pharmacokinetic software model was developed and validated with data of ¹³¹I, ¹²³I and ¹²⁴I. † patients with a blood serum creatinine level > 1.1 mg/dl. # The findings in one patient were compared with two patients with mild to moderate renal function. Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CCS, case-control study; CHD, chronic kidney diseases; CKD, chronic kidney diseases; COS, cohort study; CR, case report; CS, case series; DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; GD, Graves' disease; HD, haemodialysis; IPD, intermittent peritoneal dialysis; NA, not available; PC, pheochromocytoma; PET/CT, positron emission tomography/computed tomography; PTC, papillary thyroid cancer; TC, thyroid cancer; TD, thyroid disease; TM, Theoretical model; TMNG, toxic multinodular goiter.

Table 8.3 (Continued) Overview of included studies with their characteristics

Reference	Year	Study design	Number of patients	Radiopharmaceutical	Indication	Dose (MBq)	Stage of renal failure (CKD)	Type of dialysis (number of patients)	Timing of dialysis after administration radiopharmaceutical
Code ⁵⁷	2017	CCS	30	[¹⁸ F]fluodeoxyglucose	PET/CT	5.18 /kg	4 and 5	NA [†]	NA
Laffon ⁵⁸	2008	TM	NA	[¹⁸ F]fluodeoxyglucose	NA	NA	NA	NA	NA
Magné ⁵⁹	2002	CR	1	[¹³¹ I]sodium iodine	PTC	1850	5	HD	24h, 72h, 144h
McKay ⁶⁰	2019	TM	NA	[¹³¹ I]sodium iodine [*]	TD	NA	5	NA	several timing intervals were simulated
McKillop ⁶¹	1985	CR	1	[¹³¹ I]sodium iodine	GD	462.5	5	HD	3d
Mello ⁶²	1994	CR	1	[¹³¹ I]sodium iodine	PTC	2 treatments of 3700	5	HD	41h, 89h
Minamoto ⁶³	2007	COS	20	[¹⁸ F]fluodeoxyglucose	PET/CT	210–360	NA [†]	NA	NA
Miyasaka ⁶⁴	1997	CR	1	[¹³¹ I]sodium iodine	GD	740	5	HD	24h
Morish ⁶⁵	1990	CR	1	[¹³¹ I]sodium iodine	PTC	1850; 4440; 5550; 9250	5	HD	48h, 96h, 144h
Pahika ⁶⁶	2006	TM	NA	[¹³¹ I]sodium iodine	TC	NA	5	HD; CAPD	several timing intervals were simulated
Sinsaku ⁶⁷	2004	CS	2	[¹³¹ I]sodium iodine	PTC	3700; 5809	5	HD	20h–24h
Tobes ^{68, #}	1989	CCS	1	[¹³¹ I]jobenguane	PC	18.5	5	HD	NA
Toriihara ⁶⁹	2015	CCS	24	[¹⁸ F]fluodeoxyglucose	PET/CT	3.7 /kg	5	HD	NA
Toubert ⁷⁰	2001	CR	1	[¹³¹ I]sodium iodine	FTC	814	5	CAPD	4 times a day
Vernandel ⁷¹	2020	CS	6	[¹³¹ I]sodium iodine	TC	1842–3747	5	HD	42h, 90h
Wang ⁷²	2003	CS	2	[¹³¹ I]sodium iodine	PTC	3700; 5550	5	CAPD	4 times a day
Willegaignon ⁷³	2010	CR	1	[¹³¹ I]sodium iodine	DTC	3700	5	CAPD	NA
Yeyin ⁷⁴	2016	CS	3	[¹³¹ I]sodium iodine	DTC	2775 and 1850; 2775; 1850	5	HD	24h, 48h

^{*} Although the study describes hyperthyroidism as well, the reported case was treated with [¹³¹I]sodium iodine for thyroid cancer. [†] 12 patients were on dialysis, type and timing were not specified. [#] In this study a pharmacokinetic software model was developed and validated with data of [¹³¹I], [¹²³I] and [¹²⁴I]. [†] patients with a blood serum creatinine level > 1.1 mg/dl. [#] The findings in one patient were compared with two patients with mild to moderate renal function. Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CCS, case-control study; CHD, continuous haemodialysis; CKD, chronic kidney diseases; COS, cohort study; CR, case report; CS, case series; DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; GD, Graves' disease; HD, haemodialysis; IPD, intermittent peritoneal dialysis; NA, not available; PC, pheochromocytoma; PET/CT, positron emission tomography/computed tomography; PTC, papillary thyroid cancer; TC, thyroid cancer; TD, thyroid disease; TM, Theoretical model; TMNG, toxic multinodular goiter.

Table 8.4 Newcastle-Ottawa Scale assessment for case-control studies^{34, 35}

Study	Selection			Comparability		Exposure			Total score
	Adequate definition of case	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Study controls for any additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	
Aktaş ⁴²	0	0	0	0	0	0	0	*	0
El-Zeftawy ⁵¹	0	*	0	0	*	*	0	*	0
Kode ⁵⁷	0	*	0	0	*	*	0	*	0
Tobes ⁶⁸	0	0	0	0	0	0	0	*	0
Torihiara ⁶⁹	0	*	0	*	*	*	0	*	0

*** means one awarded point. Good-quality: awarded 3–4 stars in the selection domain and 1–2 stars in the comparability domain and 2 stars in the exposure domain. Fair studies: awarded 2 stars for selection and 1–2 stars for comparability and 1–2 stars for exposure. Poor-quality: awarded 0–1 stars for selection or 0 for comparability or 0 for exposure³⁵.

Table 8.5 Newcastle-Ottawa Scale assessment for cohort studies^{34, 35}

Study	Selection			Comparability		Outcome			Total score	
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Study controls for any additional factor	Assessment of outcome	Follow-up long enough for outcomes to occur		Adequacy of follow-up of cohorts
Akers ⁴¹	*	*	0	0	0	0	0	*	*	4
Minamimoto ⁶³	*	*	0	*	*	0	0	*	*	6

*** means one awarded point. Good-quality: awarded 3–4 stars in the selection domain *and* 1–2 stars in the comparability domain *and* 2 stars in the outcome domain. Fair studies: awarded 2 stars for selection *and* 1–2 stars for comparability *and* 1–2 stars for outcome. Poor-quality: awarded 0–1 stars for selection *or* 0 for comparability *or* 0 for outcome³⁵.

8.3.3 Diagnostic radiopharmaceuticals and renal insufficiency

Regarding diagnostic radiopharmaceuticals in patients with renal insufficiency, we found dose recommendations and advice only for the radiopharmaceutical FDG (Table 8.6). The following section summarises our findings for this radiopharmaceutical.

[¹⁸F]fludeoxyglucose (FDG)

A total of five studies reported the use of FDG in a total of 132 patients with renal insufficiency in several stages of renal failure. Two of these studies recommended that no adjustment in dose or protocol is needed for patients with renal insufficiency. These studies based their recommendation on evidence that standardised uptake values in patients with renal insufficiency were comparable to those in patients with normal kidney function^{41, 57}. One study suggested that a slight decrease in uptake in the brain and a slight increase in normal blood pool activity were caused by a higher FDG concentration in the blood and decreased uptake by tissues, and it concluded that these changes would not have a large impact on the assessment of the scan⁶³. However, another study indicated that FDG uptake in background organs or blood pool might influence interpretation of the scan. In this case-control study, the standard uptake values (SUV)—normalised by body weight, as the control subjects had a greater body weight—in the gluteal muscles, subcutaneous fat, spleen, and right atrium were higher in patients on HD than in control subjects. The increased background uptake may influence quantitative measurements when the SUV of the background is used as a reference to assess tumour treatment response⁶⁹. A last study suggested, based on a theoretical assessment, to increase the time between radiopharmaceutical administration and imaging⁵⁸.

Table 8.6 Overview of dose recommendations and other advice for diagnostic radiopharmaceuticals

Radiopharmaceutical	Stage of renal failure (CKD)	Dose recommendation	Other advice
¹⁸ F]fludeoxyglucose	1, 2, 3, 4 or 5	No adjustment in dose or protocol is needed ^{41, 57} .	No adjustment in image time ^{41, 57} .
		Dose adjustment should be based on the optimized radiation dose ⁵⁸ .	The more severe the renal failure, the later the imaging should be, without necessarily beginning the acquisition beyond 160 min after injection ⁵⁸ .
		ND	No large impact on assessment of scan ⁶³ .
	5	ND	The effect of elevated FDG uptake in the background organs or blood pool may influence interpretation of the image in patients with renal impairment on haemodialysis ⁶⁹ .

Abbreviations: CKD, chronic kidney diseases; FDG, [¹⁸F]fludeoxyglucose; ND, 'not determined'.

8.3.4 Therapeutic radiopharmaceuticals and renal insufficiency

For the use of therapeutic radiopharmaceuticals in patients with renal insufficiency, we found dose recommendations and other advice for the treatment of hyperthyroidism and thyroid cancer with [^{131}I]sodium iodine and for the treatment of pheochromocytoma with [^{131}I]iokebenguane (Table 8.7). The following sections summarise findings for these treatments.

[^{131}I]sodium iodine for the treatment of hyperthyroidism

Three case reports reported a total of three patients with renal insufficiency (CKD stage 5) on HD treated with [^{131}I]sodium iodine for hyperthyroidism. Two of these studies calculated the dose of [^{131}I]sodium iodine based on the 24-hour radioiodine uptake and the weight of the thyroid gland^{49, 64}. In one of these two studies, HD was started after 24 hours. Approximately one-third of the calculated dose was administered, although the reason for reducing the dose in this way was not given⁶⁴. The other study emphasised the importance of consistency in the timing of dialysis for both the iodine uptake assessment and the treatment, and it stated that the most reasonable time for dialysis is 24 hours after administration⁴⁹. The third case-report study did not specify dose calculations, but it stated that standard management for hyperthyroidism is effective⁶¹. Of the three patients in these case reports, one developed hypothyroidism three months after treatment and later reached a euthyroid state⁶¹, and two patients remained in a euthyroid state^{64, 49}. Exact follow-up times were not given for these three patients.

[^{131}I]sodium iodine for the treatment of thyroid cancer

A total of 25 studies and case reports reported a total of 80 patients with renal insufficiency treated with [^{131}I]sodium iodine for thyroid cancer. Of these studies, 24 (96.0%) included patients with CKD stage 5 who were on dialysis. Only one study included patients with CKD stages 3 and 4.

The latter study described the treatment of 27 patients with [^{131}I]sodium iodine for ablation after thyroid cancer and reported a longer hospital stay and delayed renal clearance. It concluded that guidelines should consider adjusting the dose of [^{131}I]sodium iodine in these patients to avoid increased radiation exposure⁵¹, but it did not specify the exact adjustment needed.

The dose recommendations differed in the studies with patients with CKD stage 5. Eleven studies (45.8%) recommended a lower therapeutic dose, whereas two studies (8.3%) recommended a higher therapeutic dose. Eight studies (33.3%) indicated that the therapeutic dose should be calculated by individual patient dosimetry, and three studies (12.5%) did not give dose recommendations but offered other advice. One study recommended that when it is not possible to calculate the therapeutic dose by individual patient dosimetry, a lower dose of 25% of the normal dose should be given⁵³. In the following paragraphs we describe the various dose recommendations for [¹³¹I]sodium iodine treatment of thyroid cancer in patients with CKD stage 5.

Two studies recommended a lower therapeutic dose in patients with CKD stage 5 but did not quantify the optimal dose^{42, 66}. One of these studies based this recommended dose on a theoretical pharmacokinetic model that included both CAPD and HD with several regimes starting after 24 hours or 48 hours⁶⁶. The other study—performed in 10 patients, with four patients on CAPD and six patients on HD starting after 24 hours—based their advice on higher and more persistent salivary gland, nasal, oral, and gastrointestinal uptake of [¹³¹I]sodium iodine in this group of patients. In this study, six patients experienced persistent xerostomia and one patient a transient epistaxis⁴².

One study reduced the dose to 75% of the standard dose in two patients, based on literature also included in our review, and started HD 24 hours after administration of the dose, followed by daily HD until a safe radiation dose rate was reached⁵². Another study recommended a 30% reduction in dose for ablative or adjuvant therapies and a dose based on pretherapeutic dosimetry studies for metastatic patients. This study based these recommendations on absorbed dose in the bone marrow estimated from normalised measured whole-body activity⁷¹.

Two studies recommended a dose reduction of up to 50% of the dose given to individuals without renal insufficiency. In the first study, in five patients, the dose was reduced by 40% up to 50%, based on a previous case report and the researchers' own experience. Dialysis in the patients in this study was started 48 hours after treatment. The patients did not experience discomfort during hospitalisation, and four were reported to be free of recurrence after a follow-up period of three years.

For one patient, treatment was too recent for a valid follow-up⁴³. The second study described the successful treatment of one patient with a 50% reduction in dose based on maintaining a comparable area under the curve of a plot of ¹³¹I-iodine activity as function of time⁴⁴.

Five studies recommended a dose reduction to 25% of a standard dose, but the type and timing of dialysis varied by study. One of these studies successfully treated three patients with this dose based on a blood activity concentration–time curve⁴⁸. The second study successfully treated a patient with a lower dose based on the literature, although this patient did experience mild transient sialadenitis, which is a known adverse effect⁷⁵. The authors provided a mathematical analysis showing that a patient on HD receiving 21%–28% of a normal dose in combination with dialysis on days 2, 3, and 4 receives the same dose as a patient with normal kidney function⁵³. The third study used a dose of 25% of the normal dose based on the measurement of blood activity of a small tracing dose of [¹³¹I]sodium iodine in a patient with HD and reported successful ablation of tumour remnants⁵⁴. The fourth study successfully used 22% of a normal dose in a patient on CAPD⁷⁰. The last of these five studies reduced the doses given to two CAPD patients to 18%–20% of the dose given to a patient with normal kidney function. There was no recurrence of thyroid cancer in either patient after treatment after a follow-up period of seven to eight years⁵⁶.

Two studies recommended higher doses for dialysis patients than the doses used in patients with normal kidney function. Surprisingly, in one of these studies the authors suggested a dose of 125% of the normal dose, although they had treated a patient successfully with only 50% of a normal dose and started dialysis at 24 hours. They based their recommendation for the higher dose on the shorter half-life of ¹³¹I calculated from dialysate samples (2.7 +/- 0.8 hours) in comparison with the half-life of ¹³¹I in a patient with normal kidney function (11.4 hours)⁵⁹. The second study treated a patient with a higher dose than normal after an unsuccessful first treatment with a lower than normal dose⁶⁵. The two studies disagreed on the timing of dialysis. One study recommended initiating dialysis right after [¹³¹I]sodium iodine administration⁵⁹, while the other study suggested delaying dialysis to 48 hours after treatment to achieve a higher dose⁶⁵. Another study indicated that the two studies recommending higher doses erred in their assumptions by not including a true

effective half-life and not accounting for the almost complete lack of iodine clearance between dialysis sessions⁵³.

Eight studies did not give a dose recommendation but mentioned that the administered dose must be determined using individual patient dosimetry. Dosimetry prior to therapy aims to calculate the required dose by estimating the absorbable doses of radiation by internal organs and organs of interest based on the individual patient's iodine kinetics using a low dose of ^{131}I ^{46, 47, 53, 55, 62, 67, 73, 74}. These studies indicated that it is difficult to make a standard recommendation because of the large range in effective half-life and other variables between patients, such as differences in the amount of thyroid remnant or residual kidney function⁵³, and differences in dialysis protocols⁴⁶. Based on a mathematical analysis, one study—also discussed in the section about studies recommending a dose reduction to 25% of a standard dose—stated that when individual calculations are not available, 25% of the normal dose should be administered⁵³. In addition to the recommendation to use individual dosimetry calculations, some studies also offered safety advice, such as stating proper precautions against contamination of dialysis and staff exposure^{46, 67}. One study emphasised that discussions between personnel from the dialysis department, radiation safety, and nuclear medicine are essential in planning and executing the treatment with ^{131}I sodium iodine⁶². Three studies did not make dose recommendations but offered other recommendations (Table 8.7). One study described a theoretical model of ^{131}I sodium iodine dosing in thyroid disease but did not specify which disease⁶⁰.

^{131}I ioibenguane

One case report reported the use of ^{131}I ioibenguane in a patient with kidney failure and compared the findings with data from two patients with mild to moderate loss of kidney function. This study did not make a specific dose recommendation, but it did indicate that the administered dose of ^{131}I ioibenguane in patients with renal insufficiency should be reduced, given their reduced renal clearance of ^{131}I ioibenguane⁶⁸.

Table 8.7 Overview of dose recommendations and other advice for therapeutic radiopharmaceuticals

Radiopharmaceutical	Indication	Stage of renal failure (CKD)	Dose recommendation	Other advice
^[131] Iodine	Hyperthyroidism	5	This study used a dose based on the 24-h radiiodine uptake and the weight of the gland ⁴⁹ . This study used a dose of approximately one-third of the dose based on the 24-h radiiodine uptake and the weight of the gland ⁴⁸ .	Timing of dialysis should be consistent for both 24-h uptake study and treatment, and the most reasonable time for dialysis is 24 hours after administration ⁴⁹ . ND
			ND	Standard methods of management for hyperthyroidism are effective ⁶¹ .
	Thyroid cancer	3 and 4	Guidelines should consider adjusting the dose of ^[131] Iodine to avoid possible harmful effects of excess ^[131] Iodine on vital organs ⁵¹ .	ND
		5	Lower therapeutic doses are recommended ^{42, 66} . Lower therapeutic doses are recommended. The patient has to be administered around 75% of normal dose ^{52, 71} . Lower therapeutic doses are recommended. The patient has to be administered around 50% of normal dose ^{43, 44} .	Reconsider alternate treatment ⁴² . The dialysis frequency and the time interval between dose administration and dialysis can both be used effectively ⁶⁶ . Daily HD until a safe value of radioactivity for discharge was reached ⁵² . For metastatic patients pretherapeutic dosimetry studies are recommended ⁷¹ . Administer the dose as soon as possible after dialysis, while the 48-hour dialysis schedule of the patient could be carried on after ^[131] Iodine iodine treatment ⁴³ . For metastatic patients pretherapeutic dosimetry studies are recommended ⁷¹ .

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney diseases; HD, haemodialysis; ND, 'not determined'; rhTSH, recombinant human thyroid stimulating hormone.

Table 8.7 (Continued) Overview of dose recommendations and other advice for therapeutic radiopharmaceuticals

Radiopharmaceutical	Indication	Stage of renal failure (CKD)	Dose recommendation	Other advice
¹³¹ I]sodium iodine	Thyroid cancer	5	Lower therapeutic doses are recommended. The patient has to be administered around 25% of normal dose ^{48, 53, 54, 56, 70} .	First dialysis 24 hours after radiiodine administration ⁴⁸ . Dialysis ideally should be performed just prior to the dose of [¹³¹ I]sodium iodine. For radiation monitoring and precautions should be used for the first 3-4 dialysis sessions after treatment for thyroid cancer ⁵³ . Treatment requires multidisciplinary approach involving the endocrinologist, nuclear medicine physician, nephrologist, radiation safety team, and dialysis team ⁵³ . Arrange dialysis 48 hours after the dose ⁵⁴ . Based on the calculations for CAPD ⁵⁶ .
			Higher therapeutic doses are recommended ^{55, 56} .	Initiate the first dialysis after administration ⁵⁹ . Treatment procedure can be performed easily without significant radiation contamination or danger to personnel if proper precautions are observed ⁵⁹ . Delaying dialysis to 48 hours ⁶⁵ . Proper precautions for contamination of dialysis equipment and staff exposure should be taken ⁶⁶ . If individual dosimetry is not available, administer 25% of the normal dose ⁵³ .
			Individual patient dosimetry/calculations are needed to make a dose recommendation ^{46, 47, 53, 55, 62, 67, 73, 74} .	Daily HD during the first 5 days of treatment ⁵⁵ . Discussions with personnel from the dialysis department, radiation safety and nuclear medicine are essential in planning and execution ⁶² . Careful considerations regarding the timing of dialysis must be made ⁶⁷ . Considerations about safety must be made ⁶⁷ . Dialysis could be done earlier to decrease the absorbed dose ⁴⁵ . Stimulation with rhTSH simplifies the selection of ¹³¹ I-doses in euthyroid dialysis patients ⁵⁰ . Use of CAPD because of ease with which contamination with radiation could be prevented ⁷² .
¹³¹ I]jobenguane	Thyroid disease (not specified)		Factor of 3x dose reduction ⁶⁰ .	Optimum thyroid/reminder cumulated activity ratio for dialysis starting between 36 and 48 hours ⁶⁰ .
	Pheochromocytoma	5	It may be prudent to reduce the dose of [¹³¹ I]jobenguane in renal insufficiency ⁶⁸ .	The alteration in biodistribution in the face of renal disease must be considered in the interpretation of [¹³¹ I]jobenguane scintigraphy and in the radiation dosimetry ⁶⁸ .

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney diseases; HD, haemodialysis; ND, 'not determined'; rhTSH, recombinant human thyroid stimulating hormone.

8.4 DISCUSSION

Based on a systematic review of the literature, which included 34 studies, consistent recommendations about radiopharmaceutical dosing in patients with renal insufficiency cannot be given. While studies do mention difficulties with the dosing of these medicines in patients with insufficient renal function, information is available for only a few radiopharmaceuticals, and recommendations are often contradictory.

Results for the diagnostic radiopharmaceutical FDG suggest that adjustment of the dose is not required, but some effect on the uptake of FDG must be considered in interpreting the scan. We found no results for other diagnostic radiopharmaceuticals. This finding was unexpected and may suggest that, even though altered biodistribution due to renal insufficiency may lead to a poor target-to-non-target ratio with diagnostic radiopharmaceuticals, no significant influence on image quality is apparent in daily practice. We hypothesise that for most diagnostic radiopharmaceuticals insufficient renal function may be less important because inadequate tissue distribution and background clearance do not lead to clinically significant issues published, and technical and patient-related factors have a more important influence on scan quality. Further work is needed to investigate the effect of insufficient renal function on the biodistribution of diagnostical radiopharmaceuticals and the diagnostic outcome.

For the therapeutic radiopharmaceutical [^{131}I]sodium iodine, the dosing recommendations are not in agreement. For treatment of thyroid cancer, most studies recommend dosing based on individual patient dosimetry calculations. Other studies recommend changing the dose, with advice varying from lowering the dose by 75% to increasing the dose. The variations in dose recommendations for [^{131}I]sodium iodine might be explained by variability in individual patients and in used methods, including (a) differences in the amount of remnant thyroid tissue and tumour stage in general; (b) variation in residual kidney function; (c) variability in effective half-life; and (d) differences in method, timing, and frequency of dialysis treatment^{43, 44, 66, 67, 76}.

Although the findings for therapeutic radiopharmaceuticals were limited, some studies indicated that dose adjustments in patients with insufficient renal function are important, and that altered biodistribution does affect therapeutic response and the risk of toxicity for non-target organs. A non-optimised dose in patients with renal insufficiency may lead to inadequate treatment⁴², increased radiation exposure⁵¹, or an increased risk of adverse effects (for example, bone marrow toxicity, xerostomia, epistaxis, sialadenitis, or xerostomia from treatment with [¹³¹I]sodium iodine)^{42, 43, 53, 71}.

We found studies for only two therapeutic radiopharmaceuticals, and none providing dose recommendations for radiopharmaceuticals, such as [¹⁷⁷Lu]Lu-oxodotreotide or [⁹⁰Y]Y-octreotide, even though renal insufficiency is described as a risk factor in ¹⁷⁷Lu-somatostatin analogue treatment^{77, 78}, and the radiopharmaceutical's Summary of Product Characteristics warns that special consideration regarding the dose is required in these patients⁷⁹. In this regard, the European Medicines Agency has indicated that safety and efficacy studies often exclude patients with renal insufficiency⁸⁰. Therefore, we recommend including patients with insufficient renal function in studies, listing pharmacokinetic information regarding the influence of decreased kidney function, and providing specific dosing recommendations for therapeutic radiopharmaceuticals.

With the introduction of new therapeutic radiopharmaceuticals, there is increased interest in patient-specific dosimetry. Although the practice of patient-specific dosimetry for therapeutic radiopharmaceuticals has been shown to vary across Europe⁸¹, efforts are underway to optimise and standardise this practice^{82, 83}. Patient-specific dosimetry could play a role in predicting or verifying the dose of therapeutic radiopharmaceuticals in patients with renal insufficiency, and we suggest including renal insufficiency in future work on this topic.

Another finding is that most studies describe patients with CKD stage 5; only a few studies (8.8%) include patients in other CKD stages. As the estimated prevalence of CKD is 11%–13% in the general population, with the majority in CKD stage 3 and only 0.1% in CKD stage 5, one would expect more information to be available on patients in CKD stages 1–4⁸. It is difficult to explain these results. Possible explanations are that the effects of CKD stages 1–4 on the results of the nuclear

medicine examination are less pronounced than those of CKD stage 5, that information on kidney function in patients in lower CKD stages is not available to the nuclear medicine staff, or that to date kidney function has not been considered when planning for a patient. To develop a full picture of the dosing of radiopharmaceuticals in all CKD stages future studies should include not only patients with CKD stage 5, but also those in other stages.

Regarding patients in CKD stage 5 on renal treatment therapy, studies indicate that dialysis complicates the dosing of the radiopharmaceutical. Clearance of the radiopharmaceutical during dialysis may be altered or influenced by many aspects. First, characteristics of the substance such as molecular weight, solubility, binding to proteins, and volume of distribution are important to consider. In addition, dialysis-specific aspects such as the characteristics of the dialysis membrane, transmembrane pressure, dialysate flow rate, and timing and frequency of dialysis impact the clearance of the pharmaceutical⁸⁴. These aspects complicate the treatment of patients with a therapeutic radiopharmaceutical and necessitate careful consideration of the timing and frequency of dialysis^{66, 67}. Other challenges for patients on renal treatment therapy receiving a therapeutic radiopharmaceutical include contamination of dialysis equipment and radiation exposure to staff. However, studies have shown that with proper precautions in planning and execution, the procedure can be performed safely^{46, 59, 62, 67}. A multidisciplinary approach, including the nuclear medicine physician, endocrinologist, nephrologist, radiation safety team, and dialysis team, is advised for treatment⁵³.

We believe our systematic review identifies an important gap in research for the dosing of radiopharmaceuticals in patients with renal insufficiency. The strength of our review is that we used a systematic approach and formulated a well-defined search string to identify available studies on radiopharmaceuticals and renal insufficiency. The researchers screened the included studies independently, which decreased the possibility of bias in this review.

A limitation of our review is that we only included published information on the dosing of radiopharmaceuticals in patients with renal insufficiency. Other data, such as data on file available from marketing authorisation holders or studies published in another language, may provide more insight into this subject. Although outside

the scope of this study, an evaluation by an expert panel with diverse areas of expertise may also aid in compiling recommendations. Forming such an expert opinion is described for the safety evaluation of other drugs in combination with disease conditions and may well be a next step in clarifying the dosing of radiopharmaceuticals in patients with renal insufficiency⁸⁵.

The quality of the included studies is not adequate for making reliable radiopharmaceutical dosing recommendations for patients with renal insufficiency. Most of the observational studies (71.4%) were determined to be of 'poor' quality. For many included studies (79.4%), a quality assessment using the NOS was not possible because they were case reports and theoretical models. The quality of evidence is low, as many studies report only one case (such as dialysis patients) or consider only one factor (such as one radiopharmaceutical). It is apparent that more well-designed research needs to be done to include all radiopharmaceuticals and to include patients with renal insufficiency in various CKD stages.

Uniform dose recommendations for radiopharmaceuticals based on kidney function are difficult to provide. Therefore, we recommend that additional research should be conducted to address this absence of information about radiopharmaceuticals and renal function insufficiency and to provide appropriate dose recommendations for clinical practice. With the introduction of new therapeutic radiopharmaceuticals, such as those based on alpha-emitting radionuclides, including patients with renal insufficiency may become even more important⁸⁶.

8.5 CONCLUSION

This study has determined that information on the dosing of radiopharmaceuticals in patients with renal insufficiency is limited. While some studies do mention difficulties with dosing these medicines in these patients, information is available for only a few radiopharmaceuticals and for only some CKD stages. Moreover, recommendations are sometimes contradictory. Further research on the dosing of radiopharmaceuticals in patients with insufficient renal function is needed to determine whether specific dosing is required.

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Chapter 9

Summary, future perspectives, and conclusions

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9.1 INTRODUCTION AND AIM

Nuclear medicine plays an important role in the diagnosis and treatment of patients. The field relies on radioactive compounds called radiopharmaceuticals, consisting of a tracer part that is linked to a radioactive marker or nuclide. The tracer part is a molecule or particle and determines where the radiopharmaceutical will localise in the body. The radioactive marker is a radionuclide and emits radiation that can be detected with a scan or delivers a radiation dose to a target area. In that way, healthcare professionals can visualise diseases with an imaging technique or treat disease, depending on the characteristics of the radiopharmaceutical¹. Most radiopharmaceuticals are used for diagnostic purposes and enable visualisation of most physiological processes in the human body using imaging techniques such as planar imaging, SPECT, or PET. Today, SPECT and PET are often combined with CT. These hybrid cameras are then referred to as SPECT/CT or PET/CT and offer better imaging than SPECT or PET alone, because they have the ability to image both processes in the body as well as anatomy, which allows for accurate localization of abnormalities^{1–3}. Healthcare professionals use other radiopharmaceuticals for therapeutic purposes to deliver a radiation dose to a specific target in the body in order to damage or eradicate abnormal tissues⁴.

Drug safety is an important aspect of medical practice. As with any drug, radiopharmaceuticals go through extensive safety evaluation which must show a favourable benefit-risk profile before manufacturers can market them. One aspect of drug safety relates to adverse reactions. An adverse reaction is defined by the WHO as ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’. We need to distinguish this from an adverse event. An adverse event is not necessarily related to the drug and is defined by the WHO as ‘any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment’^{5,6}.

During the past decades, radiopharmaceuticals have proven to be very safe⁷. Undoubtedly, the reason for this is that radiopharmaceuticals generally do not have a pharmacologic effect due to use in very low quantities—in the range of

micrograms¹. Therefore, adverse reactions due to a pharmacologic action will not occur for most radiopharmaceuticals. However, adverse events with radiopharmaceuticals may occur. These adverse events are unusual, relate to an individual patient and cannot be predicted on the basis of the pharmacological action. Examples of these unusual adverse events are allergic reactions. Furthermore, radiopharmaceuticals are often used only once or a few times in an individual patient since the goal is generally diagnostic imaging. Accordingly, problems with drug safety, such as those associated with long-term use of other drugs, are unlikely to occur with radiopharmaceuticals. However, another reason for this low occurrence may be that these studies mainly rely on voluntary identification and reporting of adverse events by healthcare professionals, which is subject to underreporting. Furthermore, little research has been done on adverse events of radiopharmaceuticals from the patient's perspective. Current studies do not report detailed information about such aspects as severity and impact to the patient^{8–15}. Patients themselves can be a valuable source of information about adverse events^{16–18}. Assessing adverse events from the perspective of a patient may yield important information about severity and the impact on their lives and may shed light on the true frequency of adverse reactions.

Another aspect of drug safety of radiopharmaceuticals is the biodistribution (i.e., the distribution of the drug in the body). After all, the biodistribution will also determine the localisation of the radiopharmaceutical and is crucial to diagnostic or therapeutic outcomes. Interactions with other drugs may alter the biodistribution and might ultimately affect diagnostic or therapeutic outcomes^{19, 20}. In the case of interactions of a diagnostic radiopharmaceutical with another drug, the interaction might influence the scan—e.g., reduce the uptake in areas of interest or cause abnormal uptake in non-relevant areas—and in that way lead to wrong or incomplete information that could ultimately affect the patient's diagnosis^{21–23}. Even though many drugs that interact with the biodistribution of radiopharmaceuticals are known, for some interactions the mechanism is still unknown and recommendations for clinical practice are lacking. Research in this area may help in providing clear guidance.

In addition to the aspect of biodistribution, certain groups of patients need additional attention in order to ensure optimal outcome and avoid safety issues. These patients need extra precautions, such as special preparations or a change in dose, to ensure the safe use of radiopharmaceuticals. For some groups of patients, such as children and pregnant or breastfeeding women, guidelines are available^{24, 25}. For other groups of patients, such as patients with renal insufficiency or patients carrying the acute porphyria gene, clear recommendations are not yet available.

Finally, patients' radiation exposure may be a concern with the use of radiopharmaceuticals. Nevertheless, patients' exposure to radiation from nuclear medicine procedures is not excessive and the incremental risks are small and outweighed by the benefits²⁶.

Despite the fact that radiopharmaceuticals have an excellent safety profile, relatively little is known about adverse events, interactions and use in some specific patient groups. Research on these aspects of drug safety in radiopharmaceuticals can help to gain more knowledge and improve the drug safety of radiopharmaceuticals. For this reason, we studied drug safety issues of radiopharmaceuticals in this thesis, with the main topics being adverse reactions, interactions with drugs, and considerations in specific patient populations. We aim to contribute to a better understanding of drug safety of radiopharmaceuticals and with this to improve the safe use of radiopharmaceuticals and increase patients' and health care professionals' awareness.

In this final chapter we describe the main findings of the studies that are presented in this thesis. Subsequently we describe the implications of the findings for future research.

9.2 MAIN FINDINGS

9.2.1 Adverse reactions of radiopharmaceuticals

The first drug safety topic we cover in this thesis concerns adverse reactions with the use of radiopharmaceuticals. Although healthcare professionals know that radiopharmaceuticals can cause adverse events, information is only scarcely

available in case reports and databases and may not be readily accessible to healthcare professionals. We performed a systematic review in **Chapter 2** and provided an overview of adverse events of radiopharmaceuticals for diagnostic purposes along with their characteristics as presented in literature. We found a median frequency for adverse events in diagnostic radiopharmaceuticals reported in literature of 0.0016%. Most reported adverse events are skin disorders (such as rash and itching) and general disorders (such as fever). Interestingly, very little attention has been paid to the patient's experience with adverse events from radiopharmaceuticals. To our knowledge, only one small study from a patient perspective, using one radiopharmaceutical was performed (in contrast, in our review we found 100 studies written from the perspective of the healthcare professionals). However, the researchers did not specify detailed information about the method of recording and analysing the adverse events²⁷.

In order to study adverse events of radiopharmaceuticals from a patient perspective, the development of a validated questionnaire is needed to collect reliable information from patients about adverse events, time course, severity, and outcome. In **Chapter 3**, we describe the development and validation of such a questionnaire. The questionnaire was developed with input from patients undergoing a nuclear medicine examination. Some questions and answer options were revised, partly due to the input from patients, in the initial questionnaire to improve clarity. One hundred patients undergoing nuclear medicine examination tested this version and demonstrated the acceptability of the questionnaire. The developed questionnaire proved to be a suitable and valid instrument.

In **Chapter 4**, we used the developed questionnaire in a larger study of 1,002 patients in a regional hospital in the Netherlands (Isala Hospital in Zwolle). In this study we aimed to determine the characteristics and frequency of patient-reported adverse events of radiopharmaceuticals and to assess the outcome of these adverse events from the patient's perspective. Using the questionnaire, we collected patient-reported information on adverse events that patients attributed to the radiopharmaceutical; we included events that occurred immediately after administration of the radiopharmaceutical as well as those that occurred later. Two independent researchers analysed, coded, and assessed the adverse events for

causality. Most patient-reported adverse events of radiopharmaceuticals were a hot feeling, a sense of oppressed breathing, chest discomfort, headache, and fatigue. Of the patient-reported adverse events, 43.0% were possibly or probably causally related to radiopharmaceuticals. The other adverse events were not or were unlikely to be causally related to radiopharmaceuticals. We found the frequency of patient-reported adverse drug reactions to diagnostic radiopharmaceuticals to be 2.8%. This is higher than the frequency of 0.0016% as we found in the literature. No important medical events were related to the administration of diagnostical radiopharmaceuticals. Most adverse events (80%) occurred shortly after administration of the radiopharmaceutical and resolved within a few hours. Some events (20%) emerged after patients had left the nuclear medicine department, took longer to resolve, and sometimes (27.5%) prompted the patient to consult a healthcare professional. Our study findings imply that adverse events of diagnostic radiopharmaceuticals, as experienced by patients, are more common than previously assumed. Our study shows that patients can provide useful information about radiopharmaceuticals adverse events, complementing the information available in the literature. In addition to this systematic research, the analysis of individual cases can also contribute to more knowledge about adverse reactions. In **Chapter 5**, we describe an example of a case report of a 49-year-old woman developing an anaphylactic reaction to [^{99m}Tc]Tc-macrosalb used for pulmonary scintigraphy (a nuclear medicine examination to evaluate the blood supply to the lungs).

9.2.2 Interactions of radiopharmaceuticals with drugs

The second drug safety topic we cover in this thesis concerns interactions with other drugs. One well-known interaction is the high uptake of [^{18}F]fludeoxyglucose (FDG) in the colon seen on PET scans in patients using the oral antidiabetic drug metformin. Although healthcare professionals do not generally use FDG PET to study primary colorectal cancer, the increased uptake of FDG in the colon could still obscure lesions and cause findings to be missed. While several studies recommended that metformin should be discontinued before the FDG PET scan, there is no consensus on the optimal discontinuation period^{28–30}. In **Chapter 6**, we therefore describe our

study examining whether discontinuing metformin for at least 48 hours prevents metformin-induced FDG uptake in all segments of the colon. For this, we included patients with type 2 diabetes who were using metformin before undergoing an FDG PET/CT scan and created two groups: patients who discontinued metformin for less than 48 hours and patients who discontinued metformin for between 48 and 72 hours. We included a control group comprised of non-diabetic patients who were not using metformin before undergoing an FDG PET/CT. We visually scored the uptake of FDG in four segments of the colon. We found that discontinuing metformin for 48 hours before undergoing an FDG PET/CT still gives a high uptake in the distal parts of the colon when compared with non-diabetic patients who are not using metformin. This raises the question of whether patients should discontinue metformin even longer than 48 hours. However, longer discontinuation periods may not be feasible for patients and could influence their diabetic control and health. Discontinuing metformin for 48 hours did normalise colonic uptake in the more proximal segments of the colon and thus 48 hours seems to be useful.

9.2.3 Specific patient populations and radiopharmaceuticals

A third and final drug safety topic we cover in this thesis is the safe use of radiopharmaceuticals in specific patient populations. For patients with renal insufficiency or patients carrying the acute porphyria gene, clear recommendations are not yet available. For this reason, we have further investigated the use of radiopharmaceuticals in these two specific patient populations.

The acute porphyrias are a group of rare metabolic disorders of the haem biosynthetic pathway. Carriers of the acute porphyria gene are prone to acute attacks, which can be precipitated by drug exposure. The symptoms of an attack of acute porphyria may include severe abdominal pain, constipation, nausea, confusion, and seizures. These attacks can be life-threatening. Hence, knowing whether a drug is safe for carriers of acute porphyria genes is important. In **Chapter 7**, we discuss our assessment of radiopharmaceuticals on their porphyrogenicity, i.e., the potential of a drug to induce an attack. For this assessment, we used an algorithm for predicting the risk that a certain drug may activate the disease in a gene carrier of acute

porphyria³¹. We based our assessment on information about metabolism, (particle) size, and plasma concentration of the drug. Of the 41 radiopharmaceuticals assessed, most radiopharmaceuticals are probably safe to use. We classified five radiopharmaceuticals ($[^{131}\text{I}]$ Iodomethyl norcholesterol, $[^{99\text{m}}\text{Tc}]$ Tc-mebrofenin, $[^{99\text{m}}\text{Tc}]$ Tc-phytate, $[^{99\text{m}}\text{Tc}]$ Tc-sestamibi and $[^{201}\text{Tl}]$ Tl-chloride) as possible porphyrogenic and concluded they should not be prescribed for patients suffering from acute porphyria unless an urgent indication is present and no safer alternative is available. In such cases, potential users should seek advice from a porphyria expert; preventive measures may be required.

Another specific group of patients where extra precautions may be needed are those suffering from renal insufficiency. As renal insufficiency will reduce excretion and elevate plasma concentrations of some pharmaceuticals and their metabolites, dose adjustment of the radiopharmaceutical may be necessary, especially when cleared by the kidney^{32–35}. However, standards for dosing of radiopharmaceuticals in renal insufficient patients are still lacking. In **Chapter 8**, we therefore discuss the systematic review we performed aiming to provide dose recommendations of radiopharmaceuticals in renal insufficient patients. Surprisingly, we could find no consistent recommendations about radiopharmaceutical dosing in patients with renal insufficiency. Although some studies mention difficulties with dosing in patients with insufficiency in renal function, information about only a few radiopharmaceuticals is available and recommendations are often contradictory.

9.3 FUTURE PERSPECTIVES

Even though radiopharmaceuticals, both for diagnostics and therapy, are in use for many decades and generally have an excellent safety track record, we do find some gaps in our knowledge and in our opinion more research could contribute to further understand and improve drug safety of radiopharmaceuticals.

Currently, promising new radiopharmaceuticals are under development, such as PET radiopharmaceuticals for myocardial perfusion imaging, dementia, and prostate cancer imaging³⁶. Furthermore, researchers are putting much effort into the development of ‘theragnostics’. The term theragnostic (sometimes theranostic) is a

combination of the words ‘therapeutics’ and ‘diagnostics’ and refers to a methodology that delivers diagnostic and therapeutic properties with one compound³⁷. Theragnostic radiopharmaceuticals bring diagnosis and therapy even closer, as they use an (almost) identical tracer part that can be bound either to a diagnostic radionuclide or to a therapeutic radionuclide. In that way using a scan we can predict where the therapeutic will localise and to what extent. This approach will improve the method for selecting patients for effective therapy and may predict adverse events³⁸. Yet another development is the introduction of new therapeutic radiopharmaceuticals based on alpha-radiation-emitting radionuclides, which have the potential to locally eradicate tumour cells with a high radiation dose while saving healthy tissue adjacent to the tumour as much as possible³⁹.

All these new radiopharmaceuticals will undergo extensive safety studies and must show a favourable benefit-risk profile. Contemporary knowledge of drug safety will also lead to more focus on drug safety aspects with the development of new radiopharmaceuticals nowadays compared to the development in the past⁴⁰. Nevertheless, some safety aspects will probably only become apparent during post-marketing surveillance or follow-up studies. We show in this thesis that the patient can play an important role during these studies. We believe that researchers should include patients more with future studies than they have in the past, as patients themselves can indicate adverse events. This information can help healthcare professionals with patient care and in the management of adverse events.

We show that the frequency of patient-reported adverse drug reactions to diagnostic radiopharmaceuticals is much higher than reported in literature, i.e., 2.8% versus 0.0016%. This suggests underreporting of adverse events of radiopharmaceuticals in literature, as is well known for other drugs⁴¹. We recommend research to determine the reasons for this underreporting and identify possible areas for improvement in reporting.

In general, we believe that researchers should pay more attention to the area of interactions and radiopharmaceuticals. Research in this area could focus on describing new or unknown interactions, unravelling the exact mechanisms of these interactions, and ultimately aiding healthcare professionals with substantiated and clear advice for management in patients. Regarding the high uptake of FDG on PET

in the colon with the use of metformin, we showed that discontinuing metformin for 48 hours seems to be useful for the more proximal segments of the colon; however, FDG uptake remained high in the more distal segments of the colon. This raises the question of whether patients should discontinue metformin even longer than 48 hours, with risk of influence on their diabetic control. For now, the mechanism behind the relationship between metformin and FDG uptake in the colon remains unclear. Understanding the exact mechanism of the interaction may aid in answering the question of whether patients using metformin and undergoing a FDG PET/CT scan should discontinue metformin even longer than 48 hours.

Finally, future research should place more emphasis on the use of radiopharmaceuticals in specific groups. In our work, we assessed porphyrogenicity of radiopharmaceuticals and classified them according to a theoretical model; however, clinical conformation is still needed. Further, we reviewed the literature on dosing of radiopharmaceuticals in patients with renal insufficiency and found that little is known. Ideally, trials with new radiopharmaceuticals should also include specific groups of patients, such as acute porphyria patients and renal insufficient patients. Another option would be to evaluate radiopharmaceuticals use in these groups with an expert panel with diverse areas of expertise. Forming such an expert opinion is reported for the safety evaluation of other drugs in combination with disease conditions⁴² and may shed light on the use of radiopharmaceuticals in specific groups of patients and aid in translating findings into clear recommendations for patients and healthcare professionals.

9.4 CONCLUSIONS

Nuclear medicine provides essential information for diagnosis and treatment of patients. The radiopharmaceuticals used are safe but not entirely free of adverse events and interactions in all patients. In this thesis we studied several topics related to radiopharmaceuticals drug safety. We show that patients themselves can make an important contribution to knowledge in this area. Interestingly, patients reported adverse reactions that they attributed to the use of diagnostic radiopharmaceuticals

with a frequency of 2.8%, which is much higher than assumed in the literature. However, it remains difficult to establish the causal relationship with certainty.

We hope that this thesis contributes to a better understanding of the safety of radiopharmaceuticals, especially of some topics, such as adverse reactions, metformin induced FDG uptake in the colon, the use of radiopharmaceuticals in renal insufficiency and porphyria. This may increase awareness among patients and healthcare providers.

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Chapter 10

Nederlandse samenvatting

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10.1 INTRODUCTIE EN DOEL

Nucleaire geneeskunde speelt een belangrijke rol bij de diagnostiek en behandeling van patiënten. Het vakgebied gebruikt radioactieve verbindingen, die radiofarmaca—in enkelvoudsvorm radiofarmacon—genoemd worden en bestaan uit een tracerdeel dat gebonden is aan een radioactief deel. Het tracerdeel is een molecuul of deeltje, en zorgt ervoor dat het radiofarmacon zich richt op een specifieke plek in het lichaam en daar lokaliseert. Het radioactieve deel is een radionuclide (een radioactief atoom) en zendt straling uit die kan worden gedetecteerd met een scanner of welke een stralingsdosis afgeeft op een specifieke plek. Op deze manier kunnen aandoeningen in beeld gebracht worden of worden behandeld. De meeste radiofarmaca worden gebruikt voor diagnostische doeleinden en maken het mogelijk om afwijkende processen in het menselijk lichaam zichtbaar te maken. Hierbij worden technieken gebruikt, zoals planaire scintigrafie, ‘Single Photon Emission Computed Tomography’ (SPECT) of ‘Positron Emission Tomography’ (PET). Voor een betere beeldvorming worden tegenwoordig SPECT en PET ook vaak gecombineerd met computertomografie (CT), waarbij gebruikt wordt gemaakt van röntgenstraling. Deze hybride camera’s worden dan SPECT/CT of PET/CT genoemd, en kunnen zowel processen in het lichaam als de anatomie afbeelden, waardoor er een nauwkeurige lokalisatie van afwijkingen kan worden bepaald. Naast het gebruik van de diagnostische radiofarmaca zijn er ook therapeutische radiofarmaca die gebruikt worden voor het behandelen van aandoeningen. Deze therapeutische radiofarmaca geven een stralingsdosis af welke dan bijvoorbeeld kankercellen kan beschadigen of vernietigen.

Medicatieveiligheid is een belangrijk aspect in de medische praktijk. Zoals bij elk geneesmiddel, ondergaat ook een radiofarmacon een uitgebreide veiligheidsevaluatie. Voordat een radiofarmacon wordt toegelaten tot de markt moet er te zijn aangetoond dat er een gunstig werkzaamheid-risico profiel is. Een van de aspecten van medicatieveiligheid heeft betrekking op bijwerkingen. Een ‘bijwerking’ kan worden gedefinieerd als een onbedoelde schadelijke gebeurtenis bij gebruik van een geneesmiddel in een normale dosering. We dienen hierbij onderscheid te maken tussen een ‘bijwerking’ en een ‘vermoede bijwerking’. Een

vermoede bijwerking hoeft namelijk niet gerelateerd te zijn aan het geneesmiddel en wordt dan ook gedefinieerd als een gebeurtenis die optreedt bij het gebruik van het geneesmiddel, maar waarbij het niet duidelijk is of er daadwerkelijk een verband tussen de bijwerking en het geneesmiddel is.

Gedurende het gebruik van radiofarmaca in de afgelopen decennia is gebleken dat zij over het algemeen erg veilig in het gebruik zijn. De reden hiervan is dat radiofarmaca in het algemeen geen farmacologisch effect hebben door het gebruik van zeer lage hoeveelheden—vaak in de ordegrootte van microgrammen of nog minder. Hierdoor zullen bijwerkingen ten gevolge van een farmacologisch effect bij de meeste radiofarmaca niet optreden. Toch kunnen bijwerkingen bij radiofarmaca voorkomen. Deze bijwerkingen zijn ongebruikelijk, hebben betrekking op een individuele patiënt en zijn op grond van het farmacologisch effect vaak niet te voorspellen. Voorbeelden van deze ongebruikelijke bijwerkingen zijn allergische reacties. Verder worden radiofarmaca vaak maar één of enkele keren gebruikt bij een individuele patiënt, aangezien het doel in het algemeen diagnostische beeldvorming is. Daarom is het uitermate onwaarschijnlijk dat er problemen met de geneesmiddelenveiligheid op zullen treden bij radiofarmaca, zoals die wel bekend zijn bij langdurig gebruik en in veel hogere doses van andere geneesmiddelen. Echter een andere reden waarom verondersteld wordt dat bijwerkingen zeldzaam zijn, zou kunnen zijn dat de beschreven studies voornamelijk gebruik maken van vrijwillige herkenning en rapportage van bijwerkingen door zorgverleners, waarbij er sprake kan zijn van een onderrapportage. Daarnaast is er tot op heden nog maar weinig onderzoek uitgevoerd naar bijwerkingen van radiofarmaca vanuit het perspectief van de patiënt. Huidige studies geven geen gedetailleerde informatie over aspecten zoals de ernst en impact voor de patiënt. De patiënt zelf kan een waardevolle bijdrage leveren aan de informatie over bijwerkingen. Beoordeling van bijwerkingen vanuit dit perspectief zou mogelijk belangrijke gegevens kunnen opleveren over de ernst en impact op hun welzijn en betere informatie geven over de frequentie daarvan.

Een ander aspect van medicatieveiligheid van radiofarmaca heeft betrekking op de biodistributie (de verspreiding van een geneesmiddel in het lichaam). De biodistributie bepaalt immers mede het lokaliseren van het radiofarmacon en daarmee een succesvolle beeldvorming of therapie uitkomst. Interacties met

geneesmiddelen kunnen de biodistributie van radiofarmaca mogelijk veranderen en daarmee de beeldvorming of behandeling beïnvloeden. De scan wordt dan verstoord of de behandeling beïnvloed. In het geval van interacties van een diagnostisch radiofarmacon met een ander geneesmiddel kan de opname op de bedoelde plekken afnemen of juist een abnormale opname geven op niet gewenste plekken. Dit kan leiden tot foutieve of onvolledige informatie die uiteindelijk de diagnose zou kunnen beïnvloeden. Ondanks dat voor veel geneesmiddelen de interacties met radiofarmaca bekend zijn, zijn voor een aantal interacties de mechanismen onbekend en ontbreken adviezen voor de klinische praktijk. Onderzoek in dit gebied kan helpen om tot duidelijke adviezen te komen.

Naast het aspect van biodistributie is er in het kader van medicatieveiligheid ook aandacht nodig voor een aantal specifieke patiëntgroepen om een optimaal resultaat te garanderen en veiligheidsproblemen te voorkomen. Extra voorzorgen, zoals bijzondere bereidingen of dosisaanpassingen, zijn nodig om het veilig gebruik van radiofarmaca bij deze patiënten mogelijk te maken. Voor een aantal patiëntgroepen, zoals moeders die borstvoeding geven of kinderen, zijn duidelijke richtlijnen beschikbaar. Voor andere groepen zijn deze richtlijnen nog niet beschikbaar, zoals bijvoorbeeld voor patiënten met nierinsufficiëntie of patiënten die drager zijn van het gen dat verantwoordelijk is voor acute porfyrie.

Tenslotte kan er bij het gebruik van radiofarmaca bezorgdheid zijn over de stralingsbelasting voor de patiënt. In het algemeen echter is de stralingsbelasting voor patiënten van nucleair geneeskundige onderzoeken laag en is de toename van het risico op significante schade als gevolg van deze straling zeer laag. Dit kleine risico weegt niet op tegen de voordelen die een diagnostisch onderzoek voor de patiënt oplevert.

Ondanks het feit dat radiofarmaca een excellent veiligheidsprofiel hebben, is er relatief weinig bekend over bijwerkingen, interacties en het gebruik in een aantal specifieke patiëntengroepen. Onderzoek naar deze aspecten van medicatieveiligheid bij radiofarmaca kan ertoe bijdragen dat er meer bekend wordt en medicatieveiligheid van radiofarmaca verbeterd. Vandaar dat wij in dit proefschrift nader onderzoek hebben uitgevoerd naar medicatieveiligheidsaspecten van radiofarmaca, met als belangrijkste onderwerpen: bijwerkingen zelf, interacties met

geneesmiddelen, en afwegingen in speciale patiëntgroepen. Wij beogen hiermee een bijdrage te leveren aan een beter begrip van de medicatieveiligheid van radiofarmaca en hiermee het veilig gebruik van radiofarmaca en het bewustzijn onder patiënten en zorgverleners te verbeteren.

In dit laatste hoofdstuk beschrijven wij de belangrijkste bevindingen van de studies die opgenomen zijn in dit proefschrift. Vervolgens beschrijven wij wat de bevindingen kunnen betekenen voor toekomstig onderzoek.

10.2 BELANGRIJKSTE BEVINDINGEN

10.2.1 Bijwerkingen van radiofarmaca

Het eerste onderwerp over medicatieveiligheid dat wij in dit proefschrift bespreken, zijn bijwerkingen. Hoewel het bekend is dat bijwerkingen kunnen optreden bij het gebruik van radiofarmaca, is er slechts weinig informatie in de literatuur beschikbaar, is deze slechts beperkt beschikbaar en vaak afkomstig uit casusbesprekingen of niet eenvoudig toegankelijke databanken en niet altijd makkelijk beschikbaar voor zorgverleners. In **hoofdstuk 2** hebben wij een systematische review van de literatuur uitgevoerd en geven wij een overzicht van bijwerkingen van diagnostische radiofarmaca en hun karakteristieken. Wij vonden een mediane frequentie van bijwerkingen van diagnostische radiofarmaca, zoals gerapporteerd in de literatuur, van 0,0016%, en vonden als meest gerapporteerde bijwerkingen huidaandoeningen (zoals huiduitslag en jeuk) en algemene aandoeningen (zoals koorts). Opmerkelijk genoeg is er weinig aandacht voor de ervaringen van de patiënt rond de bijwerkingen van radiofarmaca. Voor zover wij weten is er slechts één kleine studie vanuit het perspectief van de patiënt verricht waarbij ook slechts één radiofarmacon werd gebruikt (in tegenstelling tot de 100 studies welke wij in onze review vonden en die geschreven zijn vanuit het gezichtspunt van de zorgverlener). De onderzoekers van deze studie gaven echter geen gedetailleerde beschrijving van de methode van het noteren en analyseren van de bijwerkingen.

Om de bijwerkingen van radiofarmaca vanuit het perspectief van de patiënt goed te kunnen onderzoeken moest eerst een gevalideerde vragenlijst worden ontwikkeld,

die betrouwbare informatie van patiënten over de bijwerkingen, het verloop in de tijd, de ernst en uitkomst oplevert. In **hoofdstuk 3** beschrijven wij de ontwikkeling van een dergelijke vragenlijst. De vragenlijst werd ontwikkeld met inbreng van zowel experts als patiënten. Een aantal vragen en antwoordopties in de eerste versie van de vragenlijst werden, mede door de input van patiënten, verbeterd. Vervolgens testten honderd patiënten die een nucleair geneeskundig onderzoek ondergingen deze vragenlijst. In deze testfase lieten we zien dat de vragenlijst goed werd geaccepteerd door de patiënten, en toonden we aan dat de ontwikkelde vragenlijst bruikbaar en valide was.

In **hoofdstuk 4** gebruikten we de ontwikkelde vragenlijst in een grotere studie onder 1002 patiënten in een groot regionaal ziekenhuis in Nederland (Isala in Zwolle). Hierbij hadden wij als doel om de karakteristieken en frequentie van bijwerkingen van radiofarmaca vanuit het perspectief van de patiënt te bepalen en de uitkomst van deze bijwerkingen te beoordelen. Met de vragenlijst verzamelden wij informatie over bijwerkingen die patiënten toeschreven aan het gebruikte radiofarmacon. Hierbij beoordeelden wij zowel de bijwerkingen direct na toediening als de bijwerkingen die plaatsvonden na het verlaten van de afdeling Nucleaire Geneeskunde. Vermoede bijwerkingen werden geanalyseerd, gecodeerd en beoordeeld op de sterkte van het oorzakelijk verband. De meeste door de patiënt gerapporteerde vermoede bijwerkingen waren: een heet gevoel, benauwdheid, druk op de borst, hoofdpijn en vermoeidheid. Van de door de patiënten gemelde vermoede bijwerkingen bleken na beoordeling van het oorzakelijke verband 43% mogelijk of waarschijnlijk gerelateerd aan het radiofarmacon. De overige vermoede bijwerkingen waren niet gerelateerd aan het radiofarmacon, of was het onwaarschijnlijk dat dit het geval was. Zo vonden wij een frequentie van patiënt-gerapporteerde bijwerkingen van diagnostische radiofarmaca van 2,8%. Dit is hoger dan de frequentie van 0,0016% zoals wij die vonden in de literatuur. In onze studie vonden wij geen reacties gerelateerd aan diagnostische radiofarmaca die volgens formele criteria als ernstig geclassificeerd worden. De meeste vermoede bijwerkingen (80%) traden kort na de toediening van het radiofarmacon op en patiënten herstelden over het algemeen binnen een aantal uren weer. Sommige vermoede bijwerkingen (20%) traden op nadat de patiënten de afdeling Nucleaire

Geneeskunde hadden verlaten. Het duurde langer voordat deze hersteld waren en in een aantal gevallen (27,5%) consulteerde de patiënt een zorgverlener. De bevindingen van onze studie impliceren dat bijwerkingen van diagnostische radiofarmaca zoals de patiënt ze ervaart, vaker voorkomen dan voorheen aangenomen. Onze studie laat zien dat patiënten waardevolle informatie over bijwerkingen bij radiofarmaca kunnen verstrekken, welke een nuttige aanvulling is op wat we vanuit de literatuur weten.

Naast dit systematisch onderzoek kan ook de analyse van individuele casussen bijdragen aan meer kennis over bijwerkingen. Een voorbeeld van een casusbespreking presenteren wij in **hoofdstuk 5**, waar wij beschrijven hoe een 49 jarige vrouw een anafylactische reactie ontwikkelde na toediening van [^{99m}Tc]Tc-macrosalb, dat gebruikt werd voor longscintigrafie (een nucleair geneeskundig onderzoek waarbij de bloedvoorziening in de longen wordt onderzocht).

10.2.2 Interacties van radiofarmaca met geneesmiddelen

Het tweede onderwerp over medicatieveiligheid dat wij in dit proefschrift bespreken gaat over interacties met andere geneesmiddelen. Een bekende interactie is de verhoogde opname van [^{18}F]fludeoxyglucose (FDG) in de dikke darm op PET-scans bij patiënten die het orale antidiabetes geneesmiddel metformine gebruiken. Hoewel FDG PET in zijn algemeenheid niet wordt gebruikt om kanker van de dikke darm te onderzoeken, zou de verhoogde opname van FDG in de dikke darm poliepen en voorstadia van darmkanker kunnen overstralen waardoor ze worden gemist. Hoewel verschillende studies aangeven dat metformine gestopt dient te worden voor de FDG PET-scan, is er op dit moment geen consensus over de optimale duur van stoppen. Daartoe onderzochten we in **hoofdstuk 6** of het stoppen van metformine gedurende in elk geval 48 uur de opname van FDG in alle delen van de dikke darm voorkomt. Hierbij includeerden wij patiënten met diabetes type 2 die metformine gebruikten en een FDG PET/CT-scan ondergingen. Wij creëerden twee groepen: patiënten die metformine korter dan 48 uur gestopt hadden en patiënten die metformine tussen 48 uur en 72 uur gestopt hadden. Een controlegroep werd samengesteld uit niet-diabetes patiënten die geen metformine gebruikten en een FDG PET/CT-scan ondergingen.

De opname van de FDG in vier verschillende delen van de dikke darm werd geanalyseerd. We vonden dat zelfs het stoppen van metformine gedurende 48 uur of langer nog steeds een verhoogde FDG opname gaf in de distale delen van de dikke darm, vergeleken met niet-diabeten die geen metformine gebruiken. Hierbij kan men zich afvragen of het zinvol is om patiënten nog langer te laten stoppen met de metformine. Dit langer stoppen is onwenselijk voor patiënten, omdat dit de controle van hun diabetes en daarmee gezondheid kan beïnvloeden. Het stoppen van metformine gedurende 48 uur gaf wel een normalisering van de storende FDG opname voor de proximale delen van de dikke darm en daarom lijkt 48 uur stoppen wel een nuttig advies.

10.2.3 Speciale patiëntgroepen en radiofarmaca

Een derde en laatste onderwerp over medicatieveiligheid dat wij belichten in dit proefschrift gaat over het gebruik van radiofarmaca bij specifieke patiëntgroepen. Voor patiënten met nierinsufficiëntie of patiënten die drager zijn van het gen dat verantwoordelijk is voor acute porfyrie zijn duidelijk aanbevelingen nog niet beschikbaar. Vandaar dat wij nader onderzoek hebben gedaan naar het gebruik van radiofarmaca bij patiënten met nierinsufficiëntie en bij patiënten met acute porfyrie.

Acute porfyrie omvat een groep van zeldzame metabole stofwisselingsziekten die te maken hebben met de biosynthese van heem (welke onder andere nodig is voor hemoglobine in rode bloedcellen). Draggers van het acute porfyrie gen zijn vatbaar voor acute aanvallen, die kunnen worden aangezet door blootstelling aan geneesmiddelen. De symptomen van een aanval van acute porfyrie kunnen zijn: ernstige buikpijn, obstipatie, misselijkheid, verwardheid en toevallen. Deze aanvallen kunnen levensbedreigend zijn. Vandaar dat het van belang is te weten of een geneesmiddel veilig is voor dragers van het acute porfyrie gen. Daarom beoordeelden we in **hoofdstuk 7** radiofarmaca op hun potentieel om een aanval te veroorzaken. Bij deze beoordeling maakten we gebruik van een algoritme voor het voorspellen van het risico dat een bepaald geneesmiddel de ziekte activeert in een drager van het acute porfyrie gen. Informatie over geneesmiddel, zoals het metabolisme, (deeltjes)grootte en plasmaconcentratie, wordt meegenomen in dit

algoritme. Van de 41 beoordeelde radiofarmaca bleken de meeste radiofarmaca waarschijnlijk veilig gebruikt te kunnen worden. Van vijf radiofarmaca ($[^{131}\text{I}]$ iodomethyl norcholesterol, $[^{99\text{m}}\text{Tc}]$ Tc-mebrofenin, $[^{99\text{m}}\text{Tc}]$ Tc-phytate, $[^{99\text{m}}\text{Tc}]$ Tc-sestamibi and $[^{201}\text{Tl}]$ Tl-chloride) werd echter gevonden dat zij mogelijk de ziekte kunnen activeren. Deze radiofarmaca kunnen beter niet worden gebruikt bij dragers van het acute porfyrie gen, tenzij er een urgente indicatie aanwezig is en er geen alternatief beschikbaar is. In deze gevallen dient er advies gezocht te worden van een porfyrie specialist; mogelijk dat voorzorgsmaatregelen getroffen dienen te worden.

Een andere speciale patiëntengroep waar mogelijk extra voorzorgen genomen moeten worden, zijn patiënten met nierinsufficiëntie. Aangezien nierinsufficiëntie de uitscheiding van een aantal geneesmiddelen en hun metabolieten vermindert en de concentratie in het plasma verhoogt, kan het nodig zijn om de dosering van het radiofarmacon aan te passen, vooral als deze door de nier worden geklaard. Echter richtlijnen voor dosering van radiofarmaca in patiënten met nierinsufficiëntie ontbreken op dit moment. Vandaar dat wij in **hoofdstuk 8** een systematische review uitvoerden met als doel om te komen tot doseringsadviezen voor radiofarmaca bij patiënten met nierinsufficiëntie. Verassend genoeg konden wij echter geen consistente algemene aanbevelingen over de dosering van radiofarmaca in deze groep patiënten geven. Hoewel er studies zijn die de moeilijkheden van het doseren bij nierinsufficiëntie beschrijven, is er slechts van enkele radiofarmaca daadwerkelijk informatie beschikbaar waarbij deze informatie ook niet eens eenduidig is.

10.3 TOEKOMSTPERSPECTIEF

Hoewel radiofarmaca zowel voor diagnostiek als therapie al vele decennia in gebruik zijn en in het algemeen uiterst veilig zijn gebleken, vinden we toch lacunes op dit gebied en kan meer onderzoek naar onze mening bijdragen om de medicatieveiligheid van radiofarmaca te begrijpen en te verbeteren.

Momenteel zijn er veelbelovende nieuwe radiofarmaca in ontwikkeling, zoals PET-radiofarmaca voor hartonderzoek, dementie en prostaatkanker. Verder wordt er

op dit moment veel onderzoek gedaan naar de ontwikkeling van zogenaamde ‘theragnostica’. De term theragnostica (soms theranostica) is een combinatie van de woorden ‘therapie’ en ‘diagnostiek’, en beschrijft een methode waarbij met één verbinding zowel diagnostiek als therapie kan worden uitgevoerd. Bij theragnostische radiofarmaca worden hierbij diagnostiek en therapie nog dichter bij elkaar gebracht en wordt er gebruik gemaakt van een (nagenoeg) gelijk tracer deel, dat kan worden gebonden aan hetzij een diagnostisch radionuclide hetzij een therapeutisch radionuclide. Zo kan doormiddel van de scan voorspeld worden waar het therapeuticum terecht komt en in welke mate. Dit kan ervoor zorgen dat patiënten makkelijker geselecteerd kunnen worden voor een effectieve therapie en bijwerkingen mogelijk kunnen worden voorspeld. Een andere ontwikkeling zijn de nieuwste therapeutische radiofarmaca, die gebaseerd zijn op alfastraling-uitzendende radionucliden en de mogelijkheid geven om kankercellen heel lokaal te vernietigen met hoge stralingsdoses waardoor aangrenzend gezond weefsel zoveel mogelijk wordt gespaard.

Al deze nieuwe radiofarmaca zullen eerst een veiligheidsevaluatie ondergaan, waarbij aangetoond moet worden dat er een gunstig werkzaamheid-risico profiel is. Hedendaagse inzichten op het gebied van veiligheid van geneesmiddelen zorgen ervoor dat er tegenwoordig ook meer aandacht is voor medicatieveiligheidsaspecten bij de ontwikkeling van nieuwe radiofarmaca dan dat er in het verleden was. Toch zullen sommige veiligheidsaspecten mogelijk pas aan het licht komen als het radiofarmacon op de markt is. In dit proefschrift lieten we zien dat de patiënt een belangrijke rol kan spelen bij studies naar ervaringen bij het gebruik van het radiofarmacon. Wij vinden dat de patiënt meer betrokken moet worden bij toekomstige studies, juist de patiënt zelf kan vermoede bijwerkingen aangeven. Deze informatie kan de zorgverlener in staat te stellen bijwerkingen beter te herkennen, te begrijpen, hierop te anticiperen en op een juiste manier te handelen.

In ons proefschrift toonden we aan dat de frequentie van door patiënten gerapporteerde bijwerkingen op diagnostische radiofarmaca aanzienlijk hoger is dan gerapporteerd in de literatuur, namelijk 2,8% versus 0,0016%. Dit wijst op een onderrapportage in de literatuur, zoals ook bekend bij andere geneesmiddelen. Er

zou onderzoek gedaan moeten worden om de redenen voor deze onderrapportage vast te stellen en te komen tot mogelijke verbeteringen.

In zijn algemeenheid denken wij dat er meer aandacht moet worden gevestigd op het gebied van interacties van radiofarmaca met geneesmiddelen. Onderzoek op dit gebied zou zich kunnen concentreren op het beschrijven van nieuwe of onbekende interacties en het ontrafelen van de exacte mechanismen van deze interacties. Verkregen resultaten kunnen de zorgprofessional helpen met onderbouwde en duidelijke adviezen voor de behandeling van patiënten. Met betrekking tot een hogere FDG opname bij PET in de dikke darm bij het gebruik van metformine toonden we aan dat ondanks het stoppen gedurende 48 uur, de FDG-opname hoog blijft in de distale delen van de dikke darm. Hierbij kan men zich afvragen of het zinvol is om patiënten nog langer te laten stoppen met de metformine, met het risico op beïnvloeding van de controle van hun diabetes. Aangezien het mechanisme achter de relatie tussen metformine en FDG opname in de dikke darm tot op heden onopgehelderd is, zou inzicht hierin kunnen helpen bij het beantwoorden van de vraag wat het beste beleid is voor patiënten die metformine gebruiken en een FDG PET/CT-scan moeten ondergaan.

Tenslotte moet er meer nadruk worden gelegd op het gebruik van radiofarmaca bij specifieke groepen patiënten in onderzoek. In ons werk hebben we de porfyrogeniciteit van radiofarmaca beoordeeld en deze geclassificeerd volgens een theoretisch model, maar het is nog steeds nodig om dit ook in patiënten te onderzoeken. Daarnaast hebben we de literatuur over de dosering van radiofarmaca bij patiënten met nierinsufficiëntie bestudeerd en vastgesteld dat er weinig bekend is. Idealiter zouden bij trials met nieuwe radiofarmaca ook specifieke groepen patiënten meegenomen moeten worden, zoals patiënten met nierinsufficiëntie en patiënten met acute porfyrie. Een andere mogelijkheid is om het gebruik in deze groepen te evalueren met een expertpanel vanuit diverse expertisegebieden. Het vormen van een dergelijk deskundig oordeel kan helpen om te komen tot duidelijke aanbevelingen voor de patiënten en zorgverleners.

10.4 CONCLUSIES

Nucleaire geneeskunde levert essentiële informatie voor de diagnostiek en behandeling van vele soorten patiënten. De gebruikte radiofarmaca zijn veilig maar toch niet helemaal vrij van bijwerkingen en interacties in alle groepen patiënten. In dit proefschrift hebben wij verschillende aspecten van medicatieveiligheid van radiofarmaca onderzocht. Wij hebben laten zien dat de patiënten zelf een belangrijke bijdrage kunnen leveren aan de kennis op dit gebied. Hierbij viel op dat patiënten zelf in 2,8% bijwerkingen meldden welke zij toeschrijven aan het gebruik van het diagnostische radiofarmacon, veel meer dan wat er in de literatuur bekend was. Het blijft echter moeilijk het oorzakelijk verband met zekerheid vast te stellen.

Wij hopen met dit proefschrift te hebben bijgedragen aan een beter begrip van medicatieveiligheid, en speciaal ook een beter begrip van enkele onderwerpen, zoals bijwerkingen, de FDG opname in de dikke darm bij het gebruik van metformine, het gebruik van radiofarmaca bij nierinsufficiëntie en porfyrie. Wellicht leidt dit tot meer aandacht voor medicatieveiligheid onder patiënten en zorgverleners.

Appendices

List of publications

Curriculum Vitae

Dankwoord

Supplementary material

Index of radiopharmaceuticals

LIST OF PUBLICATIONS

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CURRICULUM VITAE

Nanno Schreuder was born on 28 April 1972 in Bathmen, The Netherlands. After attending high school (VWO) at ‘het Wagenings Lyceum’ in Wageningen he studied Pharmacy at the University of Groningen. In 1995 he received his Master’s degree with specialisation Bioanalysis and Toxicology. After obtaining his Pharmacist degree in 1997, he started working as a pharmacy manager in a community pharmacy in Rosmalen, with a special interest in the compounding of pharmaceuticals. In 2002 he made a switch in his career and started working for Amersham (now GE Healthcare). In 2003 he obtained his radiation safety level 3 examination and was certified as Nuclear Pharmacist at Purdue University in West Lafayette (IN), the United States. In the period of 2002 to 2004 he was responsible for setting up the GE Healthcare Radiopharmacy in Zwolle. Since the opening of this pharmacy in 2004 he is the manager of this facility and responsible for all pharmaceutical, radiation safety, clinical trial and operational aspects. In addition to these managerial tasks, he has a special focus on learning and development, is responsible for the training program of the GE Healthcare radiopharmacies and provides guest lectures about radiopharmacy at several institutes including the University of Groningen. During the last few years, he developed a special interest in drug safety of radiopharmaceuticals. In 2016 he started his PhD research at the Groningen Research Institute of Pharmacy, Pharmacotherapy, -Epidemiology & -Economics of the University of Groningen under supervision of Prof. E.P. van Puijenbroek, Prof. J.G.W. Kosterink and Dr. P.L. Jager. The outcomes of his research are presented in this thesis.

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My enthusiasm for the field of nuclear pharmacy started with my certification program at the Purdue University in West-Lafayette. Thank you, Kara Duncan Weatherman for all your teachings and practical training. And I would like to thank Stan Shaw, who, although no longer with us, continues to inspire by his example.

I would also like to thank Greg Ryan for providing my internship at the Phoenix nuclear pharmacy. My curiosity for drug safety and radiopharmaceuticals was encouraged by one of the pioneers in this field, Stuart Hesslewood. Thank you, Stuart, for your introduction into the aspects of drug safety and radiopharmaceuticals and for all the years we worked together. Dear Dharmesh, thank you for the wonderful times we had together working at GE Healthcare. As you finished your PhD some time ago, I could reflect together with you on my own PhD project. Somehow this was often combined with a night out on the town!

Het onderzoek wat wij mochten uitvoeren was alleen mogelijk door een continue steun vanuit de organisaties GE Healthcare, Isala en het bijwerkingencentrum LAREB. Iedereen die op de een of andere manier heeft bijgedragen aan dit proefschrift, wil ik dan ook hartelijk bedanken. In het bijzonder wil ik mijn collega's van GE Healthcare en het team in Zwolle bedanken voor hun steun en belangstelling gedurende de afgelopen jaren. Dankbaar ben ik ook voor de hulp en inzet van de vele ziekenhuismedewerkers van het Isala ziekenhuis in Zwolle. Dit onderzoek was niet mogelijk geweest zonder de hulp van de nucleair geneeskundigen en medisch nucleair werkers van dit ziekenhuis. In het bijzonder wil ik Stoffer Reiffers bedanken voor alle steun tijdens het opzetten van de radiofarmaca apotheek in Zwolle en de continue belangstelling, zelfs na je pensionering. Ook wil ik Siert Knollema bedanken voor de fijne samenwerking en de steun voor mijn promotieonderzoek binnen Isala. Verder wil ik Amarins Blaauwbroek en Joris van Dijk bedanken voor hun steun vanuit het Isala researchteam. Ook ben ik dankbaar voor de hulp van de medewerkers van het bijwerkingencentrum LAREB. Jullie instructiemomenten hebben mij goed op weg geholpen bij mijn onderzoek.

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bij het opzetten van de literatuur zoekstrategie. Saskia Abbes wil ik graag bedanken voor haar hulp met het opzetten van de vragenlijst in researchmanager. I would like to thank Jane Knight for her excellent instruction on the use of MedDRA.

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De vele bezoeken aan Groningen afgelopen jaar waren ook een mooie gelegenheid om vrienden vaker te zien. Na mijn afspraken op de Universiteit vond er stevast een ‘Culinair recept’ plaats en ik wil dan ook Monique en Wianda, naast Adriaan en Mechiel, bedanken voor de gezelligheid en ook de belangstelling naar mijn promotiewerk. Het dankwoord is niet compleet zonder de mentorgroep te noemen. Het is toch heel bijzonder dat wij nog steeds na al die jaren contact houden. Esther, Magda, Marleen, Martine, Melanie en Renate bedankt daarvoor!

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Een speciaal plekje in dit proefschrift is gereserveerd voor Hanna en Ria. Het boekje is af! De avonden en weekenden op zolder coderen, lezen en schrijven zijn afgelopen. Ook de steeds maar toenemende hoeveelheid artikelen en boeken kunnen nu worden opgeruimd. Bedankt voor jullie steun en ik hoop nog vele jaren te mogen genieten van jullie gezelschap!

Supplementary material 1: Final version of the questionnaire

Questionnaire in Dutch

Vragenlijst ‘ervaringen met nucleair geneeskundig onderzoek’[†]

Informatie over vragenlijst

Bedankt dat u mee doet aan dit wetenschappelijke onderzoek. Dit onderzoek bestaat uit een aantal vragen met betrekking op uw recente nucleaire onderzoek. Voor het invullen van deze vragenlijst heeft u ongeveer 10 tot 20 minuten nodig.

U gaat naar de volgende pagina door op de knop 'verder' te klikken. Als u alle vragen heeft beantwoord kan de vragenlijst worden verstuurd. Dit kan op de laatste pagina door op de knop 'verstuur' te klikken.

Bij het geven van bepaalde antwoorden kunnen extra vragen verschijnen. Wij willen u verzoeken deze ook in te vullen. Als u tijdens het invullen van de vragen uw antwoord wilt verwijderen, klik dan op het rode knopje voor de vraag.

Lees voor het beantwoorden van de vragen eerst de uitleg bovenaan de pagina, dit kan verwarring voorkomen.

Begin aan de vragenlijst door op de knop 'verder' rechts onderin uw scherm te klikken.

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Algemeen

Onderstaande vragen worden gesteld om meer over u te weten te komen. Met behulp van deze informatie kunnen wij u indelen in een bepaalde groep.

1. Wat is uw geslacht?
 - a. Man
 - b. Vrouw
 - c. Anders/wil niet zeggen

2. Wat is uw geboortedatum?
 - a. ../../....

3. Wat is uw gewicht?
 - a. kg

4. Wat is uw lengte?
 - a. cm

5. Wat is uw hoogst behaalde opleiding?
 - a. Geen onderwijs afgerond
 - b. Basisonderwijs
 - c. Lager beroepsonderwijs (LBO, MAVO, VMBO)
 - d. HAVO of VWO
 - e. Middelbaar beroepsonderwijs (MBO)
 - f. Hoger beroepsonderwijs (HBO)
 - g. Universiteit (WO)

6. Gebruikt u middelen van de drogist of zelfzorgmiddelen (bijvoorbeeld; paracetamol)?[‡]
 - a. Ja
 - i. Welke middelen van de drogist of zelfzorg gebruikt u?
 - b. Nee

[‡] Question was added during content validation

Gezondheid[§]

Onderstaande vragen worden gesteld om een beeld te krijgen van uw huidige gezondheidstoestand.

7. Klik bij iedere groep in de lijst hieronder een hokje voor de zin die het best past bij uw eigen gezondheidstoestand vandaag.

Mobiliteit

- a. Ik heb geen problemen met lopen
- b. Ik heb enige problemen met lopen
- c. Ik ben bedlegering

Zelfzorg

- a. Ik heb geen problemen om mijzelf te wassen of aan te kleden
- b. Ik heb enige problemen om mijzelf te wassen of aan te kleden
- c. Ik ben niet in staat mijzelf te wassen of aan te kleden

Dagelijkse activiteiten (bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)

- a. Ik heb geen problemen met mijn dagelijkse activiteiten
- b. Ik heb enige problemen met mijn dagelijkse activiteiten
- c. Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren

Pijn/klachten

- a. Ik heb geen pijn of andere klachten
- b. Ik heb matige pijn of andere klachten
- c. Ik heb zeer ernstige pijn of andere klachten

Stemming

- a. Ik ben niet angstig of somber
- b. Ik ben matig angstig of somber
- c. Ik ben erg angstig of somber

[§] © EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation

We willen weten hoe goed of slecht uw gezondheid VANDAAG is. Deze meetschaal loopt van 0 tot 100. 100 staat voor de beste gezondheid die u zich kunt voorstellen. 0 staat voor de slechtste gezondheid die u zich kunt voorstellen. Verschuif het balkje van de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.

- a. Meetschaal (0–100)

Onderzoek/ Verleden

Onderstaande vraag gaat over nucleaire onderzoeken die u eventueel in het verleden heeft gehad. Deze vraag gaat NIET over uw meest recente nucleaire onderzoek.

8. Heeft u eerder een nucleair geneeskundig onderzoek ondergaan?
 - a. Weet ik niet
 - b. Nee
 - c. Ja
 - i. Welk type nucleair onderzoek is er eerder bij u uitgevoerd? (meerdere antwoorden mogelijk)
 1. Bot
 2. Hart
 3. Lymfe
 4. Schildklier
 5. Long
 6. Nier
 7. PET/CT
 8. Anders
 - a. Welk type nucleair onderzoek is bij u uitgevoerd?
 - ii. Heeft u direct of binnen 7 dagen na dit onderzoek één of meerdere bijwerkingen of lichamelijke veranderingen ervaren die u in verband brengt met het nucleaire onderzoek?
 1. Weet ik niet
 2. Nee
 3. Ja

- a. Bij welk type nucleair onderzoek trad de mogelijke bijwerking of verandering op?
- Bot
 - Hart
 - Lymfe
 - Schildklier
 - Long
 - Nier
 - PET/CT
 - Anders
1. Welk type nucleair onderzoek is bij u uitgevoerd?
- b. Op welke datum vond het onderzoek plaats? (bij voorkeur de exacte datum, anders een schatting)
-
- c. Kunt u kort de mogelijke bijwerking of verandering beschrijven?
-
- d. Binnen hoeveel tijd na het onderzoek trad de mogelijke bijwerking of verandering op? (minuten, uren, dagen)
-
- e. Heeft u uw behandelend arts/huisarts of andere zorgverlener geïnformeerd?
- Geen zorgverlener geïnformeerd
 - Behandelend arts ziekenhuis
 - Huisarts
 - Apotheker
 - Verpleegkundige
 - Anders

1. Welke zorgverlener heeft u nog meer geïnformeerd?
- f. Is de mogelijke bijwerking of verandering behandeld?
- i. Ja
 1. Op wat voor manier is de mogelijke bijwerking of verandering behandeld?
 - ii. Nee
- g. Heeft u zelf iets gedaan om de mogelijke bijwerking of verandering te behandelen?
- i. Ja
 1. Hoe heeft u de mogelijke bijwerking of verandering zelf behandeld?
 - ii. Nee
- h. Hoe gaat het op dit moment met de mogelijke bijwerking?
- i. Hersteld
 1. Binnen hoeveel tijd is de mogelijke bijwerking hersteld (minuten, uren, dagen)?
 - ii. Een deel van de bijwerking is hersteld, maar nog niet volledig
 1. Wat zijn de resterende klachten?
 - iii. De bijwerking is nog niet hersteld
- i. Heeft de mogelijke bijwerking of verandering geleid tot een van de volgende criteria?

- i. Ziekenhuisopname
- ii. Levensbedreigende situatie
- iii. Blijvende arbeidsongeschiktheid
- iv. Aangeboren afwijking
- j. Zijn er naar uw mening mogelijk andere omstandigheden of oorzaken die deze mogelijke bijwerking of lichamelijke verandering kunnen hebben veroorzaakt of verergerd?
 - i. Ja
 - 1. Wat heeft volgens u de mogelijk bijwerking veroorzaakt?
 - ii. Nee

Onderzoek/ Voorbereiding

Onderstaande vragen gaan over uw voorbereiding op uw meest RECENTE nucleaire onderzoek.

9. Wat vond u van de patiënteninformatie die u voorafgaand aan het onderzoek heeft gekregen?
 - a. Heel duidelijk
 - b. Duidelijk
 - c. Neutraal
 - d. Onduidelijk
 - e. Heel onduidelijk
 - f. Ik heb de verstrekte patiënteninformatie niet gelezen
 - i. Wat was de reden dat u de verstrekte patiënteninformatie niet heeft gelezen? (meerdere antwoorden mogelijk)
 1. Patiënteninformatie was niet beschikbaar
 2. Tijdgebrek
 3. Geen interesse
 4. Moeite met het lezen van de tekst

5. Anders

- a. Wat was nog meer de reden dat u de verstrekte patiënteninformatie niet heeft gelezen?

10. Heeft u voor het onderzoek één of meer van de onderstaande voorbereidende handelingen moeten verrichten? (meerdere antwoorden mogelijk)

- a. Nuchter
- b. Extra vocht inname
- c. Extra zoutinname
- d. Gestopt met innemen geneesmiddel(en)
- e. Geen koffie, thee, cola of energiedrankjes gedronken
- f. Geen chocolade of bananen gegeten
- g. Telebrix gastro gedronken
- h. Voor het onderzoek waren geen voorbereidende handelingen nodig
- i. Anders
 - i. Welke andere voorbereidende handelingen heeft u voor het onderzoek moeten verrichten?

Onderzoek/Toediening

Onderstaande vragen gaan over uw meest RECENTE nucleaire onderzoek.

11. Welk type nucleair onderzoek is er als laatste bij u uitgevoerd? **

- a. Bot
- b. Hart
- c. Lymfe
- d. Schildklier
- e. Long
- f. Nier
- g. PET/CT
- h. Anders

** Question was added during content validation

- i. Welk type nucleair onderzoek is bij u uitgevoerd?
 - i. Weet ik niet
12. Is er tijdens het onderzoek een radioactieve stof bij u toegediend?
 - a. Nee
 - b. Weet ik niet
 - c. Ja
 - i. Heeft u kort na toediening van de radioactieve stof een mogelijke bijwerking of lichamelijke verandering gemerkt?
 1. Nee
 2. Ja
 - a. Kunt u kort beschrijven wat er gebeurde?
 - b. Hoeveel tijd zat er tussen de injectie met de radioactieve stof en deze mogelijke bijwerking of verandering?
 - i. min
 - c. Heeft u deze mogelijke bijwerking of verandering gemeld aan het ziekenhuispersoneel?
 - i. Ja
 - ii. Nee
 - d. Is de mogelijke bijwerking of verandering behandeld?
 - i. Ja
 1. Op wat voor manier is de mogelijke bijwerking of verandering behandeld?
 - ii. Nee
 - e. Hoe gaat het op dit moment met de mogelijke bijwerking?
 - i. Hersteld

1. Binnen hoeveel tijd is de
mogelijk bijwerking
hersteld? (minuten, uren,
dagen)
 - ii. Een deel van de bijwerking is
hersteld, maar nog niet volledig
 1. Wat zijn de resterende
klachten?
 - iii. De bijwerking is nog niet hersteld
 - f. Zijn er naar uw mening mogelijk andere
omstandigheden of oorzaken die deze
mogelijke bijwerking kunnen hebben
veroorzaakt of verergerd?
 - i. Ja
 1. Wat heeft volgens u de
mogelijke bijwerking
veroorzaakt?
 - ii. Nee
13. Heeft u tijdens het onderzoek röntgencontrastmiddel toegediend gekregen?
- a. Nee
 - b. Weet ik niet
 - c. Ja
 - i. Heeft u kort na toediening van het röntgencontrastmiddel
een mogelijke bijwerking of lichamelijke verandering
gemerkt?
 1. Nee
 2. Ja
 - a. Kunt u kort beschrijven wat er gebeurde?
 - b. Hoeveel tijd zat er tussen de injectie van
het röntgencontrastmiddel en deze
mogelijke bijwerking of verandering?

- i. min
- c. Heeft u deze mogelijke bijwerking of verandering gemeld aan het ziekenhuispersoneel?
 - i. Ja
 - ii. Nee
- d. Is de mogelijke bijwerking of verandering behandeld?
 - i. Ja
 - 1. Op wat voor manier is de mogelijke bijwerking of verandering behandeld?
 - ii. Nee
- e. Hoe gaat het op dit moment met de mogelijke bijwerking?
 - i. Hersteld
 - 1. Binnen hoeveel tijd is de mogelijke bijwerking hersteld? (minuten, uren, dagen)
 - ii. Een deel van de bijwerking is hersteld, maar nog niet volledig
 - 1. Wat zijn de resterende klachten?
 - iii. De bijwerking is nog niet hersteld
- f. Heeft u eerder een bijwerking ervaren van röntgencontrastmiddel?
 - i. Ja
 - 1. Was de bijwerking vergelijkbaar?
 - a. Ja
 - b. Nee

- i. Wat
waren de
verschille
n met de
vorige
keer?

- ii. Nee

- g. Zijn er naar uw mening mogelijk andere
omstandigheden of oorzaken die deze
mogelijke bijwerking kunnen hebben
veroorzaakt of verergerd?

- i. Ja

- 1. Wat heeft volgens u de
mogelijke bijwerking
veroorzaakt?

- ii. Nee

14. Zijn er naar uw mening ongewone dingen gebeurd tijdens het onderzoek?

- a. Ja

- i. Kunt u uitleggen wat volgens u afwijkend was?

- b. Nee

Thuis na het onderzoek

Onderstaande vragen gaan over de periode thuis na uw meest RECENTE nucleaire onderzoek.

15. Heeft u thuis na het onderzoek bepaalde handelingen verricht die aangegeven waren vanuit het ziekenhuis?

- a. Ja
 - i. Wat waren deze handelingen?
- b. Nee

16. Heeft u binnen 7 dagen na het onderzoek een of meerdere bijwerkingen of lichamelijke veranderingen ervaren die u in verband brengt met het nucleaire onderzoek?

- a. Nee
- b. Ja
 - i. Kunt u kort de mogelijke bijwerking of verandering beschrijven?
 - ii. Binnen hoeveel tijd na het onderzoek trad de mogelijke bijwerking of verandering op (minuten, uren, dagen)?
 - 1.
 - iii. Heeft u uw behandelend arts/huisarts of andere zorgverlener geïnformeerd?
 - 1. Geen zorgverlener geïnformeerd
 - 2. Behandelend arts ziekenhuis
 - 3. Huisarts
 - 4. Apotheker
 - 5. Verpleegkundige
 - 6. Anders
 - a. Welke zorgverlener heeft u nog meer geïnformeerd?
 - iv. Is de mogelijke bijwerking of verandering behandeld?
 - 1. Ja

- a. Op wat voor manier is de mogelijke bijwerking of verandering behandeld?
2. Nee
- v. Heeft u zelf iets gedaan om mogelijke bijwerking of verandering te behandelen?
 1. Ja
 - a. Hoe heeft u de mogelijk bijwerking of verandering zelf behandeld?
 2. Nee
- vi. Hoe gaat het op dit moment met de mogelijke bijwerking of verandering?
 1. Hersteld
 - a. Binnen hoeveel tijd is de mogelijke bijwerking hersteld? (minuten, uren, dagen)
 2. Een deel van de bijwerking is hersteld, maar nog niet volledig
 - a. Wat zijn de resterende klachten?
 3. De bijwerking is nog niet hersteld
- vii. Zijn er naar uw mening mogelijk andere omstandigheden of oorzaken die deze mogelijke bijwerking kunnen hebben veroorzaakt of verergerd?
 1. Ja
 - a. Wat heeft volgens u de mogelijke bijwerking veroorzaakt?
 2. Nee

Opmerkingen

Tot slot kunt u hieronder nog dingen kwijt die u niet in de rest van de vragenlijst kwijt kon.

17. Heeft u nog op/of aanmerkingen over het complete nucleaire onderzoek?
 - a. Ja
 - i. Wat voor op/of aanmerkingen heeft u over het complete nucleaire onderzoek?
 - b. Nee
18. Heeft u verder nog opmerkingen?
 - a. Ja
 - i. Wat voor opmerkingen heft u verder nog?
 - b. Nee

Bedankt voor het invullen van deze vragenlijst. U kunt de vragenlijst versturen door eerste op 'volgende' te klikken en vervolgens op de knop 'verstuur' te klikken.

Aanvullende informatie^{††}

- a. Radiofarmacon
- b. Activiteit
- c. Type onderzoek
- d. Nierfunctie
- e. Geneesmiddelen
- f. Indicaties

^{††} Section to be completed by researchers

English Translation of Questionnaire

Questionnaire: ‘Experiences with Nuclear Medicine Examinations’^{††}

Information about the questionnaire

Thank you for participating in this scientific research. This research comprises questions related to your recent nuclear examination. You will need approximately 10 to 20 minutes to complete the questionnaire.

Clicking the ‘continue’ button will take you to the next page. When you have answered all of the questions, the questionnaire can be sent by clicking the ‘send’ button on the final page.

Additional questions may appear when certain answers are given. Please complete these as well. If you wish to delete your answer while filling in the questions, click the red button in front of the question.

Before answering each question, please first read the explanation at the top of the page.

Start the questionnaire by clicking the ‘continue’ button at the bottom right of your screen.

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General

The questions below are asked to learn more about you. With the help of this information, we can classify you into a specific group.

1. What is your gender?
 - a. Male
 - b. Female
 - c. Other/I don't want to say

2. What is your date of birth?
 - a. .../.../...

3. What is your weight?
 - a. kg

4. What is your height?
 - a. cm

5. What is your highest level of education?
 - a. Have not completed any education
 - b. Primary education
 - c. Lower secondary education
 - d. Upper secondary education
 - e. Post-secondary non-tertiary education
 - f. Bachelor's or equivalent level
 - g. Master's or equivalent level

6. Do you use drugs from the drugstore or self-care products (e.g., paracetamol)?^{§§}
 - a. Yes
 - i. What drugs from the drugstore or self-care products do you use?
 - b. No

^{§§} Question was added during content validation

Health status^{*}**

The questions below are asked to get an idea of your current health status.

7. By ticking a box in each of the below groups, please indicate which statements best describe your state of health today.

Mobility

- a. I have no problems with walking about
- b. I have some problems with walking about
- c. I am confined to bed

Self-Care

- a. I have no problems with washing or dressing myself
- b. I have some problems with washing or dressing myself
- c. I am unable to wash or dress myself

Usual Activities (e.g., work, study, housework, family or leisure activities)

- a. I have no problems with performing my usual activities
- b. I have some problems with performing my usual activities
- c. I am unable to perform my usual activities

Pain/Discomfort

- a. I have no pain or discomfort
- b. I have moderate pain or discomfort
- c. I have extreme pain or discomfort

Anxiety/Depression

- a. I am not anxious or depressed
- b. I am moderately anxious or depressed
- c. I am extremely anxious or depressed

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Please indicate on a scale of 0 to 100 how good or bad your health is today, in your opinion (0 being the worst state you can imagine and 100 being the best state you can imagine). Slide the bar on the scale to indicate your health today.

- a. Scale (0–100)

Past nuclear examinations

The question below is about nuclear examinations you may have had in the past. This question is NOT about your most recent nuclear medicine examination.

8. Have you previously undergone a nuclear medicine examination?
 - a. I don't know
 - b. No
 - c. Yes
 - i. What type of nuclear medicine examination has previously been performed on you? (multiple answers possible)
 1. Bone
 2. Heart
 3. Lymph
 4. Thyroid
 5. Lung
 6. Kidney
 7. PET/CT
 8. Other
 - a. What type of nuclear medicine examination has been performed on you?
 - ii. Have you experienced one or more side effects or physical changes that you relate to the nuclear medicine examination immediately after or within seven days of this examination?
 1. I don't know
 2. No
 3. Yes

- a. With what type of nuclear medicine examination did you notice possible side effects or physical changes?
 - i. Bone
 - ii. Heart
 - iii. Lymph
 - iv. Thyroid
 - v. Lung
 - vi. Kidney
 - vii. PET/CT
 - viii. Other
 1. What type of nuclear medicine examination was performed on you?
- b. On what date did the examination take place? (preferably the exact date, otherwise an estimate)
 - i.
- c. Can you briefly describe what happened?
 - i.
- d. How much time passed between the administration of the drug and the adverse events or changes? (minutes, hours, days)
 - i.
- e. Have you informed your doctor or other health care provider of these side effects or changes?
 - i. I did not inform a health care professional
 - ii. I informed my referring physician's hospital
 - iii. I informed my general practitioner

- iv. I informed my pharmacist
- v. I informed my nurse
- vi. Other
 - 1. Which health care professional did you inform?
- f. Was the adverse event or change treated?
 - i. Yes
 - 1. How was the adverse event or change treated?
 - ii. No
- g. Have you done something yourself to treat possible side effects or changes?
 - i. Yes
 - 1. How did you treat the possible side effects or changes?
 - ii. No
- h. What is the status of the possible side effects or changes at the moment?
 - i. I have fully recovered
 - 1. How much time did you take to recover from the possible side effects or changes? (minutes, hours, days)
 - ii. I have partially recovered, but not yet completely
 - 1. What are the remaining complaints?
 - iii. I have not yet recovered

- i. Did the adverse event or change lead to one of the following situations?
 - i. Hospitalisation
 - ii. A life-threatening situation
 - iii. Persistent work disability
 - iv. Congenital defect
- j. In your opinion, are there other circumstances that could have caused or worsened these potential side effects or changes?
 - i. Yes
 - 1. What do you think caused the possible side effects?
 - ii. No

Preparation for nuclear medicine examination

The questions below are about the preparation for your most recent nuclear medicine examination.

- 9. What did you think of the patient information you received before the examination?
 - a. Very clear
 - b. Clear
 - c. Neutral
 - d. Unclear
 - e. Very unclear
 - f. I did not read the patient information that was provided
 - i. Why did you not read the patient information provided?
(multiple answers possible)
 - 1. Patient information was not available
 - 2. Lack of time
 - 3. Not interested
 - 4. Difficulty reading the text
 - 5. Other

a. Why did you not read the patient information provided?

10. Before the examination, did you have to adhere to one or more of the following preparatory instructions? (multiple answers possible)

- a. Attend the examination on an empty stomach
- b. Extra fluid intake
- c. Extra salt intake
- d. Stop taking medicine(s)
- e. Drink no caffeinated drinks (e.g., coffee, tea, cola or energy drinks)
- f. Do not eat chocolate or bananas
- g. Drink Telebrix gastro
- h. No preparatory measures were required for the examination
- i. Other
 - i. What other preparatory instructions did you have to follow for the examination?

Administration of the radiopharmaceutical

The below questions are about your most recent nuclear medicine examination.

11. What type of nuclear medicine examination was performed on you?^{†††}

- a. Bone
- b. Heart
- c. Lymph
- d. Thyroid
- e. Lung
- f. Kidney
- g. PET/CT
- h. Other
 - i. What type of nuclear medicine examination was performed on you?

^{†††} Question was added during content validation

- i. I don't know

12. Was a radioactive substance administered to you during the examination?

- a. No
- b. I don't know
- c. Yes

- i. Did you notice any possible side effects or physical changes shortly after the administration of the radioactive substance?

- 1. No
- 2. Yes

a. Can you briefly describe what happened?

- b. How much time passed between the administration of the drug and the adverse events or changes?

- i. min

- c. Did you report these adverse events or changes to hospital staff?

- i. Yes
- ii. No

- d. Were the adverse events or changes treated?

- i. Yes

- 1. How were the adverse events or changes treated?

- ii. No

- e. What is the status of the possible side effects or changes at the moment?

- i. I have fully recovered

- 1. How much time did you take to recover from the possible side effects or

changes? (minutes, hours, days)?

- ii. I have partially recovered, but not yet completely

- 1. What are the remaining complaints?

- iii. I have not yet recovered

- f. In your opinion, are there other circumstances that could have caused or worsened these possible side effects?

- i. Yes

- 1. What do you think caused the possible side effects?

- ii. No

13. Did you receive an X-ray contrast agent during the study?

- a. No
- b. I don't know
- c. Yes

- i. Did you notice any possible side effects or physical changes shortly after the administration of the X-ray contrast agent?

- 1. No
 - 2. Yes

- a. Can you briefly describe what happened?

- i.

- b. How much time passed between the administration of the X-ray contrast agent and the adverse events or changes? (minutes, hours, days)

- i.

- c. Did you report these adverse events or changes to hospital staff?

- i. Yes
 - ii. No
- d. Were the adverse events or changes treated?
 - i. Yes
 - 1. How were the adverse events or changes treated?
 - 2.
 - ii. No
- e. What is the status of the possible side effects or changes at the moment?
 - i. I have fully recovered
 - 1. How much time did you take to recover? (minutes, hours, days)?
 - ii. I have partially recovered, but not yet completely
 - 1. What are the remaining complaints?
 - iii. I have not yet recovered
- f. Have you previously experienced any side effects from X-ray contrast agents?
 - i. Yes
 - 1. Were the previous side effects comparable with the latest ones?
 - a. Yes
 - b. No
 - i. How were the previous side

effects
different
from the
latest
ones?

ii. No

g. In your opinion, are there other circumstances that could have caused or worsened these potential side effects?

i. Yes

1. What do you think caused the possible side effects?

ii. No

14. In your opinion, did unusual things happen during the examination?

a. Yes

i. What do you think was different?

b. No

Time after nuclear examination

The questions below are about the period at home after your most recent nuclear medicine examination.

15. Did you perform certain actions at home after the examination that were indicated by the hospital?

a. Yes

i. What were these actions?

b. No

16. Did you experience one or more side effects or physical changes within 7 days of the examination that you relate to the nuclear examination?

a. No

b. Yes

- i. Can you briefly describe what happened?
 1.
- ii. How much time passed between the administration of the drug and adverse events or changes? (minutes, hours, days)
 1.
- iii. Have you informed your referring physician/doctor or other health care provider?
 1. I did not inform a health care professional
 2. I informed my referring physician's hospital
 3. I informed my general practitioner
 4. I informed my pharmacist
 5. I informed my nurse
 6. Other
 - a. Which other health care professional did you inform?
- iv. Were the adverse events or changes treated?
 1. Yes
 - a. How were the adverse events or changes treated?
 2. No
- v. Have you done something yourself to treat possible side effects or changes?
 1. Yes
 - a. How did you treat the possible side effects or changes?
 2. No
- vi. What is the status of the possible side effects or changes at the moment?
 1. I have fully recovered

- a. How much time did you take to recover from the possible side effects or changes? (minutes, hours, days)
 - 2. I have partially recovered, but not yet completely
 - a. What are the remaining complaints?
 - 3. I have not yet recovered
- vii. In your opinion, are there other circumstances that could have caused or worsened these potential side effects?
 - 1. Yes
 - a. What do you think caused the possible side effects?
 - 2. No

Other remarks

Finally, you can add comments below that you could not include in the other parts of the questionnaire.

- 17. Do you have any comments on the complete nuclear medicine examination?
 - a. Yes
 - i. What are your comments/remarks about the complete nuclear medicine examination?
 - b. No
- 18. Do you have any further remarks?
 - a. Yes
 - i. What other remarks do you have?
 - b. No

Thank you for completing this questionnaire. You can send the questionnaire by first clicking 'next' and then clicking the 'send' button.

Additional information^{†††}

- a. Radiopharmaceutical
- b. Activity
- c. Type of examination
- d. Renal function
- e. Drugs
- f. Indications

^{†††} Section to be completed by researchers

Supplementary material 2: Questions that were removed during the validation process

1. Heeft u allergieën die bekend zijn?
 - a. Ja
 - i. Allergie voor Hooikoorts
 - ii. Allergie voor Huisstofmijt
 - iii. Allergie voor Huisdieren
 - iv. Voedselallergie
 - v. Contactallergie
 - vi. Allergie voor contrastmiddel
 - vii. Anders, namelijk; ...
 - b. Nee
2. Wat was uw mening voor het onderzoek dat u zou worden ingespoten met een radioactieve stof?
3. Heeft u zich op de dag van het onderzoek ruim op tijd kunnen melden op de afdeling nucleaire geneeskunde?
 - a. Ja
 - b. Nee
 - c. Anders, namelijk;.....
4. Hoe voelde u zich tijdens het wachten voor het onderzoek?
 - a. 0 (niet zenuwachtig) – 7 (heel erg zenuwachtig)
5. Wat vond u van de injectie met de radioactieve stof?
6. Wat was de plaats van de injectie?
7. Na toediening van de radioactieve stof heeft u ongeveer 1 uur gewacht in de voorbereidingsruimte, wat vond u hiervan?

8. Was voor u de reden voor het verblijf in de voorbereidingsruimte duidelijk?
 - a. Ja
 - b. Nee
 - c. Namelijk;

9. Hoe voelde u zich tijdens het wachten in de voorbereidingsruimte?
 - a. 0 (niet zenuwachtig) – 10 (heel erg zenuwachtig)

10. Heeft u tijdens het wachten in de voorbereidingsruimte een lichamelijke verandering gemerkt?
 - a. Nee
 - b. Ja
 - i. Kunt u kort beschrijven wat er gebeurde?
 - ii. Hoeveel tijd zat er tussen de injectie en deze verandering?
 - iii. Heeft u deze verandering gemeld aan het ziekenhuispersoneel?
 1. Ja
 2. Nee
 - iv. Is de reactie behandeld?
 1. Ja
 2. Nee
 - v. Hoe is de reactie afgelopen?
 1. Hersteld
 2. Herstellende
 3. Hersteld met rest verschijnselen
 4. Niet hersteld
 5. Onbekend

11. Hoe voelde u zich tijdens het scannen?
 - a. 0 (niet zenuwachtig) – 7 (heel erg zenuwachtig)

12. Heeft u tijdens het scannen in de een lichamelijke verandering gemerkt?

- a. Nee
- b. Ja
 - i. Kunt u kort beschrijven wat er gebeurde?
 - ii. Hoeveel tijd zat er tussen de injectie en deze verandering?
 - 1.
 - iii. Heeft u deze verandering gemeld aan het ziekenhuispersoneel?
 - 1. Ja
 - 2. Nee
 - iv. Is de reactie behandeld?
 - 1. Ja
 - 2. Nee
 - v. Hoe is de reactie afgelopen?
 - 1. Hersteld
 - 2. Herstellende
 - 3. Hersteld met rest verschijnselen
 - 4. Niet hersteld
 - 5. Onbekend

13. Heeft u na de scan een korte verbleven in een ruimte voordat u naar huis mocht?

- a. Nee
- b. Ja
 - i. Was voor u de reden voor het verblijf in deze ruimte duidelijk?
 - 1. Ja
 - 2. Nee
 - a. Want;
- c. Hoe voelde u zich tijdens het wachten?
 - i. 0 (niet zenuwachtig) – 10 (heel erg zenuwachtig)
- d. Heeft u tijdens het wachten een lichamelijke verandering gemerkt?

- i. Nee
 - ii. Ja
- e. Heeft u kort na toediening van het contrastmiddel een lichamelijke verandering gemerkt?
 - i. Kunt u kort beschrijven wat er gebeurde?
 - ii. Hoeveel tijd zat er tussen de injectie en deze verandering?
 - 1.
 - iii. Heeft u deze verandering gemeld aan het ziekenhuispersoneel?
 - 1. Ja
 - 2. Nee
 - iv. Is de reactie behandeld?
 - 1. Ja
 - 2. Nee
 - v. Hoe is de reactie afgelopen?
 - 1. Hersteld
 - 2. Herstellende
 - 3. Hersteld met rest verschijnselen
 - 4. Niet hersteld
 - 5. Onbekend
- 14. Heeft u dezelfde mening over radioactieve stoffen als voorheen?
 - a. Ja
 - i. Namelijk;
 - b. Nee
 - i. Namelijk;

English translation of questions that were removed during the validation process

1. Do you have any known allergies?
 - a. Yes
 - i. Hay fever
 - ii. Dust mite allergy
 - iii. Pet allergy
 - iv. Food allergy
 - v. Contact dermatitis
 - vi. Allergic reaction to contrast agent
 - vii. Otherwise, namely: ...
 - b. No
2. What was your opinion before the examination that you would be injected with a radioactive substance?
3. Were you able to report to the nuclear medicine department in time on the day of the examination?
 - a. Yes
 - b. No
 - c. Otherwise, namely: ...
4. How did you feel while waiting for the examination?
 - a. 0 (not nervous) – 7 (very nervous)
5. What did you think of the injection with the radioactive substance?
6. What was the site of injection?
7. After the administration of the radioactive substance, you have waited about 1 hour in the preparation room, what did you think about this?

8. Was the reason for your stay in the preparation room clear to you?
 - a. Yes
 - b. No
 - c. Namely: ...
9. How did you feel while waiting in the preparation room?
 - a. 0 (not nervous) – 10 (very nervous)
10. Did you notice a physical change while waiting in the preparation room?
 - a. No
 - b. Yes
 - i. Can you describe briefly what happened?
 - ii. How much time was there between the injection and this change?
 - iii. Have you reported this change to hospital staff?
 1. Yes
 2. No
 - iv. Has the reaction been treated?
 1. Yes
 2. No
 - v. What was the outcome of the reaction?
 1. Recovered
 2. Recovering
 3. Recovered with residual symptoms
 4. Not recovered
 5. Unknown
11. How did you feel during the scan?
 - a. 0 (not nervous) – 7 (very nervous)
12. Did you notice a physical change during the scan?
 - a. No

- b. Yes
 - i. Can you describe briefly what happened?
 - ii. How much time was there between the injection and this change?
 - 1.
 - iii. Have you reported this change to hospital staff?
 - 1. Yes
 - 2. No
 - iv. Has the reaction been treated?
 - 1. Yes
 - 2. No
 - v. What was the outcome of the reaction?
 - 1. Recovered
 - 2. Recovering
 - 3. Recovered with residual symptoms
 - 4. Not recovered
 - 5. Unknown

13. Did you stay in a room after the scan before you were allowed to go home?

- a. No
- b. Yes
 - i. Was the reason for your stay in this room clear to you?
 - 1. Yes
 - 2. No
 - a. Because: ...
- c. How did you feel while waiting?
 - i. 0 (not nervous) – 10 (very nervous)
- d. Did you notice a physical change while waiting?
 - i. No
 - ii. Yes
- e. Have you noticed a physical change shortly after the administration of the contrast agent?

- i. Can you describe briefly what happened?
- ii. How much time was there between the injection and this change?
 1.
- iii. Have you reported this change to hospital staff?
 1. Yes
 2. No
- iv. Has the reaction been treated?
 1. Yes
 2. No
- v. What was the outcome of the reaction?
 1. Recovered
 2. Recovering
 3. Recovered with residual symptoms
 4. Not recovered
 5. Unknown

14. Do you have the same opinion about radioactive substances as before?

- a. Yes
 - i. Namely: ...
- b. No
 - i. Namely: ...

Supplementary material 3: Reported adverse events of the radiopharmaceuticals and causality assessment using the Naranjo and Silberstein algorithms

Radiopharmaceutical	AEs	Naranjo category	Silberstein
[¹⁸ F]fludeoxyglucose	Paraesthesia	Possible	Unlikely
[¹⁸ F]fludeoxyglucose	Fatigue	Possible	Unlikely
[²²³ Ra]Ra-dichloride	Nausea	Possible	Unlikely
[²²³ Ra]Ra-dichloride	Backpain	Probable	Possible
[^{99m} Tc]Tc-oxidronic acid	Fatigue	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Dyspnoea	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Chest discomfort	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Nausea	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Fatigue	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Feeling hot	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Abdominal discomfort	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Fatigue	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Pain in extremity	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Nausea	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Feeling hot	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Abdominal discomfort	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Fatigue	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Limb discomfort,	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Sense of oppression,	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Chest discomfort	Possible	Unlikely
[^{99m} Tc]Tc-tetrofosmin	Fatigue	Possible	Unlikely
[^{99m} Tc]Tc-exametazime-labelled cells	Fatigue	Possible	Unlikely

Index of radiopharmaceuticals

- $[^{198}\text{Au}]$ Au-colloid, 70
 $[^{51}\text{Cr}]$ chromate labelled cells and $[^{125}\text{I}]$ I-human albumin, 64
 $[^{51}\text{Cr}]$ Cr-edetate, 58
 $[^{51}\text{Cr}]$ Cr-erythrocytes, 175
 $[^{18}\text{F}]$ fluciclovine, 35, 37, 51, 68, 75, 127
 $[^{18}\text{F}]$ fludeoxyglucose, 11, 17, 19, 35, 36, 44, 52, 68, 73, 75, 103, 105, 106, 123, 127, 128, 134, 149–162, 175, 184, 191, 192, 193, 196, 197, 204, 223, 224, 226, 227, 228, 240, 241, 244, 245, 295
 $[^{18}\text{F}]$ fluorocholine, 16, 105, 127
 $[^{18}\text{F}]$ fluorodihydroxyphenylalanine (DOPA), 18, 36, 52, 68, 75
 $[^{67}\text{Ga}]$ Ga-citrate, 35, 50, 51, 67, 72, 175
 $[^{68}\text{Ga}]$ Ga-DOTA-NOC, 52, 68
 $[^{68}\text{Ga}]$ Ga-DOTA-TATE, 35, 52, 68
 $[^{68}\text{Ga}]$ Ga-edotreotide (DOTA-TOC), 36, 52, 68, 127
 $[^{308}\text{Hg}]$ chlormerodrin, 70
 $[^{111}\text{In}]$ In-colloid, 71
 $[^{111}\text{In}]$ In-oxinate-labelled cells, 51, 67, 176
 $[^{111}\text{In}]$ In-pentetic acid, 35, 36, 44, 45, 55, 175
 $[^{111}\text{In}]$ In-pentetreotide, 52, 127, 176, 177
 $[^{111}\text{In}]$ In-platelets, 71
 $[^{111}\text{In}]$ In-satumomab pentetide, 35, 53, 69
 $[^{113\text{m}}\text{In}]$ In-colloid, 60
 $[^{113\text{m}}\text{In}]$ In-pentetic acid, 71
 $[^{125}\text{I}]$ I-albumin, 176
 $[^{131}\text{I}]$ I-human albumin, 35, 36, 70, 73
 $[^{131}\text{I}]$ I-macrosalb, 35, 36, 44, 62, 73
 $[^{123}\text{I}]$ iobenguane, 35, 50, 53, 68, 127, 175, 176
 $[^{131}\text{I}]$ iobenguane, 35, 69, 174, 175, 176, 184, 191, 193, 198, 201, 203
 $[^{123}\text{I}]$ iodofiltic acid (BMIPP), 64
 $[^{123}\text{I}]$ iodohippurate, 58
 $[^{125}\text{I}]$ iodohippurate, 17
 $[^{131}\text{I}]$ iodohippurate, 17, 37, 58
 $[^{131}\text{I}]$ iodomethyl norcholesterol, 36, 37, 54, 70, 168, 176, 177, 180, 225, 242
 $[^{123}\text{I}]$ iofetamine (IMP), 55
 $[^{123}\text{I}]$ ioflupane, 11, 16, 44, 55, 127, 176, 177
 $[^{123}\text{I}]$ iolopride, 175, 176
 $[^{131}\text{I}]$ I-rose bengal, 60
 $[^{123}\text{I}]$ sodium iodine, 49, 63, 72, 105, 127, 128, 131, 134, 175
 $[^{124}\text{I}]$ sodium iodine, 127, 128
 $[^{131}\text{I}]$ sodium iodine, 17, 36, 63, 72, 125, 127, 128, 175, 184, 191, 192, 193, 198–205
 $[^{177}\text{Lu}]$ Lu-oxodotreotide, 205
 $[^{32}\text{P}]$ sodium phosphate, 175
 Pyrophosphate (non-radioactive), 33, 49, 64
 $[^{223}\text{Ra}]$ Ra-dichloride, 11, 106, 125, 127, 128, 131, 175, 295
 $[^{81}\text{Rb}]$ Rb-krypton gas, 175
 $[^{82}\text{Rb}]$ Rb-chloride, 123, 127
 $[^{186}\text{Re}]$ Re-etidronate, 175
 $[^{75}\text{Se}]$ tauroselcholic acid, 46, 60, 176, 177
 $[^{153}\text{Sm}]$ Sm-lexidronam, 175
 $[^{89}\text{Sr}]$ Sr-chloride, 175
 Stannous agent (non-radioactive), 33, 49, 64
 $[^{99\text{m}}\text{Tc}]$ Tc-albumin, 176
 $[^{99\text{m}}\text{Tc}]$ Tc-albumin colloid, 60
 $[^{99\text{m}}\text{Tc}]$ Tc-antimony sulfide colloid, 60
 $[^{99\text{m}}\text{Tc}]$ Tc-arcitumomab, 69
 $[^{99\text{m}}\text{Tc}]$ Tc-bicisate, 175
 $[^{99\text{m}}\text{Tc}]$ Tc-butedronic acid, 56

- [^{99m}Tc]Tc-diethylenetriaminepentaacetic acid-galactosyl human serum albumin (GSA), 60
- ^{99m}Tc-diphosphonates, 16, 56
- [^{99m}Tc]Tc-erythrocytes, 176
- [^{99m}Tc]Tc-ethylenedicysteine, 58
- [^{99m}Tc]Tc-exametazime, 45, 55, 176, 177
- [^{99m}Tc]Tc-exametazime-labelled cells, 51, 67, 106, 127, 295
- [^{99m}Tc]Tc-fanolesomab, 35, 36, 44, 67, 73
- [^{99m}Tc]Tc-gluceptate, 58
- [^{99m}Tc]Tc-human albumin, 64
- [^{99m}Tc]Tc-human albumin - DTPA, 64
- [^{99m}Tc]Tc-human immunoglobulin (HIG), 67
- [^{99m}Tc]Tc-iron hydroxide, 71
- [^{99m}Tc]Tc- or [^{113m}In]In-iron precipitate, 71
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