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Adverse Events of Diagnostic Radiopharmaceuticals: A Systematic Review

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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, 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.

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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 quantities[3]—generally in the range of micrograms—and therefore do generally not have a pharmacologic 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 algorithm[6] and the method described by Silberstein.[7]

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

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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 patients.[8] 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 defects[16]; one review, published as a letter to the editor, presents data on the prevalence of adverse events for radiopharmaceuticals.[17] Additionally, several information databases have been developed to provide information about adverse events related to radiopharmaceuticals, although 2 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.

Methods

This review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[21] and the review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under number 42016042831.

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.

Study Selection

The first author (N.S.) assessed all titles obtained. For potentially relevant articles, the full text was obtained and 2 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.

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 al.[22] For each article, the reviewers scored 8 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.

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.

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 system.[23] The ATC system divides active substances into several groups according to the organ or system on which the substance acts and its therapeutic, pharmacologic, 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) terminology[24] 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 5 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 Group.[25] 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-threating, 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 event.[26] 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.

Results

Search Results

The initial search found 18,464 titles, and the second search (until July 10, 2018) found 1899 titles, for a total of 20,363 titles; another 24 articles were identified through references. Figure 1 outlines the selection process, and Table 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 none[117]; this study was included, as it relates to the frequency of adverse events in radiopharmaceuticals. Some articles mention adverse events related to the

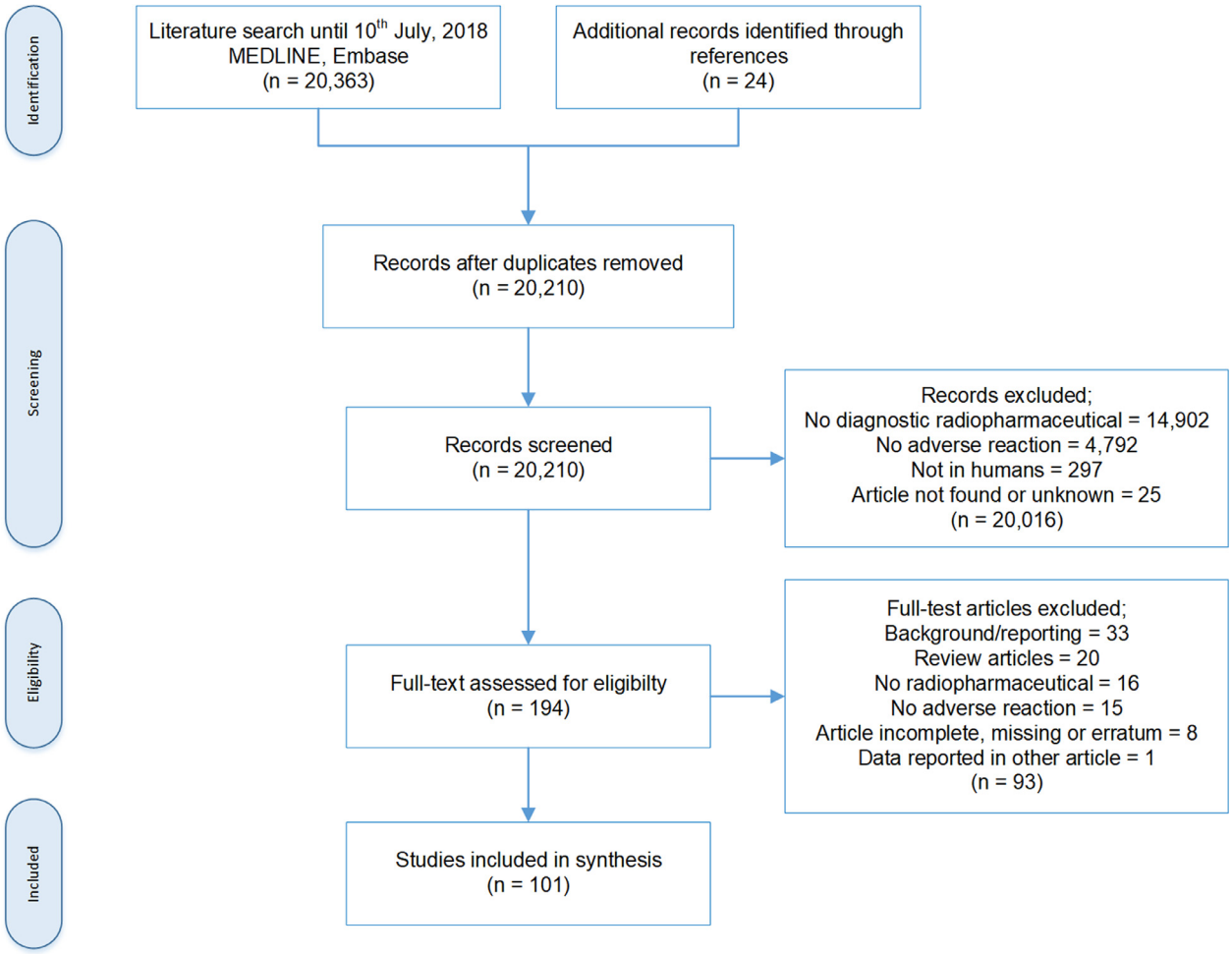

Figure 1 Selection of studies according to the PRISMA statement.[21]

Table 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	In-111 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	Tl-201 chloride	1	ND
Bach-Gansmo[31]	2016	PS	714	F-18 fluciclovine	4	ND
Bagheri[32]	1996	PS	14,794	Various	3	B
Balan[33]	2003	C	1	Tc-99m medronic acid	1	ND
Banerji[34]	1972	RS	88	I-131 human albumin	36	ND
Barnes[35]	1972	C	5	I-131 human albumin	5	ND
Bliek[36]	1971	C	1	I-131 human albumin	1	ND
Block[37]	1970	C	1	Tc-99m sulfur colloid	1	ND
Bohdiewicz[38]	1998	PS	1041	In-111 satumomab pendetide	45	ND
Burton[39]	2003	C	1	Tc-99m nanocolloid	1	ND
Chicken[40]	2007	C	1	Tc-99m nanocolloid	1	ND
Child[41]	1975	C	1	Tc-99m macrosalb	1	ND
Codreanu[42]	2013	C	1	F-18 fludeoxyglucose	1	N
Collins[43]	1988	C	1	Tc-99m medronic acid	1	CO
Commandeur[44]	1992	C	1	Ga-67 citrate	1	ND
Cotrina-Monroy[45]	2010	C	1	Tc-99m nanocolloid	1	ND
Deppen[46]	2016	PS	97	Ga-68 DOTA-TATE	3	ND
Detmer[47]	1965	C	1	I-131 human albumin	1	ND
Doerr[48]	1991	PS	116	In-111 satumomab pendetide	7	ND
Dos Santos Almeida[49]	2013	PS	55	Tc-99m medronic acid	1	ND
Doukaki[50]	2010	C	1	Tc-99m sestamibi	1	ND
Dramov[51]	1971	C	2	I-131 human albumin	2	ND
Dworkin[52]	1966	C	1	I-131 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	Tc-99m fanolesomab	63	ND
Ford[61]	1978	SC	57	Various	57‡	ND
Hart[62]	1989	C	1	Tc-99m oxidronic acid	1	ND
Hertel[63]	1990	PS	800	Various	1	ND
Hesse[64]	2011	C	1	Tc-99m 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	I-123 iobenguane	4	ND
Hurman[69]	1982	C	1	Tc-99m pentetic acid	1	ND
Ishibashi[70]	2009	C	1	I-131 iobenguane	1	ND
James[71]	1992	PS	115	Various	17	ND
Jayabalan[72]	1975	C	3	In-111 pentetic acid	3	ND
Johnston[73]	2015	PS	60	Tc-99m sulfur colloid	11	PA
Jonas[74]	1972	C	1	I-131 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	F-18 fluorodihydroxyphenylalanine (DOPA)	1	ND
Kusakabe[80]	2002	RS	1,401,962	Various	24	ND
Kusakabe[81]	2006	RS	1,277,906	Various	16	ND

Table 1 (*Continued*)

First Author [Reference]	Year	Study Design	Number of Patients	Radiopharmaceutical	Number With AE	Causality Method
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	Tc-99m tilmanocept	6	ND
Laroche[†,85]	2015	SC	6,434,988[¶]	Various	256	ND
Lee[86]	2013	C	1	F-18 fludeoxyglucose	1	N
Line[87]	2004	PS	30	Tc-99m fanolesomab	12	ND
Littenberg[88]	1975	C	1	Tc-99m microspheres	1	ND
Makaryus[89]	2008	C	1	Tc-99m sestamibi	1	ND
Maltby[90]	2002	C	1	I-131 norcholesterol diagnostic	1	ND
Manoharan[91]	2017	PS	20	Ga-68 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	Tc-99m medronic acid	1	ND
Mujtaba[100]	2007	C	1	Tc-99m sestamibi	1	ND
Nicol[101]	1967	C	1	I-131 human albumin	1	ND
Núñez[102]	2007	C	1	I-131 sodium iodine diagnostic	1	ND
O'Dorisio[103]	2018	PS	26	Ga-68 edotreotide (DOTA-TOC)	9	ND
Oldham[104]	1970	C	2	I-131 human albumin	2	ND
Oosterhuis[105]	1971	PS	83	I-131 human albumin	3	ND
Peller[106]	1994	C	1	Tc-99m mertiatide	1	ND
Pravettoni[107]	2009	C	1	Tc-99m sestamibi	1	ND
Ramos-Gabatin[108]	1986	C	1	Tc-99m medronic acid	1	ND
Rhodes[109]	1971	C	1	Tc-99m microspheres	1	ND
Rhodes[110]	1974	PS	30	In-111 pentetic acid	6	ND
Rhodes[111]	1976	C	66	In-111 pentetic acid	66	ND
Rhodes[†,112]	1980	SC	8,000,000[#]	Various	47[‡]	ND
Roberts[113]	1970	C	1	I-131 macrosalb	1	ND
Schafer[†,114]	2016	PS	52	Ga-68 edotreotide (DOTA-TOC)	NA	ND
Schaub[115]	1983	C	1	Tc-99m sulfur colloid	1	ND
Silberstein[116]	2014	PS	1,024,177	Various	21[‡]	S
Silberstein[117]	1998	PS	81,801	Various	0	S
Silberstein[7]	1996	PS	783,525	Various	18[‡]	S
Smith[†,118]	1967	RS	4775	Tc-99m sulfur colloid	15	ND
Sörensen[119]	2013	PS	6	F-18 fluciclovine	1	ND
Spicer[120]	1985	C	1	Tc-99m medronic acid	1	CO
Spyridonidis[121]	2008	C	2	I-131 norcholesterol diagnostic	2	ND
Støckel[122]	1983	C	1	I-131 iodohippurate	1	ND
Thomson[123]	2001	C	1	Tc-99m sestamibi	1	ND
Vincent[124]	1968	C	1	Tc-99m macrosalb	1	ND
Williams[125]	1974	SC	77	Various	77	ND
Williams[126]	1974	C	1	Tc-99m macrosalb	1	ND

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.

*Number of patients are totals over 3 years while number of cases is over 4 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 8 years while number of cases is over 25 years.

#Estimation.

nonradioactive pharmaceuticals pyrophosphate and stannous agent, which are used in combination with radiopharmaceutical Tc-99m pertechnetate for blood pool scintigraphy; because of their clear use in a diagnostic procedure in nuclear medicine, these 2 agents were included in the results. Of the studies, 12 (12%) use a described method to determine causality: 7 use the method described by Silberstein,[7] 2 use the algorithm described by Naranjo,[6] 2 use a method developed for radiopharmaceuticals proposed by Cordova,[127] and 1 uses a method described by Bégaud.[128]

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 reported.[117] Table 2 provides a detailed overview of the assessment.

Frequency

Twenty-two studies present the frequency of adverse events for various radiopharmaceuticals in a population. Table 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").

Summary of Findings

In total, 2447 adverse events were reported in 1804 patients. We found that 84.4% of the reported adverse events with diagnostic radiopharmaceuticals were related to 6 system organ classes (Table 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."

From the reported adverse events, 165 (6.7%) were considered to be an IME. Nine deaths were reported, 5 occurring with the use of I-131 or Tc-99m 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 Tc-99m fanolesomab,[60] 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 Tc-99m fanolesomab. Two deaths occurred with F-18 fluorodeoxyglucose[85]; 1 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 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)

Iodine Ioflupane (I-123). For I-123 ioflupane, we found 17 adverse events in 7 patients. The most reported were erythema, injection site pain, pruritus, and rash. No IMEs were reported.

Indium (In-111) Pentetic Acid. For In-111 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 5 patients, all suffering from meningitis after the use of In-111 pentetic acid. 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.

In-111 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 In-111 pentetic acid injection found that 10% of patients had a temperature increase greater than 1°F within 8 hours of injection. It is now commonly accepted that pyrogens are involved in the pathogenesis.[110] Cases of meningitis with In-111 pentetic acid were reported between 1973 and 1982,[27,56,61,111] with no new reports on adverse events after 1982.

Technetium (Tc-99m) Exametazime. For Tc-99m exametazime, we found 13 adverse events in 7 patients. The most reported adverse event was erythema. No IMEs were reported.

Table 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
Bliek[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
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

Table 2 (*Continued*)

First Author [Reference]	Q1*	Q2*	Q3*	Q4*	Q5*	Q6*	Q7*	Q8*	Assessment†
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
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
Støckel[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 dose-response 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.

Skeleton (ATC Group V09B)

Technetium (Tc-99m) Medronic Acid. For Tc-99m 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 Tc-99m medronic acid found 1 patient reported an adverse event, for a frequency of adverse events of 1.8%.[49] Three IMEs were reported; 1 patient had an anaphylactic reaction described by the author as mild,[7] another developed erythema multiforme 48 hours after use,[120] and 1 involved respiratory distress.[80]

Table 3 Study Characteristics Relevant for Assessment of Frequency of Reported AEs

Reference	Year	Country	Duration of Study (y)	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.
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 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	Sub Total
V09A central nervous system	22	88	10	19 (2)	29 (14)		3	2	2	8	4	1	6 (5)				1							195 (21)
V09B skeleton	111 (2)	90	59	33 (6)	16	16 (3)	11 (3)	12	4	5	5	5	1		2			1						371 (14)
V09C renal system	47	34	37	38 (3)	8	15	7 (2)	9	4	2	5	5		1	1		1					1		215 (5)
V09D hepatic & reticulo endothelial system	26	90	9	9 (2)	6	59 (2)	7	6 (1)	6 (1)		1			10	1 (1)									230 (7)
V09E respiratory system	22 (3)	33 (5)	5	18 (2)	32	31 (2)	24 (6)	3 (1)	13 (5)		4				2 (1)	1								188(25)
V09F thyroid	10	8	4	8 (2)	4	9	1	9	1		1		1											56 (2)
V09G cardiovascular system	70 (4)	36 (1)	26	32 (3)	14	10 (4)	10	8	1 (1)	1	2	4			1	3					1			219 (13)
V09H inflammation and infection detection	49	19 (4)	9	9 (1)	11	3	8 (2)	5	6 (3)	2	2		3	2				1						129 (10)
V09I tumor detection	75 (9)	53 (2)	23	17 (2)	9	5 (1)	2	8	4 (1)	3	3			1		1 (1)			1 (1)	1				206 (17)
V09X other diagnostic radiopharmaceuticals	21	146	29	26 (1)	65 (41)	27 (2)	16	20	10 (1)	26	10	3	5 (5)	2	1 (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 (1)	2	2	1 (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	

Numbers in parentheses represent the number of important medical events.

Table 5 Overview of AEs per Radiopharmaceutical

Central Nervous System (ATC Group V09A)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
I-123 iofetamine (IMP)	57,75-77,81-83,94,95,98	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 hyperemia, dyspnea, eczema, flushing, headache, heart rate increased, pallor, pyrexia, respiration abnormal, urticaria	29
I-123 ioflupane	66,96-98	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	17
In-111 pentetic acid	27,56,61,72,78,110-112	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), generalized tonic-clonic seizure (2), CSF test abnormal, meningitis	21
			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 hemorrhage	112
Tc-99m exametazime	55,76,81,93,96	7	*IME:* none reported	–
			Other AEs: erythema (2), anxiety, blood pressure increased, chills, cyanosis, headache, nasal congestion, palpitations, pruritus, pyrexia, rash, vasovagal symptoms	13
Yb-169 pentetic acid	56	3	*IME:* none reported	–
			Other AEs: Adverse reaction (3)	3

Skeleton (ATC Group V09B)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
Bisphosphonates (not specified)	53-55,61,65,66	68	*IME:* anaphylactoid reaction, unresponsive to stimuli	2
			Other AEs: dizziness (4), nausea (3), rash (3), vomiting (3), arthralgia (2), headache (2), hyperhidrosis (2), lethargy (2), pruritus (2), pruritus generalized (2), rash generalized (2), cyanosis, dyspnea, hypersensitivity, injection site pain, limb discomfort, mouth swelling, myalgia, edema	41

Table 5 (*Continued*)

Skeleton (ATC Group V09B)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
			peripheral, oral mucosal blistering, pyrexia, syncope, throat irritation, thrombophlebitis, vision blurred	
Tc-99m butedronic acid	55	2	*IME:* none reported	–
			Other AEs: adverse reactions not specified	–
Tc-99m medronic acid	7,29,33,43,49,55-59,75,76,80,82,83,92,93,96-99,108,112,116,120	82	*IME:* anaphylactic reaction, erythema multiforme, respiratory distress	3
			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 hyperemia, conjunctivitis, cough, dizziness, dry mouth, general symptoms, hypertension, hypoesthesia, hypotension, injection site erythema, injection site pain, jaundice, liver function test abnormal, malaise, myalgia, nasal congestion, edema peripheral, oliguria, oropharyngeal pain, pharynx discomfort, rash maculopapular, renal function test abnormal, skin reaction, skin test positive, swelling face, tachycardia, throat irritation	101
Tc-99m oxidronic acid	7,55,57-59,62,75-77,80-83,85,92-94,96-98,108,112	61	*IME:* loss of consciousness (4), anaphylactic shock, angioedema, respiratory arrest, respiratory failure, seizure	9
			Other AEs: rash (26), edema (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 edema (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 generalized exanthematous pustulosis, asthenia, blood creatine phosphokinase increased, diarrhea, dyspnea, eczema, flushing, incontinence, injection site erythema, injection site pain, laziness, mood altered, mouth swelling, pallor (2), papule, presyncope, pruritus generalized, rash erythematous, rash pruritic, stomatitis, vasculitis, white blood cell count increased	191
Tc-99m pyrophosphate	58,61,76,77,80,83,93,112	18	*IME:* none reported	–
			Other AEs: adverse drug reaction (7), adverse reaction, defecation urgency, dizziness, erythema (2), flushing, injection site erythema, nausea (4), presyncope, pruritus, vomiting (4)	24

Table 5 (*Continued*)

Renal System (ATC Group V09C)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Cr-51 edetate	54,56,59,78	5	*IME:* none reported	–
			Other AEs: adverse reaction, chromaturia, hypersensitivity, local reaction, retching, testicular swelling	6
I-123 iodohippurate	56,59	2	*IME:* none reported	–
			Other AEs: local reaction, presyncope	2
I-131 iodohippurate	28,56,57,122	18	*IME:* depressed level of consciousness	1
			Other AEs: hypersensitivity (11), nonspecific reaction (4), abdominal pain, dyspnea, flushing, hypotension, nausea, presyncope, pruritus generalized, sense of oppression, tachycardia, toxicity to various agents	25
Tc-99m ethylenedicysteine	75,80,81,83,92,94,95,96	10	*IME:* respiratory distress	1
			Other AEs: nausea (3), rash (3), erythema (2), pruritus (2), vomiting (2), abdominal pain lower, blood pressure increased, diarrhea, discomfort, dyspnea, flushing, heart rate increased, hypertension, laziness, palpitations, sneezing	23
Tc-99m gluceptate	29,58,61,112	6	*IME:* none reported	–
			Other AEs: presyncope (2), adverse drug reaction, chills, dizziness, nausea, nonspecific reaction, rash, urticaria	9
Tc-99m mertiatide	53-55,65,66,80,94,106,116	23	*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 generalized, skin reaction, somnolence, syncope, vomiting	38
Tc-99m pentetic acid	7,28,29,53-56,58,59,61,65,69, 76,77,80,81,82,112,125	50	*IME:* paralysis, respiratory distress, seizure	3
			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 hyperemia, cyanosis, depressed mood, dizziness, dry eye, dysgeusia, dyspnea, emotional distress, eye disorder, flushing, grunting, headache, hypoesthesia, malaise, muscle twitching, pallor, pruritus, rash generalized, venous pressure jugular increased. For Tc-99m pentetic acid with Fe used in the preparation 6 AEs were found in 1 patient, being: adverse drug reaction, dizziness, erythema, hypotension, pruritus, swelling	72
Tc-99m succimer	29,53-55,59,61,65,66,75,76, 82,83,94,96,116	32	*IME:* none reported	–

Table 5 (*Continued*)

Renal System (ATC Group V09C)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
			Other AEs: rash (7), headache (4), nausea (4), erythema (3), vomiting (3), adverse drug reaction (2), dizziness (2), discomfort, erythema of eyelid, hypersensitivity, hypoesthesia oral, nonspecific reaction, pallor, pyrexia, rash macular, rash pruritic, swollen tongue	35

Hepatic and Reticuloendothelial System (ATC Group V09D)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
I-131 rose bengal	61,112	3	*IME:* none reported	–
			Other AEs: adverse drug reaction (2), adverse reaction	3
In-113m colloid	28	34	*IME:* none reported	–
			Other AEs: hypersensitivity (27), toxicity to various agents (6), pyrexia	34
Se-75 tauroselcholic acid (SehCAT)	54,57,59,78	5	*IME:* anaphylactic reaction	1
			Other AEs: hypersensitivity (3), pruritus (2), rash (2), burning sensation, dizziness, dyspepsia, dyspnea, flushing, local reaction, nausea, pain, swelling, throat tightness	17
Tc-99m albumin colloid	53,56,58	6	*IME:* none reported	–
			Other AEs: hypersensitivity (3), administration site reaction, urticaria	5
Tc-99m antimony sulfide colloid	56,57,59	6	*IME:* none reported	–
			Other AEs: hypersensitivity (6)	6
Tc-99m diethylenetriami-nepentaacetic 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	11
Tc-99m nanocolloid	39,40,45,54,65-67	8	*IME:* none reported	–
			Other AEs: urticaria (4), headache, hypotension, mouth swelling, peripheral swelling, pruritus, pruritus generalized, rash, rash macular	12
Tc-99m phytate	58	2	*IME:* none reported	–
			Other AEs: adverse reaction (2)	2
Tc-99m rheniumsulfide colloid	56	1	*IME:* none reported	–
			Other AEs: hypersensitivity	1

Table 5 (*Continued*)

Hepatic and Reticuloendothelial System (ATC Group V09D)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Tc-99m 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	6
			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	129
Tc-99m tin colloid	57-59	3	*IME:* none reported	–
			Other AEs: hypersensitivity (2), adverse reaction	3

Respiratory System (ATC Group V09E)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
I-131 macrosalb	28,36,52,113	7	*IME:* death (2), anuria, hemorrhagic infarction, hypersensitivity vasculitis, pulmonary hemorrhage, skin necrosis	7
			Other AEs: body temperature increased (2), dyspnea (2), hemoptysis (2), heart rate increased (2), hypersensitivity (2), nonspecific reaction (2), agitation, anemia, blood pressure decreased, blood pressure immeasurable, blood urea increased, bundle branch block right, chest pain, cough, cyanosis, dizziness, hematuria, heart rate decreased, hyperhidrosis, lung consolidation, pleuritic pain, PO2 decreased, rash, rhinorrhea, sinus tachycardia, tachypnea, venous pressure increased	33
Tc-99m microspheres	29,56,58,61,88,109,112	48	*IME:* anaphylactic shock, anaphylactoid shock, choking, respiratory distress	4
			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	44
Tc-99m macrosalb	7,28,41,53-55,57,58,61,65,66,71,76,80,83,112,124-126	59	*IME:* death (3), apnea (2), cardiac arrest (2), angioedema, bradycardia, loss of consciousness, respiratory arrest, right ventricular failure, unresponsive to stimuli, ventricular arrhythmia	14
			Other AEs: hypersensitivity (11), adverse reaction (9), dyspnea (5), dizziness (4), rash (4), nausea (3), pruritus (3), urticaria (3), cyanosis (2),	70

Table 5 (*Continued*)

Respiratory System (ATC Group V09E)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
			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 edema, local reaction, mood altered, edema, presyncope, rash generalized, respiratory disorder, syncope, tachycardia, wheezing	
Tc-99m technegas	[71,78]	15	*IME:* none reported	–
			Other AEs: oxygen saturation decreased (15), paresthesia	16

Thyroid (ATC Group V09F)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
I-123 sodium iodine	[56,58,59]	3	*IME:* none reported	–
			Other AEs: adverse reaction, hypersensitivity, presyncope	3
I-123 sodium iodine (capsule)	[76,102]	2	*IME:* none reported	–
			Other AEs: pruritus, rash, urticaria	3
I-131 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
I-131 sodium iodine diagnostic (capsule)	[102]	*	*IME:* none reported	–
			Other AEs: urticaria	1
Tc-99m 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
Cr-51 chromate-labeled cells and I-125 human albumin	[56]	1	*IME:* none reported	–
			Other AEs: adverse reaction	1
I-123 iodofiltic acid (BMIPP)	[57,81,83,95]	5	*IME:* none reported	–
			Other AEs: erythema (2), rash (2), blood pressure decreased, dyspnea, headache, hypersensitivity, nausea, rash	10

Table 5 (*Continued*)

Thyroid (ATC Group V09F)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Pyrophosphate (nonradioactive)	29,32,116	5	*IME:* injection site necrosis, loss of consciousness	2
			Other AEs: blood pressure immeasurable, injection site inflammation, malaise, neurologic symptom, nonspecific reaction, skin reaction, vomiting	7
Stannous agent (nonradioactive)	7	3	*IME:* anaphylactic reaction (2)	2
			Other AEs: dizziness	1
Tc-99m 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
Tc-99m human albumin—DTPA	75,80,81,92	5	*IME:* none reported	–
			Other AEs: rash (3), erythema (2), pruritus (2), dizziness, nausea, edema peripheral, pyrexia	11
Tc-99m stannous agent-labeled cells	29,58,59	6	*IME:* none reported	–
			Other AEs: adverse reaction (2), hypersensitivity (2), nonspecific reaction	5
Tc-99m sestamibi	7,50,53,54,64-67,76,80-83,89,92-95,100,107,116,123	30	*IME:* dermatitis exfoliative (2), anaphylactic reaction, angioedema, erythema multiforme	5
			Other AEs: vomiting (5), malaise (4), dysgeusia (3), erythema (3), hypertension (3), nausea (3), pruritus (3), pruritus generalized, rash (3), dizziness (2), eosinophilia (2), feeling cold (2), flushing (2), swollen tongue (2), blood pressure increased, discomfort, drooling, dyspnea, dysstasia, eyelids pruritus, headache, hyperhidrosis, injection site pain, injection site swelling, neck pain, neurologic symptom, edema, paresthesia, rash generalized, rash macular, rash maculopapular, skin exfoliation, skin reaction, speech disorder, syncope, tachypnea, wheezing	61
Tc-99m tetrofosmin	54,55,65,66,77,78,82,83,93,97,116	21	*IME:* epilepsy	1
			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, dyspnea, fatigue, flushing, hyperhidrosis, hypertension, induration, lacrimation increased, oropharyngeal pain, rash generalized, rhinorrhea, slow response to stimuli, swelling, thrombophlebitis	40
Tl-201 chloride	30,55,58,65,75-77,80-83,92,93,95,97,98	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),	60

Table 5 (*Continued*)

Thyroid (ATC Group V09F)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
			acute generalized exanthematous pustulosis, adverse reaction, affective disorder, amnesia, asthenia, chills, claustrophobia, conjunctival hyperemia, discomfort, dizziness, dyspnea, eyelid edema, feeling hot, flushing, hypersensitivity, hypotension, incontinence, leukocytosis, local reaction, oral mucosa erosion, papule, presyncope, red blood cell sedimentation rate increased, respiration rate increased, skin burning sensation, skin irritation, urticaria, vision blurred	

Inflammation and Infection Detection (ATC Group V09H)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when >1)	Total Number AEs
Ga-67 citrate	7,44,54,56,57,59,61,65,75-77,81-83,92-94	39	*IME:* altered state of consciousness, bradycardia	2
			Other AEs: rash (15), pruritus (11), pyrexia (5), rash generalized (5), adverse reaction (3), erythema (3), nausea (3), urticaria (3), blood pressure decreased (2), dyspnea (2), hyperhidrosis (2), hypersensitivity (2), vomiting (2), affective disorder, arthralgia, asthenia, burning sensation, C-reactive protein increased, discomfort, dysgeusia, feeling cold, flushing, generalized erythema, heart rate increased, hepatic function abnormal, local reaction, palpitations, paresthesia, rash morbilliform, skin plaque, sneezing, syncope, tachycardia, thirst, viral upper respiratory tract infection	80
In-111 oxinate-labeled cells	53,58,116	3	*IME:* none reported	–
			Other AEs: headache, hypersensitivity, myalgia, nausea, skin reaction	5
Tc-99m fanolesomab	60,87	75	*IME:* cardiac arrest (2), cardio-respiratory arrest (2), sudden cardiac death (2), hypoxia	7
			Other AEs: human antimouse antibody positive (5), paresthesia (2), viral upper respiratory tract infection (2), ankle sprain, blood lactate dehydrogenase increased, contusion, dyspnea, flushing, hypotension, malaise, toothache, transaminase increased	18
Tc-99m human immunoglobulin (HIG)	54	1	*IME:* none reported	–
			Other AEs: nausea	1
Tc-99m exametazime-labeled cells	54,65,66	5	*IME:* none reported	–

Table 5 (*Continued*)

Inflammation and Infection Detection (ATC Group V09H)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
Tc-99m sulesomab	54,65	3	*Other AEs:* dyspnea (2), emotional distress, flushing, malaise, pruritus generalized, rash pruritic	7
			IME: pulmonary edema	1
			Other AEs: blister, cyanosis, dizziness, hyperhidrosis, hypertension, nausea, pruritus, rash erythematous	8

Tumor Detection (ATC Group V09I)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
F-18 fluciclovine	31,119	5	*IME:* none reported	–
			Other AEs: adverse event (4), injection site erythema	5
F-18 fludeoxyglucose	42,78,83,85,86,92-95,97,98,116	17	*IME:* angioedema (3), dermatitis exfoliative (3), seizure (2), sudden cardiac death (2), anaphylactic reaction	11
			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, diarrhea, discomfort, head tituba-tion, heart rate increased, hypotension, malaise, mental status change, oral pruritus, papule, rash generalized, skin reaction	69
F-18 fluorodihydroxy-phenylalanine (DOPA)	79	1	*IME:* carcinoid crisis	1
Ga-68 DOTA-NOC	78	†	*Other AEs:* none reported	–
			IME: none reported	–
			Other AEs: rash maculopapular	1
Ga-68 DOTA-TATE	46	3	*IME:* none reported	–
			Other AEs: injection site pruritus, oxygen saturation decreased, tachycardia	3
Ga-68 edotreotide (DOTA-TOC)	91,103,114	13	*IME:* none reported	
			Other AEs: adverse event (9), nausea (2), discomfort, dysgeusia, flushing, headache, pain, paresthesia	17
I-123 iobenguane	53,54,59,65-68,75,77,82,97,116	28	*IME:* none reported	–
			Other AEs: injection site pain (8), nausea (3), vomiting (3), dysgeusia (2), dyspnea (2), adverse reaction, blood gases abnormal, blood pressure decreased, discomfort, dizziness, flushing, heart rate increased, hypersensitivity, hypertension, hypoesthesia, hypotension, palpitations,	41

Table 5 (*Continued*)

Tumor Detection (ATC Group V09I)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
			persistent depressive disorder, presyncope, procedural nausea, pruritus, pruritus generalized, rash, rash generalized, skin odor abnormal, skin reaction, syncope, urticaria	
I-131 iobenguane diagnostic	[70]	1	*IME:* erythema multiforme	1
			Other AEs: rash erythematous, rash pruritic	2
In-111 satumomab pendetide	[48,53]	53	*IME:* angioedema (2), bradycardia, thrombocytopenia	4
			Other AEs: pyrexia (6), pruritus (4), hypersensitivity (3), abdominal pain (2), flank pain (2), human antimouse antibody positive (2), hypertension (2), nausea (2), rash (2), arthralgia, asthenia, chest pain, chills, confusional state, crying, diarrhea, dizziness, headache, hyperhidrosis, hypotension, hypothermia, injection site reaction, nervousness, pain, urticaria, vasodilatation, vomiting	43
Tc-99m arcitumomab	[63]	1	*IME:* none reported	–
			Other AEs: human antimouse antibody positive, urticaria	2
Tc-99m tilmanocept	[84]	6	*IME:* none reported	–
			Other AEs: adverse event (5), injection site irritation	6

Other Diagnostic Radiopharmaceuticals (ATC Group V09X)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
Au-198 colloid	[28,56,57,125]	6	*IME:* none reported	–
			Other AEs: hypersensitivity (5), adverse reaction	6
Hg-308 chlormerodrin	[28]	3	*IME:* none reported	–
			Other AEs: hypersensitivity (3)	3
I-131 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	47
			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,	109

Table 5 (*Continued*)

Other Diagnostic Radiopharmaceuticals (ATC Group V09X)

Diagnostical Radiopharmaceutical	References	Total Number Patients	AEs (n when > 1)	Total Number AEs
			back pain, chest discomfort, hyperreflexia, lethargy, nausea, presyncope, somnolence, toxicity to various agents	
I-131 norcholesterol diagnostic	56,75-77,80-83,90,92, 93,95-97,121	60	*IME:* anaphylactic shock, electrocardiogram ST segment depression, ventricular tachycardia	4
			Other AEs: nausea (16), back pain (14), flushing (14), discomfort (11), hypersensitivity (10), blood pressure increased (8), dyspnea (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), hypoesthesia (2), malaise (2), pruritus (2), tachycardia (2), abdominal pain, abdominal symptom, abnormal sensation in eye, arthralgia, asthma, cyanosis, emotional distress, eyelid edema, feeling hot, heart rate increased, hyperventilation, hypotension, injection site rash, nasal congestion, neck pain, ocular hyperemia, pain, papule, pulse abnormal, swelling, vertigo positional	186
In-111 colloid	57	1	*IME:* none reported	–
			Other AEs: adverse reaction	1
In-111 platelets	57	1	*IME:* none reported	–
			Other AEs: hypersensitivity	1
In-113m pentetic acid	28	1	*IME:* none reported	–
			Other AEs: hypersensitivity	1
Tc-99m iron hydroxide	28	4	*IME:* none reported	–
			Other AEs: nonspecific reaction (3), toxicity to various agents	4
Tc-99m or In-113m iron precipitate	125	45	*IME:* none reported	–
			Other AEs: adverse reaction (45)	45
Tc-99m plasmin	56	1	*IME:* none reported	–
			Other AEs: hypersensitivity	1
Diagnostic radiopharmaceuticals not specified	57	419	*IME:* none reported	–
			Other AEs: rash (110), vomiting (30), urticaria (24), pruritus (64), skin reaction, adverse reaction	230

AEs, adverse events; IME, important medical event.

*AE reported with 1 patient using both I-123 sodium iodine (capsule) as I-131 sodium iodine diagnostic (capsule) *Cardiovascular System (ATC Group V09G)*.

†Exact number of patients was not given by author.

Technetium (Tc-99m) Oxidronic Acid. For Tc-99m 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; 1 patient suffered from respiratory arrest and lost consciousness 2 minutes after injection,[76] 1 lost consciousness 1 minute after injection,[76] 1 suffered from severe respiratory failure,[94] 1 suffered 1 minute after injection from convulsions and lost consciousness,[96] 1 experienced angioedema,[85] and 1 had an anaphylactic shock and lost consciousness.[97]

Renal System (ATC Group V09C)

Technetium (Tc-99m) Mertiatide. For Tc-99m mertiatide, we found 38 adverse events in 23 patients. The most reported adverse events were nausea, dizziness, and rash. No IMEs were reported.

Technetium (Tc-99m) Pentetic Acid. For Tc-99m 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; Tc-99m 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 use.[129] Another patient experienced respiratory distress 1 hour after injection,[69] and 1 case of seizure was reported.[112]

Technetium (Tc-99m) Succimer. For Tc-99m 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)

Selenium (Se-75) Tauroselcholic Acid. For Se-75 tauroselcholic acid (SehCAT), we found 18 adverse events in 5 patients. The most reported adverse events were hypersensitivity, pruritus, and rash. No IMEs were reported.

Technetium (Tc-99m) Nanocolloid. For Tc-99m nanocolloid, we found 12 adverse events in 8 patients. The most reported adverse event was urticaria. No IMEs were reported.

Technetium (Tc-99m) Sulfur Colloid. For Tc-99m 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 Tc-99m sulfur colloid found a frequency of adverse events of 0.1%-0.9%.[118] A study into pain level during Tc-99m sulfur colloid use found that 11 (18.3%) of the 60 patients experienced significant pain.[73] The product's preparation method might cause the injection site pain and is most likely related to the stabilizers used, especially Dextran and Gelatin.[118] Low pH may be another reason, with Johnston showing that bringing the pH of the Tc-99m sulfur colloid solution to the physiological level could reduce pain levels during injection[73]; Canning used anesthetic cream before injection but was unable to demonstrate a reduction in pain.[130]

Six IMEs were reported. One patient suffered from an adverse reaction of the anaphylactoid type to Tc-99m 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 necrosis.[37] One case of loss of consciousness was reported,[112] and 1 patient experienced an anaphylactic reaction with loss of consciousness.[115]

Respiratory System (ATC Group V09E)

Technetium (Tc-99m) Macrosalb. For Tc-99m 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 8 patients: 1 case of angioedema,[66] 2 cases of cardiac arrest,[53,112] 1 case in which a patient became unresponsive with bradycardia,[65] 1 case of respiratory arrest,[55] and 3 deaths. The 3 deaths included 2 patients who presented with a history of pulmonary hypertension[41,126] and 1 suffering from an advanced pulmonary vascular disease,[124] all 3 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 particles,[131] 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 children[132] 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.

Technetium (Tc-99m) Technegas. For Tc-99m 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 Tc-99m technegas; that study found that 37% of patients experienced a decrease of more than 10% in oxygen saturation.[71] No IMEs were reported.

Thyroid (ATC Group V09F)

Sodium Iodide (I-123). For I-123 sodium iodine, we found 6 adverse events in 5 patients. No IMEs were reported. One patient developed a rash after use of an I-123 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 event.[102]

Technetium (Tc-99m) Pertechnetate. For Tc-99m pertechnetate, we found 26 adverse events in 17 patients. The most reported adverse events were hypersensitivity, rash, and nausea. Two IMEs were reported: 1 patient lost consciousness immediately after injection,[80] and another lost consciousness 5 minutes after injection.[76] Both cases were classified by the author as vasovagal reactions.

Cardiovascular System (ATC Group V09G)

Pyrophosphate (Nonradioactive). For pyrophosphate, we found 9 adverse events in 5 patients. Two IMEs were reported: 1 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 site.[32]

Stannous Agent (Nonradioactive). For stannous agent, we found 3 adverse events in 3 patients. Two IMEs were reported, both anaphylactic reactions not further specified by the author.[7]

Technetium (Tc-99m) Sestamibi. For Tc-99m sestamibi, we found 66 adverse events in 30 patients. The most reported adverse events were vomiting and malaise. Five IMEs were reported: 1 patient suffered from an erythroderma affecting more than 90% of his body,[50] 1 experienced an angioedema,[89] 1 suffered an anaphylactic reaction with a painless macroglossia,[100] 1 presented with an exfoliating itching dermatitis,[107] and 1 was diagnosed with erythema multiforme after Tc-99m sestamibi administration.[123]

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 itself,[67] and one of the excipients of the formulation (eg, the presence of copper ions in some formulations of I-123 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.

Technetium (Tc-99m) Tetrofosmin. For Tc-99m 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 dipyridamole.[65]

Thallium (Tl-201) Chloride. For Tl-201 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 anaphylaxis,[55] 1 patient who experienced bradycardia postadministration after exercise on an ergometer,[77] and 1 patient who temporarily lost consciousness 5 minutes after administration of the radiopharmaceutical.[82]

Inflammation and Infection Detection (ATC Group V09H)

Gallium (Ga-67) Citrate. For Ga-67 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 bradycardia,[76] and another lost consciousness.[81] For Ga-67 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 Ga-67 citrate.[44]

Radiolabeled Leucocytes. For In-111 oxinate-labeled cells, we found 5 adverse events in 3 patients. For Tc-99m exametazime-labeled cells, we found 7 adverse events in 5 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 cells.[133] Although most procedures involve washing the labeled cells, it cannot be excluded that adverse events are related to one of the excipients used.

Technetium (Tc-99m) Sulesomab. For Tc-99m sulesomab, we found 9 adverse events in 3 patients. One IME was reported in 1 patient experiencing pulmonary edema.[54] Tc-99m sulesomab is a radiopharmaceutical based on an antibody, although it is not associated with the development of human antimouse antibodies; Fab fragments of IgG antibody lack the Fc-terminal responsible for the immune reactions.[134]

Tumor Detection (ATC Group V09I)

Fluciclovine (F-18). For F-18 fluciclovine, we found 5 adverse events in 5 patients. In a cohort study with 714 patients, 0.6% reported adverse events.[31] In a small study with 6 patients, 1 patient experienced one adverse event (frequency of 16.5%).[119] No IMEs were reported.

Fludeoxyglucose (F-18). For F-18 fludeoxyglucose, we found 80 adverse events in 17 patients. The most reported adverse

events were rash, pruritus, and erythema. Eleven IMEs were reported: 1 anaphylactic reaction,[86] 3 cases of angioedema, 3 cases of dermatitis exfoliative, 2 cases of seizures, and 2 sudden cardiac deaths.[85] 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).

Fluorodihydroxyphenylalanine (F-18). For F-18 fluorodihydroxyphenylalanine (DOPA), an adverse event classified as an IME was reported in 1 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 ketanserin.[79]

Gallium-68-Labeled Somatostatin Analogs (Ga-68 Edotreotide (DOTA-TOC), Ga-68 DOTA-TATE, Ga-68 DOTA-NOC). For the group of Ga-68-labeled somatostatin analogs, we found 21 adverse events in 16 patients. A study evaluating safety and comparing Ga-68 DOTA-TATE with In-111 pentetreotide imaging (conducted with 97 patients) found 3 adverse events in 3 patients, for a frequency of 3.09%.[46] In a multicenter trial using Ga-68 edotreotide in 20 patients, 4 adverse events possibly related to the radiopharmaceutical were found, for a frequency of 20%.[91] Another study with Ga-68 edotreotide found 9 adverse events in 26 patients (34.6%).[103] No IMEs were reported.

Iobenguane (I-123). For I-123 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 events.[68] No IMEs were reported.

Indium (In-111) Satumomab Pendetide. For In-111 satumomab pendetide, we found 47 adverse events in 53 patients. The most reported adverse events were fever, pruritus, and hypersensitivity. Clinical trials involving 1041 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 thrombocytopenia,[38] and one case of angioedema was reported.[48]

In-111 satumomab pendetide contains murine monoclonal antibodies. These antibodies might induce an immune response producing human antimouse 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 antimouse 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 antimouse antibodies test prior to administration, and inform that use could affect future use of murine-based products.[137-139]

Technetium (Tc-99m) Tilmanocept. For Tc-99m tilmanocept, we found 6 adverse events. In a multicenter trial with 85 patients, 36 reported at least 1 adverse event; the authors indicate that 85% of the reported adverse events were unrelated to Tc-99m tilmanocept.[84] No IMEs were reported.

Other Diagnostic Radiopharmaceuticals (ATC Group V09X)

Iodine (I-131) Norcholesterol Diagnostic. For I-131 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 3 patients: one case described an anaphylactic shock 15 minutes after injection,[83] 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 reaction.[90]

I-131 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 frequently.[90] The manufacturer states that no pharmacodynamic effects are expected for doses used in diagnostic imaging.[140] 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.

Discussion

Based on a systematic review of the literature, we selected and analyzed 101 of 20,363 titles and provided an overview of 2447 adverse events associated with the use of diagnostic radiopharmaceuticals. The majority of the reported adverse events with diagnostic radiopharmaceuticals (84.4%) related to 6 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 sensibilization risk changes. A limited number of case reports note a positive rechallenge: Spicer reports a case with Tc-99m medronic acid in which a patient developed a pruritic erythematous rash after the first use and erythema multiforme with the second use after 9 months,[120] and Mooser reports a case of an erythematous, pruritic rash after administration of Tc-99m medronic acid, with a rechallenge that Tc-99m was responsible for the rash.[99] Núñez reports a case of rash after the use of I-123 and I-131 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 I-123 sodium iodine capsule followed 5 months later with an I-131 sodium iodine capsule and developed an urticarial skin rash similar in appearance on both occasions.[102] Commandeur reports a case of hypersensitivity to Ga-67 chloride, with skin tests demonstrating that the preservative benzyl alcohol caused the reaction.[44]

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 9 deaths were reported: 5 occurring with the use of I-131 or Tc-99m macrosalb for pulmonary scintigraphy in cases of a severe reduction in pulmonary capacity, 2 occurring with F-18 fluorodeoxyglucose, and 2 occurring with the radiopharmaceutical Tc-99m 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%-2% reported for therapeutic drugs[143,144] and the 5%-7% reported for drug reactions in hospitalized patients.[145-147] This frequency is also lower than the earlier reported frequency range of 0.7%-3.1% with nonionic 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 I-131 human serum albumin and Tc-99m fanolesomab.

The low reported frequency with some diagnostic radiopharmaceuticals can be explained by a low dose, lack of pharmacologic 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 nonradioactive 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 nonradioactive 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 7 studies and found a pooled prevalence rate of 1.9 per 100,000 administrations.[17] 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 article,[150] 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 preset 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 event.[67]

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,

Tc-99m 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.

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 (F-18 fludeoxyglucose, F-18 fluciclovine, F-18 fluorodihydroxyphenylalanine (DOPA), and Ga-68-labeled somatostatin analogs). The majority are attributed to F-18 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 patients.[117] 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 media.[151]

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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