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USE OF RADIOPHARMACEUTICALS IN DIAGNOSTIC NUCLEAR MEDICINE IN THE UNITED STATES: 1960–2010

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Abstract

To reconstruct reliable nuclear medicine-related occupational radiation doses or doses received as patients from radiopharmaceuticals over the last five decades, we assessed which radiopharmaceuticals were used in different time periods, their relative frequency of use, and typical values of the administered activity. This paper presents data on the changing patterns of clinical use of radiopharmaceuticals and documents the range of activity administered to adult patients undergoing diagnostic nuclear medicine procedures in the U.S. between 1960 and 2010. Data are presented for 15 diagnostic imaging procedures that include thyroid scan and thyroid

uptake, brain scan, brain blood flow, lung perfusion and ventilation, bone, liver, hepatobiliary, bone marrow, pancreas, and kidney scans, cardiac imaging procedures, tumor localization studies, localization of gastrointestinal bleeding, and non-imaging studies of blood volume and iron metabolism. Data on the relative use of radiopharmaceuticals were collected using key informant interviews and comprehensive literature reviews of typical administered activities of these diagnostic nuclear medicine studies. Responses of key informants on relative use of radiopharmaceuticals are in agreement with published literature. Results of this study will be used for retrospective reconstruction of occupational and personal medical radiation doses from diagnostic radiopharmaceuticals to members of the U.S. radiologic technologist's cohort and in reconstructing radiation doses from occupational or patient radiation exposures to other U.S. workers or patient populations.

Keywords

Nuclear medicine; radiopharmaceutical use; administered activity

INTRODUCTION

Diagnostic imaging used to support medical decision-making experienced explosive growth in the second half of the 20th century and during this interval both diagnostic nuclear medicine and radiology procedures accounted for the bulk of radiation exposure to patients and hospital staff. Numerous epidemiologic studies have been conducted over the last 5 decades on populations exposed to medical radiation and/or other sources of radiation. Some studies have tried to account for personal medical exposures received though doses are almost always difficult to estimate with acceptable reliability for the component of exposure due to radiopharmaceuticals for diagnostic nuclear medicine procedures. The reason for this difficulty is due in part to poor historical information on the diagnostic use of radiopharmaceuticals and reliance upon individuals' recall of the radiopharmaceuticals and doses to which they may have been exposed. A retrospective analysis was, therefore, performed to fill the gap on the historical use of radiopharmaceuticals to facilitate future assessment of radiation doses to populations whose exposure included diagnostic nuclear medicine procedures.

To this end we will use this data to support an ongoing study by the National Cancer Institute (NCI), a long-term follow-up and cancer risk analysis, of a large cohort of U.S. radiologic technologists (USRT) who worked during the mid to late 20th century. That study focuses on exposures and evaluation of health risks, in particular, the risk of cancer (Boice et al., 1992, Sigurdson et al. 2003, Simon et al. 2006). We are in the process of reconstructing occupational radiation doses to each USRT cohort member (Simon et al. 2006, Simon et al. 2014) as well as radiation doses technologists received as part of their personal medical care. To collect information for accurate assessment of individual doses, we request each USRT cohort member to complete a self-administered questionnaire to specifically report radiopharmaceutical use in their occupational activities or personal exposure radiation (both nuclear medicine and radiology) for medical diagnosis or therapy during the years 1960–2010. A work history questionnaire module has been designed to provide an estimate of the

number of times per week each technologist performed or assisted in the performance of diagnostic radioisotope/ radiopharmaceutical procedures during ten year intervals from 1960 through 2010. Here we note that the questionnaire only inquires about the type of radioisotope procedure with which they might have assisted. Although radiopharmaceuticals used for diagnostic imaging and their typical administered activities have markedly changed over the past five decades, we intentionally did not inquire about details of the radiopharmaceuticals since the time period was too long to expect reliable answers. We assumed similar, albeit greater, recall difficulties for technologists who received exposure to radiopharmaceuticals as a patient rather than by occupational exposure.

In order to reconstruct a five-decade history reliable nuclear medicine-related occupational radiation doses and/or radiation doses from radiopharmaceuticals received as patients we needed to assess radiopharmaceuticals use in different time intervals, their relative frequency, and typical administered activities. Published data are limited, and we used information from nationwide surveys of relative use of radiopharmaceuticals and actual administered activities in the United States conducted by the Department of Health, Education, and Welfare (DHEW) in the mid-1960s through the mid-1970s (USDHEW 1968, 1970, 1976). Reports from medical market research companies provided information on the relative frequency of use of radiopharmaceuticals for selected nuclear medicine examinations in the 2000s, for example, for cardiac perfusion studies (IMV 2008). However, we were unable to find sufficient published data on the frequency of use for many of the different radiopharmaceuticals used in other time intervals.

In an attempt to fill this information gap, we collected data on the relative frequency of use of the major radiopharmaceuticals deployed in diagnostic nuclear medicine imaging from interviews of a panel of internationally recognized nuclear medicine practitioners. This paper summarizes the collective information obtained from those interviews that details the use and administered doses of radiopharmaceuticals in the practice of diagnostic nuclear medicine in the U.S. from 1960 through 2010.

MATERIALS AND METHODS

Use of radiopharmaceuticals

Key informants interview—To collect data on the relative use of radiopharmaceuticals for diagnostic nuclear medicine procedures in the U.S. in 1960–2010, we conducted a survey of knowledgeable persons who began working in the field of diagnostic imaging in the 1960s through the early 1980s. For the purposes of our data collection effort, these experts served the role as “key informants”. In this data collection, 11 of 40 prominent U.S.-based nuclear medicine experts responded on the survey. The key informants were experts working at large hospitals and medical centers including: Massachusetts General Hospital, Beth Israel Deaconess Medical Center, University of Iowa Hospitals and Clinics, University of Missouri, University of New Mexico Medical Center, Vanderbilt University Medical Center, Veteran Affairs (VA) Hospitals (Ann Arbor, Long Island, Los Angeles, Nashville), and Weill Cornell Medical Center. In completing the questionnaires, key informants were instructed to rely on their own experience and knowledge or archival records of their practice or the medical centers where they were employed.

The questionnaire completed by the key informants included 17 spreadsheets, one for each of the following nuclear medicine procedures: thyroid scan, thyroid uptake study, brain scan, brain blood flow study, lung perfusion study, lung ventilation study, bone scan, liver scan, hepatobiliary scan, bone marrow scan, pancreas scan, kidney scan, cardiac procedures, tumor localization study, gastrointestinal (GI) bleeding and Meckel's scan, non-imaging studies of blood volume, and iron metabolism studies. For each procedure, a list of the most frequently used radiopharmaceuticals, as indicated by the literature, was provided. Key informants were asked whether they used each radiopharmaceutical in their practice and to estimate its relative frequency of use in each year from 1960 to 2010. Experts were allowed to add other radiopharmaceuticals if they knew of their use in a particular year(s). The key informants were requested to maintain the total percentage of the relative use of radiopharmaceuticals for given procedures in each year to be equal to 100%. Years of approval by the U.S. Food and Drug Administration for some radiopharmaceuticals as well as an example of a completed table (for instructional purposes) were also provided to the key informants.

Relative use of radiopharmaceuticals—The data collected from the key informants' responses of the relative use of radiopharmaceuticals (in %) for each diagnostic radioisotope procedure in each year was calculated using eqn (1):

$$p_{k,l,m} = \frac{\sum_n p_{k,l,n}}{\sum_m \sum_n p_{k,l,m,n}} \times 100\%, \quad (1)$$

where $p_{k,l,m}$ is the relative use (%) of the m -th radiopharmaceutical in the l -th year for the k -th diagnostic radioisotope procedure; $p_{k,l,m,n}$ is the percentage of use of the m -th radiopharmaceutical in the l -th year for the k -th diagnostic radioisotope procedure reported by the n -th key informant.

Administered activity of radiopharmaceuticals

We also conducted an extensive literature review to collect data on activity of radiopharmaceuticals administered to adult patients in the U.S. during different time intervals. Textbooks on nuclear medicine practice in the U.S. (e.g., Bland 1965, 1971; Wagner 1968, 1995; Maynard 1969, 1971; Sodde and Early 1972, 1975; Mettler and Guiberteau 1983, 1998, 2012; Kowalsky and Falen 2004) and the U.S. Society of Nuclear Medicine procedure guidelines (e.g. Becker et al. 1999; Balon et al. 2006a, 2006b; Delbeke et al. 2006) were consulted as major reference sources. We also searched for full-text articles published between the 1960 and 2013 using PubMed, Science Direct, and journals' web-sites when necessary. In addition, references listed in each publication were used to identify publications not captured by the electronic searches. If the administered activity was given in a reference as a range, a median of that range was assumed to be the typical administered activity.

Radiopharmaceutical-weighted effective dose to patient

Information on the relative use of each radiopharmaceutical and its administered activity for each diagnostic radioisotope procedures was used to calculate a typical radiopharmaceutical-weighted effective dose as follows:

$$D_{k,l}^{eff} = \sum_{m=1}^{M_{k,l}} (p_{k,l,m}/100) \times A_{k,l,m} \times DCF_m \quad (2)$$

where $D_{k,l}^{eff}$ is the radiopharmaceutical-weighted effective dose to a patient who underwent the k -th diagnostic radioisotope procedure (mSv) in the l -th year; $A_{k,l,m}$ is the activity of the m -th radiopharmaceutical administered in the l -th year for the k -th diagnostic radioisotope procedure (MBq); DCF_m is the effective dose conversion factor, giving the effective dose per unit administered activity of the m -th radiopharmaceutical (mSv MBq⁻¹) (ICRP 1987, 1998, 2008); $M_{k,l}$ is the number of radiopharmaceuticals used in the l -th year for the k -th diagnostic radioisotope procedure.

Mixtures of radiopharmaceuticals, except for some protocols like dual isotope cardiac perfusion studies, were generally not administered to the same patient; therefore the typical radiopharmaceutical-weighted effective dose presented here is used only for illustrative purposes. The value from eqn. (2) represents a radiopharmaceutical-weighted average effective dose that reflects the overall mean dose for each procedure type and is used only to evaluate trends in patient radiation exposures over the time period from 1960 through 2010.

RESULTS

Table 1 summarizes data reported by key informants on the relative use of radiopharmaceuticals for diagnostic nuclear medicine procedures in the U.S. from 1960 through 2010. Although the experts provided estimates for each year, the data are summarized and averages are shown for 5-year periods. Based on literature reports, we also summarize in Table 2, typical administered doses (and ranges) for radiopharmaceuticals used in adult patients in diagnostic nuclear medicine in the U.S. for 5-year intervals. The data for different diagnostic radioisotope procedures are discussed in detail in the following sections.

Thyroid scan and thyroid uptake

Historically Iodine-131 (¹³¹I)-sodium iodide is the standard radiopharmaceutical used for routine thyroid studies since the late 1940s. Other radiopharmaceuticals that have also been used for thyroid studies are technetium-99m (^{99m}Tc)-pertechnetate (since the late 1960s) and ¹²³I-sodium iodide (since the mid-1970s). By the beginning of the 2000s, about half of all thyroid scans were performed with ¹²³I-sodium iodide, about 40% used ^{99m}Tc-pertechnetate, while less than 10% used ¹³¹I-sodium iodide. For thyroid uptake studies, by the late 2000s, ¹³¹I-sodium iodide and ¹²³I-sodium iodide were reported by key informants to be used almost equally, 45% and 55%, respectively. In addition to these three radiopharmaceuticals (Table 1), use of ¹²⁵I-sodium iodide for thyroid imaging was also

reported, although it is not shown in Table 1 as it was reported to be only a few percent and was primarily used for research studies conducted in the 1970s and 1980s.

The activity administered radiopharmaceuticals used for thyroid studies to adults (Table 2) varied over the last five decades. The administered activity of ^{131}I -sodium iodide for thyroid imaging before the mid-1970s was about 1.85 MBq (Harper et al. 1965; Wagner 1968; Atkins 1975; McAfee and Subramanian 1984; Drozdovitch et al. 2014), then gradually increased to 3.7 MBq (Sodee and Early 1975; Irwin et al. 1978; Mettler et al. 1986; Sisson 1997). The administered activity of ^{123}I -sodium iodide for thyroid imaging before the late-1970s was estimated to be 3.7 MBq (Robertson 1982; Wagner et al. 1986), then gradually increased to 11.1 MBq in the 1980s (Mettler and Guiberteau 1983, Mettler et al. 1986; Wagner et al. 1995; Park et al. 1994, 1997) and to 14.8 MBq in the mid-1990s (Mettler and Guiberteau 1998; Becker et al. 1999; Kowalsky and Falen 2004; Balon et al. 2006a; Joyce and Swihart 2011). The administered activity of $^{99\text{m}}\text{Tc}$ -pertechnetate for thyroid imaging before the late-1970s was estimated to be 74 MBq (Early et al. 1969; Maynard 1971; Barrall and Smith 1976), then increased to 185 MBq in the 1980s (Mettler et al. 1986; Wagner et al. 1986; NCRP 1996) and to 222 MBq in the mid-1990s (Mettler and Guiberteau 1998; Becker et al. 1999; Kowalsky and Falen 2004; Balon et al. 2006a; Joyce and Swihart 2011).

The activity administered to adult patients who underwent thyroid uptake studies is shown in Table 2 (Blahd 1965; Wagner 1968; Maynard 1971; Atkins 1975; USDHEW, 1976; Schneider 1979; Mettler and Guiberteau 1998; Kowalsky and Falen 2004; Balon et al. 2006b; Dahnert 2007; NCRP 2009).

Brain scan

Mercury-203 (^{203}Hg)- and ^{197}Hg -labeled chlormerodrin were the main radiopharmaceuticals used for brain imaging in the 1960s following their introduction by Blau and Bender (1962) and Sodee (1963). By the end of the 1960s, ^{203}Hg -chlormerodrin was replaced with $^{99\text{m}}\text{Tc}$ -pertechnetate because ^{203}Hg resulted in a high radiation dose to the kidneys due to its beta-radiation and long effective half-time. Mercury-197-chlormerodrin was also used until the early 1970s. Other $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals that were used for brain imaging were $^{99\text{m}}\text{Tc}$ -diethylenetriaminepentaacetic acid ($^{99\text{m}}\text{Tc}$ -DTPA) starting in 1970, $^{99\text{m}}\text{Tc}$ -glucoheptonate ($^{99\text{m}}\text{Tc}$ -GH) during the mid-1970s through the 1980s, $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime ($^{99\text{m}}\text{Tc}$ -HMPAO) since the late 1980s, and $^{99\text{m}}\text{Tc}$ -ethyl cysteinate diethylester ($^{99\text{m}}\text{Tc}$ -ECD (Neurolite^{TM})) since 1990. Our key informants reported use of ^{201}Tl -chloride for brain imaging only for a short period of time, in the late 1980s through early 1990s. Since the late 1980s, fluorine-18 fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) has been used for imaging brain function/metabolism; and its use has progressively increased.

In addition to the radiopharmaceuticals shown in Table 1, use of ^{123}I -iodoamphetamine (^{123}I -IMP) was also reported; however, it is not included in the analysis as it was used only for a few percent of brain scans and for only a short time period. For a number of reasons, including uncertain brain retention mechanisms, inconvenience of use/ supply, and

cost, ^{123}I -IMP did not become a routine brain imaging agent (Kowalsky and Falen 2004) and was replaced by $^{99\text{m}}\text{Tc}$ -HMPAO (Saha et al. 1994).

Activities of radiopharmaceuticals administered to adult patients for brain imaging were the following (Table 2):

- 26 MBq of $^{197, 203}\text{Hg}$ -chlormerodin (Silver 1968; Maynard 1971; Sodee and Early 1972; Drozdovitch et al. 2014);
- 463 MBq $^{99\text{m}}\text{Tc}$ -pertechnetate before the early 1970s, then gradually increasing to 555 MBq and to 740 MBq since the mid-1970s (Harper et al. 1965; Maynard 1969; Blahd 1971; O'Mara and Mozley 1971; Ramsey and Quinn 1972; Sodee and Early 1972; Brownell et al. 1974; Fischer and McKusick 1975; Holman 1976; Mettler and Guiberteau 1983, 1998; Mettler et al. 1986; Dahnert 2007);
- 740 MBq of $^{99\text{m}}\text{Tc}$ -DTPA, $^{99\text{m}}\text{Tc}$ -GH, $^{99\text{m}}\text{Tc}$ -HMPAO, and $^{99\text{m}}\text{Tc}$ -ECD (USDHEW, 1976; Robertson 1982; Mettler et al. 1986, 2008a, 2008b; McAfee 1989; Larar and Nagel 1992; Kuni and duCret 1997; Mettler and Guiberteau 1998, 2012; Donohoe et al. 2003a, 2012; Kowalsky and Falen 2004; Dahnert 2007; Juni et al. 2009; NCRP 2009; Bonte et al. 2011;);
- 111 MBq of ^{201}Tl -chloride (Saha et al. 1994; Kahn et al. 1994; Kowalsky and Falen 2004);
- 555 MBq of ^{18}F -FDG (Kowalsky and Falen 2004; Mettler et al. 2008a; Waxman et al. 2009; Mettler and Guiberteau 2012).

Brain blood flow study

Iodine-131 (^{131}I)-radioiodinated human serum albumin (^{131}I -RIHSA), introduced in the 1950s, was the first agent used for brain blood flow studies. $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals were later used for this purpose. Since the early 1980s ^{111}In -DTPA has been used for cerebrospinal fluid flow studies. According to the key informants (Table 1), by the end of the 2000s, almost half (48%) of brain blood flow studies utilized $^{99\text{m}}\text{Tc}$ -DTPA, 26% $^{99\text{m}}\text{Tc}$ -ECD, 16% ^{111}In -DTPA and 10% $^{99\text{m}}\text{Tc}$ -HMPAO. Use of $^{99\text{m}}\text{Tc}$ -glucoptate was also reported but not included in the analysis because of a very low frequency of use.

An administered activity of ^{131}I -RIHSA of 14.8 MBq, range 13.9–18.5 MBq, was used for brain imaging that included cerebral blood flow analysis during the 1960s to early 1970s (Wagner 1968; Blahd 1971; Maynard 1971; O'Mara and Mozley 1971; Brownell et al. 1974). The administered activity of ^{111}In -DTPA was 18.5 MBq (Mettler and Guiberteau 1983, 1998; Wagner et al. 1986; Kuni and duCret 1997; Kowalsky and Falen 2004; Dahnert 2007; NCRP 2009). The administered activities of $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals are presented in Table 2.

Lung perfusion study

Iodine-131 (^{131}I)-labeled macroaggregated albumin (^{131}I -MAA) was the first agent used for pulmonary perfusion imaging and was introduced in the mid-1960s by Wagner et al. (1964)

and Taplin et al. (1964) for use with the rectilinear scanner. In the mid-1970s, it was replaced with ^{99m}Tc -MAA, which became a major radiopharmaceutical for pulmonary perfusion imaging using the gamma camera. In the 1970s–1980s, ^{99m}Tc -human albumin microspheres (^{99m}Tc -HAM) were also used. Since the late 1980s, key informants indicated that ^{99m}Tc -MAA was the only agent used for lung perfusion scans (Table 1). ^{99m}Tc -iron hydroxide macroaggregates (^{99m}Tc -FHMA) were used only to a small degree. Use of ^{133}Xe was also reported but not shown as it was reported to have been used only for research studies during a short time period (1968–1971).

The typical administered activity of ^{131}I -MAA for lung perfusion scanning was 11.1 MBq (Haynie et al. 1965; Wagner 1968; Early et al. 1969; USDHEW, 1970; Blahd 1971; Sodee and Early 1975; Atkins 1975; McAfee and Subramanian 1984). The typical administered activity of ^{99m}Tc -MAA was initially 111 MBq (Blahd 1971; Sodee and Early 1975; Neuman et al. 1980) but gradually increased to 185 MBq in the 1980s (Mettler et al. 1986, 2008a; McAfee 1989; Wagner et al. 1995; Kuni and duCret 1997; NCRP 2009; Mettler and Guiberteau 2012; Jafari and Daus 2013).

Lung ventilation study

Because the noble gases are poorly soluble and chemically inert, they are good agents for ventilation imaging. Xenon-133 (^{133}Xe) was first used for evaluation of lung function in the mid-1960s. Because of the low cost of production, ^{133}Xe was the most widely used agent for lung ventilation studies until the late 1970s. Development of techniques for radio-aerosol ventilation systems in the early 1980s (Hayes et al. 1979) led to introduction of ^{99m}Tc -DTPA aerosol for lung studies. According to the key informants in our study, about two-thirds of the studies were conducted using ^{99m}Tc -DTPA as the lung ventilation agent since 2000, the remainder were performed with ^{133}Xe (Table 1). Use of other noble gases for lung ventilation imaging was limited by cost shielding requirements (^{127}Xe) and short half-life of the ^{81}Rb parent of ^{81m}Kr . Both of these agents were excellent choices for evaluation of lung ventilation, but costly and availability limited their use. Use of ^{127}Xe and ^{81m}Kr to a small extent was reported, but not included in Table 1.

Typical administered activities of radiopharmaceuticals used for lung ventilation imaging were: 555 MBq for ^{133}Xe (Robertson 1982; Mettler et al. 1983; Wagner et al. 1986, 1995; Mettler and Guiberteau 1998; Kowalsky and Falen 2004; Dahnert 2007); and 1110–1480 MBq^{††††} for ^{99m}Tc -DTPA aerosol (Wellman 1986; McAfee 1989; Sandler et al. 1996; Mettler and Guiberteau 1998, 2012; Kowalsky and Falen 2004; Mettler et al. 2008a; NCRP 2009; Parker et al. 2012).

Bone scan

Strontium-85 (^{85}Sr)-chloride and ^{85}Sr -nitrate were the main radiopharmaceuticals for bone imaging in the 1960s. In the mid-1960s – mid-1970s, ^{18}F -sodium fluoride (Na^{18}F) was also used for bone imaging using rectilinear scanners. Technetium-99m bone-scan agents,

^{††††}This is the amount that is dispensed and placed into the nebulizer (aerosolizer). However, only about 18.5–37 MBq is administered into the patient's lungs.

i.e., ^{99m}Tc -polyphosphate and ^{99m}Tc -methylene diphosphonate (^{99m}Tc -MDP), were introduced in the early 1970s (Subramanian et al. 1972, 1975) and replaced Na^{18}F with the advent of the Anger camera. Since the early 1980s, ^{99m}Tc -MDP has been used to conduct all bone scans, except PET. Use of ^{87m}Sr -chloride, ^{99m}Tc -ethane hydroxydiphosphonate (^{99m}Tc -EHDP), ^{99m}Tc -hydroxymethylene diphosphonate (^{99m}Tc -HDP) and ^{99m}Tc -hydroxyethylidene diphosphonate (^{99m}Tc -HEDP) for bone imaging were also reported by the key informants. These radiopharmaceuticals are not shown in Table 1 as their usage was very low (a few percent or less) and for only a short period of time.

The typical administered activity of ^{85}Sr -chloride and ^{85}Sr -nitrate was 3.7 MBq (Wagner 1968; Ronai et al. 1968; Early et al. 1969; Maynard 1969, 1971; USDHEW, 1970; Sodee and Early 1972; Anderton et al. 1975; Atkins 1975; Leventhal et al. 1980; Kowalsky and Falen 2004; Drozdovitch et al. 2014). The typical administered activities of ^{99m}Tc -phosphate and ^{99m}Tc -MDP were 555 MBq before the mid-1970s (Sodee and Early 1972, 1975; Subramanian et al. 1975; USDHEW, 1976; Barrall and Smith 1976), increased to 740 MBq in the 1980s (Kelly et al. 1979; Robertson 1982; Mettler and Guiberteau 1983; Mettler et al. 1986; Wagner et al. 1986; Gertz et al. 1987), and to 925 with range 740–1110 MBq for ^{99m}Tc -MDP by the mid-1990s (Mettler and Guiberteau 1998, 2012; Donohoe et al. 2003b; Kowalsky and Falen 2004; NCRP 2009; Segall et al. 2010; Brenner et al. 2012; Frank et al. 2012).

Liver scan

Iodine-131-Rose Bengal and ^{198}Au -colloid were the first agents for liver imaging using rectilinear scanners in the 1950s–1960s. In 1964, ^{99m}Tc -sulfur colloid (^{99m}Tc -SC) was introduced clinically by Harper et al. (1964) and quickly became the preferred radiopharmaceutical for liver, spleen and bone marrow imaging. According to the responses from key informants, from 80 to 100% of liver scans were performed using ^{99m}Tc -SC beginning in the early 1970s. Since the early 1980s, ^{99m}Tc -iminodiacetic acid (^{99m}Tc -IDA), which has been used primarily in gallbladder studies, was reported to be used in a small fraction of examinations to characterize the liver as well. Our key informants also reported the use of ^{99m}Tc -macroaggregated albumin (^{99m}Tc -MAA) and ^{99m}Tc -albumin colloid for liver imaging. They were reported to be used infrequently in the 1980s–1990s in tumor related cases (not shown in Table 1).

The typical administered activity of ^{131}I -Rose Bengal was 0.37 MBq in the early 1960s to evaluate liver function by measuring the rate of its blood clearance (Beierwaltes 1957; Blahd et al. 1958) while higher activities 8.33 MBq were used for imaging studies (Wagner 1968; Silver 1968; Maynard 1969, 1971; USDHEW, 1970; Blahd 1971; Sodee and Early 1972; Atkins 1975; Leventhal et al. 1980). The typical administered activity of ^{198}Au -colloid was 7.4 MBq with range of 5.55–11.1 MBq (Wagner 1968; Silver 1968; Maynard 1969; Early et al. 1969; USDHEW, 1970; Blahd 1971; Atkins 1975; Sodee and Early 1972; Kowalsky and Falen 2004; Drozdovitch et al. 2014). The typical administered activity of ^{99m}Tc -SC was 74 MBq in the late 1960s (Harper et al. 1965; Wagner 1968; Silver 1968; Early et al. 1969; Maynard 1969; USDHEW, 1970; Blahd 1971; Atkins 1975), gradually increasing to 185 MBq in the late 1970s (Mettler and Guiberteau 1983, 1998; Mettler et al. 1986; Wagner et

al. 1986, 1995; Royal et al. 2003; Jafari and Daus 2013). The typical administered activity of ^{99m}Tc -IDA is 185 MBq (Mettler and Guiberteau 1983; Kowalsky and Falen 2004; Dahnert 2007).

Hepatobiliary scan

Iodine-131-Rose Bengal was the first agent used for hepatobiliary imaging in the 1960s to early 1970s. In the mid-1970s ^{99m}Tc -mebrofenin was introduced. According to key informants, since the early 1980s, the majority of hepatobiliary studies have been conducted with ^{99m}Tc -hepatoiminodiacetic acid (^{99m}Tc -HIDA). More recently, since the early 1990s, ^{99m}Tc -labeled diisopropyliminodiacetic acid (^{99m}Tc -DISIDA) has been used for hepatobiliary scintigraphy.

The typical administered activity of ^{131}I -Rose Bengal in the mid-1960s to mid-1980s was 8.33 MBq. The same typical administered activity of ^{99m}Tc -labeled radiopharmaceuticals of 185 MBq is used for hepatobiliary imaging according the (Mettler and Guiberteau 1983, 1998, 2012; Mettler et al. 1986, 2008b; Wagner et al. 1986, 1995; Kowalsky and Falen 2004).

Bone marrow scan

Bone marrow scanning is typically conducted with particulate agents, radio-colloids. The first available tracer, ^{198}Au -colloid, was used until the early 1970s. At that time it was replaced with ^{99m}Tc -SC which is still used today for the majority of bone marrow scans. Along with ^{99m}Tc -SC, ^{99m}Tc -albumin colloid was used in up to 15% of scans in the mid-1980s. Our key informants also reported use of ^{111}In -chloride, ^{111}In -SC and ^{59}Fe . These radiopharmaceuticals are not shown in Table 1 as they were rarely used and mostly for research studies.

The typical administered activity of ^{198}Au -colloid was 55.5 MBq with a range from 37 to 74 MBq (Warner 1968; Maynard 1971). A wide range of administered activities, from 74 to 370 MBq, was reported in the early literature for use of ^{99m}Tc -SC (Harper et al. 1965; Maynard 1971). By the mid-1980s, the typical administered activity of ^{99m}Tc -SC gradually increased to 555 MBq (Sodee and Early 1975; Robertson 1982; Wagner et al. 1995) with a range from 370 to 740 MBq (Mettler and Guiberteau 1998; Kowalsky and Falen 2004; NCRP 2009).

Pancreas scan

Selenium-75 (^{75}Se)-methionine was the only radiopharmaceutical for functional imaging of the pancreas until the early 1970s, when ^{99m}Tc -SC was used to image the pancreas/liver border. According to our key informants, in the 1990s and 2000s, a majority (75%) of pancreas scans were conducted using ^{18}F -FDG PET (Table 1) in order to detect pancreatic cancer. Typical administered activities of radiopharmaceuticals for pancreas imaging were 7.4 MBq of ^{75}Se -methionine (Haynie et al. 1964; Sodee and Early 1975); 185 MBq of ^{99m}Tc -SC (Azadi et al. 2012); and 555 MBq of ^{18}F -FDG.

Kidney scan

Mercury (^{197}Hg and ^{203}Hg)-labeled chlormerodrin, introduced by Reba et al. (1962a, 1962b), was the main radiopharmaceutical for renal imaging in the 1960s. The key informants reported a wide use of ^{131}I -iodohippurate for renal imaging in the mid-1960s to mid-1980s. By the early 1970s, ^{197}Hg - and ^{203}Hg -chlormerodrin were replaced primarily by $^{99\text{m}}\text{Tc}$ -DTPA and, to a lesser degree, by $^{99\text{m}}\text{Tc}$ -glucoheptonate ($^{99\text{m}}\text{Tc}$ -GH). Starting the early 1980s, $^{99\text{m}}\text{Tc}$ -dimercaptosuccinic acid ($^{99\text{m}}\text{Tc}$ -DMSA) was used for renal cortical imaging. From the beginning of the 1990s, $^{99\text{m}}\text{Tc}$ -mercaptoacetyltriglycine ($^{99\text{m}}\text{Tc}$ -MAG3) became the major radiopharmaceutical used for renal imaging; more than 90% of kidney scans were performed using this agent. Use of ^{123}I -iodohippurate and $^{99\text{m}}\text{Tc}$ -pertechnetate for renal imaging was also reported, but results are not shown in Table 1. Because of high costs, ^{123}I -iodohippurate was used only infrequently (around 1%) for a short time. $^{99\text{m}}\text{Tc}$ -pertechnetate was not a favored renal agent and was used infrequently for a short period of time.

The typical administered activity of ^{197}Hg - and ^{203}Hg -chlormerodrin in the 1960s was 3.7 MBq and 5.55 MBq of ^{197}Hg -chlormerodrin in the 1970s (Reba et al. 1962a; Bland 1965; Wagner 1968; Silver 1968; Maynard 1969; USDHEW, 1970, 1976; Atkins 1975; Sodee and Early 1975; Leventhal et al. 1980). The typical administered activity of ^{131}I -iodohippurate was 9.25 MBq (Mettler and Guiberteau 1983, 1998; Mettler et al. 1986). Typical administered activities of $^{99\text{m}}\text{Tc}$ -DTPA and $^{99\text{m}}\text{Tc}$ -GH varied between 370 MBq and 555 MBq; while the typical administered activities of $^{99\text{m}}\text{Tc}$ -DMSA and $^{99\text{m}}\text{Tc}$ -MAG3 were 185 MBq and 370 MBq, respectively (Enlander et al. 1974; USDHEW, 1976; Shanahan and Klingensmith 1981; Robertson 1982; Mettler and Guiberteau 1983, 1998, 2012; Schultz et al. 1985; Ziessman et al. 1987; Setaro et al. 1991; Barbaric 1994; Wagner et al. 1995; Mandell et al. 1999; Kowalsky and Falen 2004; Dahnert 2007; Mettler et al. 2008a; 2008b; NCRP 2009; Jafari and Daus. 2013).

Cardiac procedures

Radiopharmaceuticals used in cardiac procedures depend on the clinical indication(s) for the procedure. In the late-1960s to early 1990s, $^{99\text{m}}\text{Tc}$ -pyrophosphate was used as infarct-avid agent. Since the early 1970s $^{99\text{m}}\text{Tl}$ -thallous chloride has been used as a favored myocardial imaging agent, while $^{99\text{m}}\text{Tc}$ -RBC was used as blood-pool marker. In the late 1980s to early 1990s, $^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin were introduced as perfusion agents for SPECT and ^{18}F -FDG was used as a metabolic PET tracer. In the 2000s, ^{82}Rb -chloride and ^{13}N -ammonia were introduced as a perfusion and myocardial imaging agent for PET. According to the key informants (Table 1), by the end of the 2000s, most of cardiac studies (88%) involved myocardial imaging using $^{99\text{m}}\text{Tc}$ -sestamibi (59% of cardiac studies), $^{99\text{m}}\text{Tc}$ -tetrofosmin (20%), with diminishing numbers of $^{99\text{m}}\text{Tl}$ -thallous chloride (9%). The remainder of cardiac imaging was for blood-pool studies using $^{99\text{m}}\text{Tc}$ -RBC (10%) and myocardial PET imaging with ^{18}F -FDG (1%) and ^{82}Rb -chloride (1%).

The typical administered activity of $^{99\text{m}}\text{Tl}$ -thallous chloride was 111 MBq (Mettler et al. 1986; Saha et al. 1992, 1996; NCRP 1996; Mettler and Guiberteau 1998; Bushberg et al. 2002; Kowalsky and Falen 2004), which increased in the late 1990s to 148 MBq (Holly et

al. 2010; Frank et al. 2012; Jafari and Daus 2013). The administered activity of ^{99m}Tc -tetrofosmin was 1110 MBq, 1110 MBq of ^{99m}Tc -sestamibi for the one-day protocol and 1480 MBq for the two-day protocol (NCRP 1996; Mettler and Guiberteau 1998, 2012; Kowalsky and Falen 2004; Mettler et al. 2008a, 2008b, Strauss et al. 2008; Holly et al. 2010; Dorbala et al. 2013). For administered activity of other cardiac agents see Table 2 (Early et al. 1969; Sodee and Early 1975; Barrall and Smith 1976; USDHEW 1976; Pavel et al. 1977; Robertson 1982; Mettler et al. 1986; Wagner et al. 1986; 1995; Mettler and Guiberteau 1998, 2012; Scheiner et al. 2002; Kowalsky and Falen 2004; Di Carli and Lipton 2007; Mettler and Guiberteau 2012; Dorbala et al. 2013).

Gastrointestinal (GI) bleeding and ectopic gastric mucosa localization (Meckel's) scan

The most frequently used method in more than 90% of procedures between 1965 and 2010 has been ^{99m}Tc -labeled red blood cells (^{99m}Tc -RBC) scintigraphy for detecting GI bleeding through visualization of extravasated tracer from the blood pool. Technetium-99m-pertechnetate was used for the detection of Meckel's diverticulum. The typical administered activity of ^{99m}Tc -RBC was 740 MBq (McKusick et al. 1981; Orecchia et al. 1985; Wagner et al. 1986; Smith et al. 1987; McAfee 1989; Suzman et al. 1996; Mettler and Guiberteau 1983, 1998) increasing in the 2000s to 740–1110 MBq (Ford et al. 1999; Kowalsky and Falen 2004; Olds et al. 2005; Mettler et al. 2008a; NCRP 2009; Mellinger et al. 2011; Mettler and Guiberteau 2012). The typical administered activity of ^{99m}Tc -pertechnetate was 185 MBq (Robertson 1982; Wagner et al. 1986), increasing to 370 MBq in the beginning of 1990s (Mettler and Guiberteau 1998; Ford et al. 1999; Kowalsky and Falen 2004).

Tumor localization

Iodine-131-HSA was reported as the first tumor-imaging agent in the 1960s to early 1970s. In the early 1970s, ^{67}Ga -gallium citrate was introduced for tumor-localization and was widely deployed until the 2000s. Since the 1990s, ^{111}In -labeled radiopharmaceuticals, in particular ^{111}In -pentetreotide and ^{111}In -capromab pendetide (ProstaScint^{TM}), have been used as tumor imaging agents. Starting in the late 1990s, the majority of tumor localization scans were conducted by PET imaging with ^{18}F -FDG – almost 90% in 2005–2010. Use of ^{99m}Tc -WBC, ^{111}In -satumomab pendetide (OncoScint^{TM}), ^{131}I -labelled carcinoembryonic antigen (^{131}I -CEA), and ^{201}Tl was also reported. The latter are not shown in Table 1 as they were used at a low level for a short period of time, some of them mainly for research studies.

The typical administered activity of ^{131}I -HSA to adult patients was 111 MBq (Sodee and Early 1975; USDHEW, 1976). The typical activity of ^{67}Ga -citrate administered to adult patients was initially 111 MBq (Sodee and Early 1975; USDHEW, 1976; Mettler et al. 1986; Wagner et al. 1986, 1995; Bernier et al. 1989; McAfee 1989), gradually increasing to 148 MBq in the early 1990s and to 185 MBq by the early 2000s (Kuni and duCret 1997; Mettler and Guiberteau 1998; Bushberg et al. 2002; Kowalsky and Falen 2004; Palestro et al. 2004a; Jafari and Daus 2013). The typical administered activity to adult patients of ^{111}In -pentetreotide and ^{111}In -capromab pendetide was 222 MBq and 185 MBq, respectively (Schirmer et al. 1995; Giles et al. 1997; Kuni and duCret 1997; Mettler and Guiberteau 1998, 2012; Petronis et al. 1998; Sinha and Freeman 1998; Raj et al. 2002; Kowalsky and Falen 2004; Manyak 2008; Mettler et al. 2008a; Jafari and Daus 2013). The administered

activity of ^{18}F -FDG to adults varied from 370 MBq (Kuni and duCret 1997; Keyes et al. 1997) to 740 MBq (Mettler and Guiberteau 1998) with typical values of 555 MBq (Coleman 1998; Schelbert et al. 1999; Kowalsky and Falen 2004; Delbeke et al. 2006; Joyce and Swihart 2011; Mettler and Guiberteau 2012).

Blood volume study

Blood volume studies were reported in the 1960s using two primary tracers: ^{131}I -RIHSA (60–62%) (plasma volume) and ^{51}Cr -RBC (34–38%) (red-cell volume). In the mid-1960s, ^{125}I -HSA was introduced and used for the studies through the mid-1990s. Blood volume studies were done less frequently after the 1990s. The administered activity of ^{131}I -RIHSA was 0.185 MBq in the 1960s–1980s (Maynard 1969; Atkins 1975; Leventhal et al. 1980), later increasing to 0.28 MBq. The administered activity of ^{51}Cr -RBC was 0.37 MBq in the 1960s (Wagner 1968), gradually increasing to 1.48 by the early 1980s (Kowalsky and Falen 2004). The administered activity of ^{125}I -HSA was 0.28 MBq (Wagner 1968; Maynard 1969; Kowalsky and Falen 2004; Dworkin et al. 2007).

Iron metabolism study

Iron metabolism studies were reported during the 1960s to mid 1990s using ^{59}Fe -citrate as the primary tracer. The administered activity of ^{59}Fe -citrate was 0.37 MBq, range 0.185–0.555 MBq (Wagner 1968; Early et al. 1969; Maynard 1971; Atkins 1975; Leventhal et al. 1980).

Typical effective dose to patient

Fig.1 shows trends in the typical radiopharmaceutical-weighted effective dose to patients (calculated using eqn (2)) from different diagnostic nuclear medicine procedures over the time period from 1960 through 2010. As can be seen from the figure, in the early 1960s, the typical radiopharmaceutical-weighted effective dose to patients was the highest for tumor localization studies (71 mSv), bone marrow imaging (61 mSv), thyroid scans (44 mSv), and brain scans (24 mSv). The radiopharmaceutical-weighted effective doses to patients from these procedures decreased substantially (12 times for bone marrow imaging) as ^{198}Au -colloid (bone marrow imaging), ^{131}I -labeled agents (tumor localization, thyroid scan) and ^{203}Hg - and ^{197}Hg -chlormerodrin (brain scan) were replaced by the early 1970s with ^{67}Ga -citrate (tumor localization), $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals (bone marrow scan, brain scan, thyroid scan) and ^{123}I -sodium iodide (thyroid scan). The decreasing trend with time of the weighted effective dose is not characteristic of all nuclear medicine procedures. Use of $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals since the 1970s–1980s led to an increase of the radiopharmaceutical-weighted effective dose to patients who underwent lung function studies (by a factor of 13) and renal imaging (by a factor of 3). By the end of 2000s, the weighted effective dose to patients varied between 2 and 11 mSv for all diagnostic imaging procedures considered here. It should be noted that the effective dose conversion factors for some radiopharmaceuticals, including ^{123}I - and ^{131}I -sodium iodide, ^{131}I -Rose Bengal, ^{197}Hg - and ^{204}Hg -chlormerodrin, and ^{198}Au -colloid, given in ICRP Publication 53 (1987) were not updated in ICRP Publication 80 (1998) and, therefore, they do not include changes in values of the tissue weighting factors introduced by ICRP Publication 60 (1991).

As can be seen from Table 2 for some diagnostic radioisotope procedures such as bone scans and GI bleeding studies, the typical administered activity of ^{99m}Tc has increased during the past 15–20 years. Higher administered activities allow shorter image acquisition times, thus enhancing patient convenience and compliance, and, to some extent, image quality. Higher administered activities also increased the efficiency of the nuclear medicine facility and made it possible to conduct more studies. Of course, the drawback to this practice is the higher radiation dose to patients (Fig. 1).

DISCUSSION

Comparison with other studies

We compared the relative use of radiopharmaceuticals in diagnostic nuclear medicine procedures reported by key informants with a literature-based description of relative use (USDHEW 1968, 1976; Parker et al. 1984; Mettler et al. 1986). The only radiopharmaceuticals that can be compared with literature data are shown in Figs. 2–4, for example, ^{99m}Tc -glucoheptonate, ^{99m}Tc -HMPAO, ^{99m}Tc -ECD, ^{201}Tl -chloride and ^{18}F -FDG are not shown for brain scanning as literature data on the frequency of their use were not found.

As can be seen from Fig. 2, there is good agreement between the results of nationwide surveys in 1966 and 1974–1975 and our study on radiopharmaceuticals used for liver imaging. According to the DHEW survey (USDHEW 1968) in 1966, ^{198}Au -colloid was used for 63% of liver scans compared to 65% reported by key informants; ^{131}I -Rose-Bengal was used for 30% of liver scans compared to 35% reported by key informants; and ^{99m}Tc -SC was used in 7% of scans. Our key informants did not report the use of ^{99m}Tc -SC in 1966, but reported a frequency of use of 30% in 1967. The DHEW survey (USDHEW 1976) reported that 100% of liver scans were conducted using ^{99m}Tc -SC in 1974–1975; the same was reported by key informants. Mettler et al. (1986) reported that in 1982 in the U.S. ^{99m}Tc -SC was used for all liver scans while the key informants reported 97%.

Good agreement was also observed between the results of nationwide surveys in 1966 and 1974–1975 and our study on radiopharmaceuticals used for brain imaging (Fig. 3). DHEW (USDHEW 1968) reported that 15% of brain scans were conducted using ^{197}Hg , 31% used ^{203}Hg , and 51% used ^{99m}Tc -pertechnetate. According to our study, a very similar relative usage was observed in 1967: 14% of brain scans were conducted using ^{197}Hg , 21% using ^{203}Hg , and 65% using ^{99m}Tc -pertechnetate. The DHEW survey (USDHEW 1976) also reported that 92% of brain scans were conducted using ^{99m}Tc -pertechnetate and 8% using ^{99m}Tc -DTPA in 1974–1975. The key informants' responses indicated a similar pattern in 1974: 83% for ^{99m}Tc -pertechnetate, 17% for ^{99m}Tc -DTPA and 3% for ^{197}Hg . Mettler et al. (1986) reported that in 1982 in the U.S., ^{99m}Tc -pertechnetate and ^{99m}Tc -DTPA were used equally for brain imaging. According to our study, ^{99m}Tc -pertechnetate was used in 34% of scans and ^{99m}Tc -DTPA for 56%.

Agreement between the literature data and the key-informant data is not as good for thyroid scans (Fig. 4). The DHEW survey (USDHEW 1976) reported that in 1974–1975 45% of thyroid scans were conducted using ^{131}I -sodium iodide, 25% using ^{123}I -sodium iodide, and

30% – with ^{99m}Tc -pertechnetate. The key informants indicated a different frequency of use in 1974: 24% for ^{131}I -sodium iodide, 7% for ^{123}I -sodium iodide, and 69% for ^{99m}Tc -pertechnetate. For the year 1981 agreement is better, Parker et al. (1984) reported that 9% of thyroid scans were conducted using ^{131}I -sodium iodide (vs 19% reported in this study), 35% with ^{123}I -sodium iodide (vs 23% in this study), and 54% with ^{99m}Tc -pertechnetate (vs 59% in this study).

Although there were some differences between literature data and responses from key informants, on the whole we believe that the results of our study adequately reflect usage patterns of radiopharmaceuticals for diagnostic nuclear medicine procedures in the U.S.

Strengths and limitations

To our knowledge, our study is the first to summarize historical information on the relative use of radiopharmaceuticals and administered activities in diagnostic nuclear medicine procedures in the U.S. over the relatively long time period between 1960 and 2010. Published data on this topic are limited by the data from the U.S. nationwide surveys done in the mid-1960s through the mid-1970s. To collect historical information we successfully conducted interviews among nuclear medicine experts from major nuclear medicine facilities across the U.S.

There are, however, some obvious limitations of our study. As is clear, we have relied on memory recall of experts and this, in itself, imposes some limitations on precision. Second, the number of experts was limited and their combined experience may not include all circumstances where radiopharmaceuticals were used. In particular, the data presented may not completely reflect the practices and usage in the large number of smaller hospitals and larger volume practices across the U.S. Some radiopharmaceuticals might not have even been reported by key informants or their reported use may not be representative of all facilities or facility types.

CONCLUDING REMARKS

We collected information for 15 diagnostic imaging radioisotope procedures: thyroid scan, thyroid uptake, brain scan, brain blood flow, lung perfusion and ventilation, bone, liver, hepatobiliary, bone marrow, pancreas and kidney scans, cardiac imaging procedures, tumor localization studies, localization of GI bleeding, and non-imaging studies of blood volume and iron metabolism. Data on relative use of radiopharmaceuticals were collected by means of key informant interviews and comprehensive literature review of administered activities.

We evaluated trends in the typical effective dose to patients from different diagnostic nuclear medicine procedures over the time period from 1960 through 2010. In general, for the majority of procedures the typical effective dose to patients decreased substantially (up to 12 times) from the 1960s through the 2000s. However, since the 1970s–1980s typical effective doses to patients who underwent lung function studies and renal imaging increased. By the end of 2000s, the typical effective dose to patients varied between 2 and 11 mSv for all diagnostic imaging procedures considered in this study.

Data on the relative use of radiopharmaceuticals and their typical administered activities that were collected in this study will be used for retrospective reconstruction of occupational and personal medical radiation doses from diagnostic radiopharmaceuticals to members of the U.S. radiologic technologists cohort and in reconstructing radiation doses from occupational or patient radiation exposures to other U.S. workers or patient populations.

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Fig. 1.

Trend in radiopharmaceutical-weighted effective dose to patients from diagnostic nuclear medicine procedures over time period from 1960 through 2010: a) thyroid scan, thyroid uptake study, brain scan, and brain blood flow study; b) liver, hepatobiliary, and pancreas scan, GI bleeding study and Meckel's scan; c) cardiac imaging procedures, lung perfusion study, lung ventilation study, and kidney scan; d) bone scan, bone marrow scan, tumor localization study, blood volume study, and iron metabolism study.

Fig. 2. Comparison of relative use of radiopharmaceuticals for liver imaging in the U.S. in 1960–2010 reported by key informants (lines) and in literature (circles).

Fig. 3. Comparison of relative use of radiopharmaceuticals for brain imaging in the U.S. in 1960–2010 reported by key informants (lines) and in literature (circles).

Fig. 4. Comparison of relative use of radiopharmaceuticals for thyroid imaging in the U.S. in 1960–2010 reported by key informants (lines) and in literature (circles).

Table 1

Relative use (%) of radiopharmaceuticals for diagnostic nuclear medicine procedures in the United States in 1960–2010.

Radiopharmaceutical	Percentage of use of radiopharmaceuticals for diagnostic nuclear medicine procedures in										
	1960–1964	1965–1969	1970–1974	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2004	2005–2010	
Thyroid scan											
¹³¹ I-sodium iodide	100	88	53	22	19	14	10	9	8	8	
¹²³ I-sodium iodide	– ^a	–	3	16	22	26	36	49	51	56	
^{99m} Tc-pertechnetate	–	12	44	62	59	60	54	42	41	36	
Thyroid uptake											
¹³¹ I-sodium iodide	100	92	93	76	67	67	60	55	48	45	
¹²³ I-sodium iodide	–	–	–	13	22	22	38	45	52	55	
^{99m} Tc-pertechnetate	–	8	7	11	11	11	2	–	–	–	
Brain scan											
²⁰³ Hg-chlormerodrin	81	36	–	–	–	–	–	–	–	–	
¹⁹⁷ Hg-chlormerodrin	19	17	3	–	–	–	–	–	–	–	
^{99m} Tc-pertechnetate	–	47	89	53	33	24	4	–	–	–	
^{99m} Tc-DTPA	–	–	8	43	56	48	35	25	20	18	
^{99m} Tc-glucophageptone	–	–	–	4	11	8	–	–	–	–	
^{99m} Tc-HMPAO	–	–	–	–	–	13	39	35	20	19	
^{99m} Tc-ECD	–	–	–	–	–	–	12	25	37	35	
²⁰¹ Tl-chloride	–	–	–	–	–	10	1	–	–	–	
¹⁸ F-FDG	–	–	–	–	–	4	9	15	23	28	
Brain blood flow											
¹³¹ I-RIHSA	100	40	15	3	–	4	9	15	23	28	
^{99m} Tc-pertechnetate	–	53	63	42	23	19	3	–	–	–	
^{99m} Tc-DTPA	–	7	22	55	67	65	50	47	48	48	
^{99m} Tc-HMPAO	–	–	–	–	–	2	25	19	11	10	
^{99m} Tc-ECD	–	–	–	–	–	–	2	17	25	26	
¹¹¹ In-DTPA	–	–	–	–	10	14	20	17	16	16	

Radiopharmaceutical	Percentage of use of radiopharmaceuticals for diagnostic nuclear medicine procedures in									
	1960–1964	1965–1969	1970–1974	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2004	2005–2010
Lung perfusion										
¹³¹ I-MAA	100	93	38	4	–	–	–	–	–	–
^{99m} Tc-MAA	–	7	58	77	81	94	100	100	100	100
^{99m} Tc-HAM	–	–	4	19	19	6	–	–	–	–
Lung ventilation										
¹³³ Xe	–	100	100	100	89	74	67	64	37	32
^{99m} Tc-DTPA aerosol	–	–	–	–	11	26	33	36	63	68
Bone scan										
⁸⁵ Sr-chloride	100	45	17	–	–	–	–	–	–	–
⁸⁵ Sr-nitrate	–	15	10	–	–	–	–	–	–	–
Na ¹⁸ F	–	25	21	–	–	–	–	–	–	–
^{99m} Tc-polyphosphate	–	15	48	50	4	–	–	–	–	–
^{99m} Tc-MDP	–	–	4	50	96	100	100	100	100	100
Liver scan										
¹⁹⁸ Au-colloid	97	47	9	–	–	–	–	–	–	–
¹³¹ I-Rose Bengal	3	18	–	–	–	–	–	–	–	–
^{99m} Tc-SC	–	35	91	100	93	82	84	83	79	78
^{99m} Tc-IDA	–	–	–	–	7	18	16	17	21	22
Hepatobiliary scan										
¹³¹ I-Rose Bengal	–	100	100	73	16	–	–	–	–	–
^{99m} Tc-mebrofenin	–	–	–	20	8	4	1	–	–	–
^{99m} Tc-HIDA	–	–	–	7	76	95	90	84	73	70
^{99m} Tc-DISIDA	–	–	–	–	–	1	9	16	27	30
Bone marrow scan										
¹⁹⁸ Au-colloid	100	65	15	–	–	–	–	–	–	–
^{99m} Tc-SC	–	35	85	100	98	85	93	100	100	100

Radiopharmaceutical	Percentage of use of radiopharmaceuticals for diagnostic nuclear medicine procedures in									
	1960–1964	1965–1969	1970–1974	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2004	2005–2010
^{99m} Tc-albumin colloid	–	–	–	–	2	15	7	–	–	–
Pancreas scan										
⁷⁵ Se-methionine	100	100	80	80	42	–	–	–	–	–
^{99m} Tc-SC	–	–	20	20	45	30	25	25	25	25
¹⁸ F-FDG	–	–	–	–	13	70	75	75	75	75
Kidney scan										
¹³¹ I-hippurate	–	41	68	34	27	18	2	–	–	–
²⁰³ Hg-chlormerodrin	56	17	–	–	–	–	–	–	–	–
¹⁹⁷ Hg-chlormerodrin	44	42	15	–	–	–	–	–	–	–
^{99m} Tc-DTPA	–	–	16	55	60	61	34	27	5	3
^{99m} Tc-glucoheptonate	–	–	1	10	7	13	1	5	2	–
^{99m} Tc-DMSA	–	–	–	1	6	8	6	9	3	4
^{99m} Tc-MAG3	–	–	–	–	–	–	57	59	90	93
Cardiac procedures										
²⁰¹ Tl-chloride	–	–	10	70	67	67	49	30	19	9
^{99m} Tc-pyrophosphate	–	100	33	12	13	13	7	–	–	–
^{99m} Tc-pertechnetate	–	–	35	–	–	–	–	–	–	–
^{99m} Tc-RBC	–	–	22	11	20	18	14	13	11	10
^{99m} Tc-HSA	–	–	–	7	–	–	–	–	–	–
^{99m} Tc-sestamibi (1 day)	–	–	–	–	–	2	26	47	53	55
^{99m} Tc-sestamibi (2 day)	–	–	–	–	–	–	2	2	3	4
^{99m} Tc-tetrofosmin	–	–	–	–	–	–	1	7	13	20
¹⁸ F-FDG	–	–	–	–	–	–	1	1	1	1
⁸² Rb-chloride	–	–	–	–	–	–	–	–	–	1
GI bleeding and Meckel's scan										
^{99m} Tc-RBC	–	100	96	83	92	89	96	97	97	97
^{99m} Tc-pertechnetate	–	–	4	17	8	11	4	3	3	3

Radiopharmaceutical	Percentage of use of radiopharmaceuticals for diagnostic nuclear medicine procedures in									
	1960–1964	1965–1969	1970–1974	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2004	2005–2010
Tumor localization										
¹³¹ I-HSA	100	100	71	7	–	–	–	–	–	–
⁶⁷ Ga-citrate	–	–	29	93	100	97	84	50	24	1
¹¹¹ In-pentetreotide	–	–	–	–	–	–	1	5	11	11
¹¹¹ In-capromab pendetide	–	–	–	–	–	–	–	3	3	1
¹⁸ F-FDG	–	–	–	–	–	3	15	42	62	87
Non-imaging studies										
Blood volume										
¹³¹ I-RIHSA	62	60	49	31	42	49	46	60	66	83
⁵¹ Cr-RBC	38	34	41	57	48	41	46	40	34	17
¹²⁵ I-HSA	–	6	10	12	10	10	8	–	–	–
Iron metabolism										
⁵⁹ Fe-citrate	100	100	100	100	100	100	100	–	–	–

^aUse of radiopharmaceutical was not reported for this time period

Table 2

Typical activity (and range) of radiopharmaceuticals administered to adults for diagnostic nuclear medicine procedures in the United States in 1960–2010.

Procedure/study	Radiopharmaceutical	Administered activity (MBq)		Years ^a
		Typical	Range	
Thyroid scan	¹³¹ I-sodium iodide	1.85	0.925–2.78	before 1975
		2.78	1.85–3.7	1975–1979
		3.7	2.8–4.4	after 1980
	¹²³ I-sodium iodide	3.7	1.85–3.7	before 1980
		7.4	3.7–11.1	1980–1984
		11.1	7.4–14.8	1985–1994
		14.8	11.1–25	after 1995
	^{99m} Tc-pertechnetate	74	37–185	before 1980
		185	74–222	1980–1994
Thyroid uptake	¹³¹ I-sodium iodide	222	185–370	after 1995
		0.185	0.148–0.222	before 2000
	¹²³ I-sodium iodide	0.26	0.148–0.37	after 2000
		7.4	3.7–11.1	–
		18.5	–	–
Brain scan	²⁰³ Hg-chlormerodrin	26	–	–
		26	–	–
	^{99m} Tc-pertechnetate	463	370–555	before 1970
		555	370–740	1970–1975
		740	–	after 1975
	^{99m} Tc-DTPA	740	370–1110	–
	^{99m} Tc-glucoheptonate	740	–	–
	^{99m} Tc-HMPAO	740	370–1100	–
	^{99m} Tc-ECD	740	370–1100	–
	²⁰¹ Tl-chloride	111	74–148	–
Brain blood flow	¹⁸ F-FDG	555	222–740	–
		14.8	13.9–18.5	–
		463	370–555	before 1970
		555	370–740	1970–1975
	^{99m} Tc-pertechnetate	740	–	after 1975
		740	370–1110	–
		740	370–1100	–
	^{99m} Tc-DTPA	740	370–1100	–
	¹¹¹ In-DTPA	18.5	–	–
Lung perfusion	¹³¹ I-MAA	11.1	7.4–13	–

Procedure/study	Radiopharmaceutical	Administered activity (MBq)		Years ^a
		Typical	Range	
	^{99m} Tc-MAA	111	74–148	before 1975
		148	111–185	1975–1979
		185	111–222	after 1980
	^{99m} Tc-HAM	111	74–148	before 1985
		185	–	after 1985
Lung ventilation	¹³³ Xe	555	370–740	–
	^{99m} Tc-DTPA aerosol	1300 ^b	1110–1480 ^b	–
Bone scan	⁸⁵ Sr-chloride	3.7	–	–
		3.7	–	–
	Na ¹⁸ F	55.5	37–74	before 1970
		74	37–111	after 1970
	^{99m} Tc-polyphosphate	555	370–740	before 1975
		740	–	after 1975
	^{99m} Tc-MDP	555	370–740	before 1975
		740	–	1975–1994
Liver scan	^{99m} Tc-MDP	925	740–1110	after 1995
	¹⁹⁸ Au-colloid	7.4	5.55–11.1	–
	¹³¹ I-Rose Bengal	0.37	0.185–0.65	before 1965
		8.3	5.55–11.1	after 1965
	^{99m} Tc-SC	74	55.5–185	before 1969
		111	74–185	1970–1974
Hepatobiliary scan	^{99m} Tc-IDA	185	148–222	after 1975
		185	–	–
	¹³¹ I-Rose Bengal	8.3	5.55–11.1	–
	^{99m} Tc-mebrofenin	185	–	–
	^{99m} Tc-HIDA	185	–	–
Bone marrow scan	^{99m} Tc-DISIDA	185	–	–
	¹⁹⁸ Au-colloid	55.5	37–74	–
		222	74–370	before 1970
	^{99m} Tc-SC	444	370–555	1970–1974
		555	370–740	after 1975
Pancreas scan	^{99m} Tc-albumin colloid	463	370–555	–
	⁷⁵ Se-methionine	7.4	7.4–9.25	–
	^{99m} Tc-SC	185	–	–
Kidney scan	¹⁸ F-FDG	555	370–740	–
	¹³¹ I-hippurate	9.25	3.7–14.8	–

Procedure/study	Radiopharmaceutical	Administered activity (MBq)		Years ^a
		Typical	Range	
	²⁰³ Hg-chlormerodrin	3.7	–	–
	¹⁹⁷ Hg-chlormerodrin	3.7	–	1960–1969
		5.55	4.6–7.4	after 1970
	^{99m} Tc-DTPA	370	–	–
	^{99m} Tc-glucoheptonate	555	370–740	before 1990
		463	–	1990–1994
		370	–	after 1995
	^{99m} Tc-DMSA	185	–	–
	^{99m} Tc-MAG3	370	185–555	–
Cardiac procedures	²⁰¹ Tl-chloride	111	74–148	before 2000
		148	111–185	after 2000
	^{99m} Tc-pyrophosphate	555	–	–
	^{99m} Tc-pertechnetate	370	–	–
	^{99m} Tc-RBC	740	–	before 1995
		833	740–925	1995–1999
		925	740–1110	after 2000
	^{99m} Tc-HSA	740	–	–
	^{99m} Tc-sestamibi (1 day)	1110	–	–
	^{99m} Tc-sestamibi (2 day)	1480	1110–1850	–
	^{99m} Tc-tetrofosmin	1110	740–1480	–
	¹⁸ F-FDG	370	–	–
	⁸² Rb-chloride	1850	–	–
GI bleeding and Meckel's scan	^{99m} Tc-RBC	740	–	before 1995
		833	740–925	1995–1999
		925	740–1100	after 2000
	^{99m} Tc-pertechnetate	185	–	before 1990
		370	–	after 1990
Tumor localization	¹³¹ I-HSA	111	74–148	–
	⁶⁷ Ga-citrate	111	74–148	before 1990
		148	111–185	1990–1999
		185	148–222	after 2000
	¹¹¹ In-pentetreotide	222	–	–
	¹¹¹ In-capromab pendetide	185	–	–
	¹⁸ F-FDG	555	370–740	–
Non-imaging studies				
Blood volume	¹³¹ I-RIHSA	0.185	–	before 1980
		0.28	0.185–0.37	after 1980

Procedure/study	Radiopharmaceutical	Administered activity (MBq)		Years ^a
		Typical	Range	
	⁵¹ Cr-RBC	0.37	–	before 1970
		0.74	0.185–0.925	1970–1974
		1.11	–	1975–1979
		1.48	1.11–1.85	after 1980
	¹²⁵ I-HSA	0.28	0.185–0.37	–
Iron metabolism	⁵⁹ Fe-citrate	0.37	0.185–0.555	–

^a Years of use is given if administered activity has been changed during entire period of use of radiopharmaceutical that is given in Table 1.

^b This is the amount that is dispensed and placed into the nebulizer (aerosolizer). However, only about 18.5–37 MBq is administered into the patient's lungs.