Determining and updating PET/CT and SPECT/CT diagnostic reference levels: A systematic review

Short title: DRL for PET/CT and SPECT

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ABSTRACT

The aim of this systematic review is to investigate the national diagnostic reference level (NDRL) methods for positron emission tomography/computed tomography (PET/CT) and single photon emission tomography/computed tomography (SPECT/CT) procedures. A search strategy was based on the preferred, reporting items for systematic review and meta-analysis (PRISMA). Relevant articles retrieved from Medline, Scopus, Web of Science, Embase, Cinahl, and Google Scholar published up to October 2017. The search yielded 1057 articles. Fourteen articles were included in the review after a screening process. Relevant information from the selected articles were summarised and analysed. Discrepancies were found between the methodologies utilised to establish and report both PET/CT and SPECT/CT NDRLs, e.g. patient sampling and administered activity. Further research should focus on reporting more NDRLs for hybrid PET/CT and SPECT/CT examinations, and establish a robust NDRL standard for the CT portion associated with PET/CT and SPECT/CT examinations. This review provides updated NDRL reommndations to deliver more comparable international radation doses for administered activity and CT dose across PET/CT and SPECT/CT clinics.

Introduction

Hybrid modalities integrating positron emission tomography (PET) or single photon emission computed tomography (SPECT) with X-ray computed tomography (CT) enable intrinsic co-registration of functional and anatomical data in a single procedure (PET/CT or SPECT/CT)[1-3]. The introduction of hybrid medical imaging technology has revolutionised the practice of diagnostic nuclear medicine (NM). PET/CT and SPECT/CT have wide acceptance for many clinical investigations such as oncology, neurology, cardiology and psychiatry[4]. The CT aspect is often a low-dose CT scan to provide attenuation correction (CT-AC), anatomical localisation (CT-AL), or diagnostic CT procedures with or without contrast media[4-6]. The fused information from PET or SPECT with CT data can result in superior diagnostic accuracy for localisation, detection, staging and monitoring of many disease mechanisms compared to PET, SPECT or CT alone[7].

A concern with PET/CT and SPECT/CT imaging is the combined radiation doses from both radiopharmaceutical and X-ray CT components[8, 9]. The lifetime attributable risk of cancer incidence for fluoride-18 fluorodeoxyglucose (^{18}F-FDG) whole-body PET/CT scans for 20-year-old males and females in the United States of America (USA) has been reported to be up to 0.323% and 0.514% respectively[10]. Therefore, it is imperative to implement a radiation dose optimisation process by utilising the "as low as reasonably achievable" (ALARA) principle to protect patients from unwarranted high radiation burdens and to minimise the probability of inducing cancer. However, McCullough[11] reported there is no reliable evidence to demonstrate risks of medical imaging at low doses (<50 mSv), which includes the majority of NM examinations.

The International Commission on Radiological Protection (ICRP) publication 60 introduced diagnostic reference levels (DRLs) in 1990, and its implementation was recommended in the

ICRP 73 1996 publication[12]. In 1997, the European medical exposure directive defined DRLs as "dose levels in medical radio-diagnostic practice or, in the case of radiopharmaceuticals, levels of activity, for typical examinations for groups of standard-sized patients or standard phantoms, for broadly defined types of equipment. These levels are not expected to be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied"[13]. DRLs are advisory in nature and not dose limits. Their role is to draw attention to the issue of radiation protection and safety and thereby reduce the radiation doses to patients. However, one needs to acknowledge that the radiation dose can acceptably exceed the national DRL (NDRL) value in some circumstances due to the patient's characteristics or disease factors that require deviation from standard procedures. The DRLs should be refined over time based on improvements in standard procedures and equipment[14].

Implementing DRLs enables identification of variations between high and low dose imaging protocols and equipment[14]. This is possible through comparing mean or median local DRL against national or regional DRL for equivalent representative groups of patients undergoing a specific typical procedure. Where the value of the mean or median local DRL dose exceeds the accepted NDRL value without convincing medical justification, this triggers the need for equipment performance or imaging protocol review for dose optimisation[3].

The DRLs in PET/CT and SPECT/CT are determined by collecting radiation doses from the administered activity (A) measured in megabecquerel (MBq) as well the CT dose in volume CT dose index ($CTDI_{vol}$) measured in milligray (mGy) and the dose length product (DLP) measured in milligray times centimetre (mGy.cm)[15]. Two different measures are used to report DRL values for the A, namely the 75^{th} percentile and guidance level. The 75^{th} percentile method is based on the evaluation of the distribution of median A from participant centres in a national or regional DRL survey. It is used to report the DRLs for both A and CT dose[16, 17]. Evidence gathered by expert professional organisations is used to establish guidance levels on

a national level for a standard-sized patient[16]. Guidance levels are used to report recommended A but not CT dose.

The achievable dose provides an additional reference level for optimising diagnostic imaging without compromising image quality[18, 19]. The achievable dose corresponds to the 50th percentile of the NDRL and is used to identify the dose commonly used in clinical practice. Centres with a local DRL just below the 75th should focus on optimising the acquisition protocol and equipment with an aim to approach the achievable dose[18, 19].

The administered activity duration product (ADP) has been proposed as an additional unit for NM DRLs[19]. The ADP is a product of the A and acquisition time (MBq.min). The ADP is considered a better measure for dose optimisation, compared to A (MBq) alone, as A and imaging time both impact on image quality[19]. The photon density in a NM image is directly proportional to the ADP. Therefore, administering the same recommended activity to patients in different centres may not yield the same image quality as some facilities will use different total acquisition times due to variations in imaging equipment sensitivity[19]. Thus, reporting both MBq and MBq.min units for DRL and ADP reference levels provides additional information about photon flux which impacts on image quality.

The establishment of DRLs for PET/CT and SPECT/CT imaging is an essential step in recognising variations between radiation doses delivered to the patient using a diverse range of equipment and changing protocols[14]. The existing PET/CT and SPECT/CT, PET, SPECT, and CT component methods are prone to some limitations due to diverse methods implemented for population selection, different reporting methods, the impact of new imaging technology, and reporting effective dose (E) from both the A and CT[15, 18-30]. The purpose of this systematic review is to determine the variations in reported NDRL methodology and values for adult PET/CT and SPECT/CT procedures.

Material and Methods

Search strategy

A research protocol for the review was selected and designed before undertaking our database-driven research. This included writing a clear protocol to address the research question, followed by creating keywords that would help us search data across a diversity of databases. No industry funding was obtained for this systematic review, which was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The preferred reporting items for PRISMA methodology was used to search for articles published up to October 2017[31]. A systematic literature search of Medline, Scopus, Web of Science, Embase, and Cinahl was performed to identify the essential articles that established hybrid DRL NM procedures for adult patients. To access more information, reference lists of published articles were examined to identify additional articles not identified in the database searches. Literature Boolean search was performed using the following method and terms: Intervention ("Diagnostic reference levels" or "Diagnostic reference activities" or "DRLs") AND cohort ("Positron emission tomography/computed tomography" or "Single photon emission computed tomography/ computed tomography" or "Positron emission tomography" or "Single photon emission tomography" or "Computed tomography" or "Nuclear medicine" or "PET/CT" or "SPECT/CT" or "PET" or "SPECT" or "CT" or "NM") OR other ("PET radiopharmaceutical" or "Radiopharmaceutical"). The search was limited to include all the articles that had been published in the English language.

Criteria for selection

All cohort studies were selected based on the inclusion and exclusion criteria developed, through the use of a population, intervention, comparison, and outcomes (PICO) methodology Table 1. Articles were considered for the review if they described NDRLs of adult patients

undergoing PET/CT and SPECT/CT procedures. Articles that did not fulfil these criteria were excluded as were case studies, posters, narrative literature reviews, and case reports. All articles included contained the theme of measurement methods for adult NDRLs with PET/CT and SPECT/CT examinations (Table 1). The funding sources for each selected study were assessed as part of the review.

Quality assessment

The quality assessment was performed by two reviewers (EA and PK). These reviewers developed an Excel data extraction sheet based on the quality assessment tool for quantitative studies, as developed by the Effective Public Health Practice Project (EPHPP)[32]. An Excel datasheet was used to assess a study's design, to determine whether it satisfied the data selection criteria. The developed Excel data extraction sheet was used independently by each reviewer to evaluate the risk of bias and to pinpoint any poor-quality or irrelevant publications.

Data extraction Two reviewers (EK and PK) independently evaluated articles for quality and for risk of bias, to ensure that they satisfied the inclusion criteria. Data extraction was undertaken, based on the following characteristics in each study: hybrid type, equipment, population, reporting for PET or SPECT, reporting method for $CTDI_{vol}$, reporting method for DLP, and E. The reviewers were aware of large variations among the included studies, in terms of their NDRL methods. Each article was reviewed based on the PICO approach; the extracted data were compared between two reviewers, and wherever there was disagreement, all variations in opinion were subsequently resolved through discussion. An identified article was independently scored as high (1), moderate (2), or low (3) by each reviewer. As recommended by the reviewer, only articles rated as high (1) or moderate (2) by reviewer were included in this review.

Results

The combined search strategy identified 1057 articles: 169 from MEDLINE (OVID), 278 from Web of Science, 326 from Embase, 265 from Scopus, 17 from CINAHL, and two from Google Scholar. Of these, 413 articles were duplicates and deleted, leaving a total number of 644 articles. The 644 articles were assessed for the eligibility, of these, 611were excluded on initial screening of titles and abstracts. Thirty-three articles met the criteria for a full-text review and were evaluated utilising the inclusion and exclusion criteria of PICO methodology. Nineteen articles were excluded due to insufficient data for evaluation of methods, reporting local DRL, conference, oral presentation, and case report. As a result, fourteen articles met the selection criteria as shown in Figure 1. All studies were rated highl and moderate and were used to assess variations in the determined NDRL method and values among adult patients undergoing PET/CT and SPECT/CT procedures. Two NDRL articles reported funding support for their surveys, but the other did not. These two articles were funded by the Japanese Society of Nuclear Medicine[21]", while the other article was funded by The English Department of Health[29].

A summary of the fourteen articles is illustrated in Tables 2 and 3. Two countries have established the NDRL for PET/CT and one for SPECT/CT examinations. Most NDRL publications were related to either PET or SPECT component and two for CT component only. Seven NDRL articles were from Europe[18, 20, 24, 25, 27, 29, 30], two from the United States of America[19, 23], two from Brazil[22, 26], and single articles from Australia and New Zealand[28], Korea[15] and Japan[21]. The articles were published between 2002 to 2017, with the majority published between 2013 to 2017.

The methodology for determining patient selection varied. Two common methods for selecting the patient sample reported in the literature were weight and non-weight restriction. The weight

restriction method involves selecting at least 20 patients whose weights are 70 ± 10 or 75 ± 25 kg[25, 27, 28]. Three articles reported NDRL values based on weight criteria for PET/CT and PET examinations. The non-weight restriction method involved selecting a range of 1 to 76 patients for each PET/CT, SPECT/CT, PET, SPECT, and CT component associated with PET and SPECT examinations. Six articles adopted non-weight restriction approach[15, 18-20, 23, 24] and five articles did not provide any details of the patient sampling[21, 22, 26, 29, 30].

The most frequent imaging procedures were ^{18}F-FDG PET and ^{99m}Tc- methyl diphosphonate (MDP) SPECT bone scans with a range of reported NDRLs for an A of 200 to 592 MBq and 600 to 999 MBq, respectively (Table 2 and 3). Some of the identified articles reported clinical indications for PET/CT and SPECT/CT examinations. A total of six articles identified tumours for PET/CT examinations. Of the six articles, two reported the ^{18}F-FDG value used for both tumour and infection/inflammation clinical indication. Only one article reported the common clinical indications for six SPECT/CT examinations and the other article reported the clinical indication for SPECT/CT thyroid metastasis[18, 24].

There were five manufacturers of PET/CT and SPECT/CT equipment using six different NM detectors installed between 2000 and 2015 reported (Table 4). Two articles reported both the manufacturer and model of PET/CT equipment[15, 24]. One article reported the number CT rows only, e.g. 2 and 16 slice[24]. One article reported CT-AC and AL acquisition parameters associated with a ^{18}F-FDG whole-body scan, while another article reported scan length for six PET/CT and SPECT/CT examinations[18, 23].

A NDRL for the CT component used for AC and AL and AC only was reported in three and one article, respectively[15, 18, 23, 24, 27]. No authors reported the NDRL for the CT component when used for diagnostic CT. All ^{18}F-FDG PET/CT whole body $CTDI_{vol}$ values were lower than the NDRL of 15 mGy, as reported by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) for diagnostic chest CT[33].

Different approaches were used to report NDRL in the review. Twelves articles reported NDRL values based on the 75th percentile[15, 18-23, 26-30], and two articles based on guidance level[24, 25]. In addition to the NDRL, two articles also reported achievable dose and one article reported ADP[18, 19]. There were seven articles reported their recommended A strategy, e.g. MBq/kg[15, 19-21, 25-27]. Two articles reported NDRLs for ^{18}F-FDG based on TOF technology[20, 27]. Seven articles reported the E, three articles for both A and CT[15, 24, 27], three articles for A only[22, 29, 30] and one article for the CT only as seen in Tables 2 and 3.

Discussion

The patient selection methods used to determine the NDRL for PET/CT, SPECT/CT, PET, SPECT and CT for hybrid imaging procedures were varied, see Table 2 and 3. The weight restriction and non-weight restriction are two commonly accepted methods for selecting patient's sample for DRL survey. The weight restriction method involves selecting at least 20 to 30 standard size patients, with the mean weight of patients in the sample being 70 ± 5 kg[3]. For the current European NDRL project, another patient weight criteria was 70 ± 15 kg; the number of samples collected using the survey was not mentioned[34]. Several NDRL articles have indicated the patient weight and these are presented under the patient characteristics of patient samples in Tables 2 and 3. Watanabe et al. argue that it is necessary to conduct NDRL articles based on weight restriction criteria because of variations in patient habitus and weight may have an impact on the results[21]. The weight restriction method allows data comparison with other published NDRL using the same approach for PET/CT and SPECT/CT imaging. For the non-weight restriction method, some NDRL methods for NM, PET/CT and SPECT/CT examinations were used to collect all present patients during a time frame acceptable for the NDRL survey[3]. The non-weight restriction method has some advantages compared to weight restriction method. Applying the weight limit criteria for the population sample may reduce the availability of data and extend the data collection period[16, 35]. Using the NDRL method

without weight restriction may result in a larger patient sample, which should lead to improved understanding of patient weights in a national population [35].

The literature showed the numbers of patients sampled using weight and non-weight restriction methods ranged from 1–76 patients. For the weight restriction method, the patient samples ranged from 20–30 patients with different weight-standard criteria[20, 25, 27]. However, two articles reported NDRLs based on sample sizes that were too small (for example, lower than ten patients)[19, 24]. For the non-weight restriction method, the samples varied and were collected over different time frames, which ranged from four months to one year. Iball et al. demonstrated UK's NDRL method aimed to collect 30 patients over five months for PET/CT and SPECT/CT examinations[18]. Iball et al. concluded that patient weight data only existed for a small number of PET/CT and SPECT/CT examinations; therefore, the UK's NDRL method was limited to reports of NDRLs based on a standard patient size of 70 ± 10 kg[18]. The average number of patients in the non-weight restricted NDRL articles was 38. The current ICRP 135 recommends when collecting 50 or more patients during NDRL survey, weight restriction is not required[3]. However, some authors found similar NDRL results, less than 2% difference, when using either weight or non-weight restriction method[36, 37]. Future PET/CT and SPECT/CT NDRL methods should involve a minimum of 50 patients with a non-weight-restriction approach[3]. A NDRL method based on the selection of a large number of patient sample enables filtering the data by different patient body sizes better enabling NDRL data comparison[38, 39], e.g. retrospectively selecting 30 patients with weight restriction (70±15 kg) acquired from a non-weight-restriction data[18, 20, 40].

Some articles reported PET/CT, PET and SPECT/CT NDRLs for clinical indications. Iball et al. provide ^{18}F-FDG PET/CT NDRL, $CTDI_{vol}$ and DLP, for two clinical indications for half body imaging and ^{99m}Tc-phosphates SPECT/CT NDRL, $CTDI_{vol}$ and DLP, for six common clinical indications for bone imaging[18]. Willegaignon et al. demonstrated that the amount of

^{18}F-FDG A for the most PET/CT common indications related to oncological and infection/inflammation was 350 MBq[22]. The European Association of Nuclear Medicine (EANM) guidelines illustrate that administered activity of ^{99m}Tc-MDP is 370-740 MBq for the most common clinical indications for three phase or whole body SPECT/CT bone scans[41]. The literature reveals that the recommended NDRL for A will be the same for common patient clinical indications in relation to PET/CT and SPECT/CT procedures. The amount of A differs when different radiopharmaceuticals are used for different PET/CT and SPECT/CT procedures (Table 2 and 3).

Body region was another area that varied across studies. Several publications have asserted that variations in CT scan range or body region associated with oncological PET/CT protocols and SPECT/CT bone protocols depend on patient clinical indication demonstrating a lack of standardisation[42-45]. For ^{18}F-FDG PET/CT procedures the most common CT range was varied from the mid-femora to the external auditory meatus, and from the top of the head to the feet for tumours that show a high probability of metastasis in the brain, skull or lower extremities, e.g. melanoma. A more limited CT range for tumour imaging may be considered when a patient returns for follow-up imaging[6, 46]. The literature reveals that the reported NDRL DLP values for ^{18}F-FDG whole body PET/CT scans varied from 400 to 750 mGy.cm due to various scan range descriptions, with only one NDRL article providing the scan range for the most common clinical indications related to ^{18}F-FDG whole body scans[15, 18, 27]. ARPANSA reported that the NDRL for PET/CT and SPECT/CT examinations takes into account the scan region and the CT used for the AC or AL to cover a wide range of clinical indication for each examination[33]. The first and second scan ranges for the whole body CT protocol are started from the eyes to the thighs and from the vertex to the toes, respectively. For SPECT/CT, Gardner et al. provides local DRL values for bone and neuro-endocrine SPECT/CT procedures takes into account different anatomical body regions and the purpose of CT used for each anatomical regions[45].

Four different anatomical body regions were identified for neuro-endocrine SPECT/CT procedures known as abdomen, abdomen/pelvis, chest/abdomen/ pelvis, and head/chest/abdomen/pelvis and the DLP values for each anatomical body region were 280, 204, 204, and 377, and 373 mGy.cm respectively[45]. Furthermore, the scan length might be increased if the NM physician found a new metastatic lesion requiring additional CT investigation[18]. However, scan length is a crucial parameter influencing a patient's CT dose and is directly associated with DLP[18]. A longer scan length involves a greater number of slices over a larger anatomical region, which subjects the patient to higher radiation exposure. Iball et al. suggested that limiting the scan length to only the area requiring investigation would optimise radiation doses delivered from PET/CT and SPECT/CT examination used in British clinical centres[18]. Thus, an NDRL method for PET/CT and SPECT/CT should provide a clear description of the clinical indications in relation to PET/CT and SPECT/CT examinations, the administered radiopharmaceutical, and the scan range of anatomical regions[18, 33, 45].

Improvements to PET/CT and SPECT/CT hardware and software allow a reduction in radiation exposure to patients or shorter scanning times while maintaining acceptable image quality[47]. Recent improvements to PET and SPECT include additional scanner rings for PET, scintillation detector materials including cadmium-zinc-telluride (CZT) detectors with novel collimators for SPECT, and reconstruction algorithms which incorporate time of flight (TOF) and point spread function (PSF) modelling[40, 48]. Kwon et al. demonstrate that using a PET/CT unit equipped with TOF technology and PSF algorithms required less administered activity[15]. Two articles reported NDRL for ^{18}F-FDG whole-body based on TOF technology. Roch et al. and Etard et al. reported that the A for ^{18}F-FDG whole-body scans decreased from 360 to 260 MBq and from 300 to 250 MBq with PET/CT systems equipped with TOF technology, respectively[20, 27]. However, Roch et al. noted that insufficient numbers of centres with SPECT/CT units equipped with CZT participated in the survey, therefore, appropriate NDRL

could not be provided for this new technology[20]. Furthermore, innovations in CT components, including automatic tube current modulation, automatic tube voltage selection (ATVS), and iterative image reconstruction algorithms, enable minimisation of radiation dose without compromising image quality[49]. Kwon et al illustrate that CT AC and AL radiation doses delivered from $CTDI_{vol}$ and DLP were significantly reduced with the use of a recently installed PET/CT instrument[15]. Many authors assert that current technical innovations in PET/CT and SPECT/CT modality enable a reduction in radiation exposure to the patients and while maintaining image quality[47, 49]. However, the literature reveals that no image quality criteria exist to assess PET and SPECT image quality; nor are there any criteria for CT to assess AC and/or AL image quality associated to PET and SPECT examinations. In diagnostic radiology, an expert group of radiologists and physicists published European guidelines on quality criteria for CT[50]. The main objective of the European guidelines is to provide minimum CT radiation dose while ensuring the obtainment of acceptable image quality criteria. Thus, NM researcher should develop methods to explore the acceptable balance between scan time and should develop image quality criteria and patient radiation dose reductions for PET/CT and SPECT/CT imaging modalities. It is recommended that when reporting NDRL the study takes into the account the manufacture date of equipment, and the current technological advances in PET/CT and SPECT/CT equipment, e.g. TOF and CZT scintillation detectors, respectively, as these technologies enable a reduction in the administered dose.

Some authors recommended that the achievable dose and ADP be used as supplementary dose measures for PET/CT and SPECT/CT NDRLs for identifying radiation doses yield suitable diagnostic image quality[18, 19]. Iball et al. found that CT doses vary significantly for the same procedures and the same clinical indication and conclude that radiation doses may be reduced by establishing both DRLs and achievable dose for British clinical practices[18]. Alessio et al. argues that NDRL and achievable dose reference levels for PET and SPECT A are limited as

they do not consider the impact of total acquired photons on image quality[19]. Alessio et al. recommends including ADP, which incorporates acquisition time, with NDRL as a practical way to overcome this limitation[19]. Determining ADP is a challenge for PET or SPECT examinations, due to variations in A and scan duration among clinical centres. Some clinical centres reduce A to patients and increase scan duration to maintain image quality. However, a drawback of increased scan duration is that some patients are unable to remain still for long durations, resulting in motion artefacts which degrade image quality[3]. In some circumstances, scanning obese patients required an increase in the A to ensure the maintenance of diagnostic image quality. From a radiation protection point of view, increasing A to patients minimises scan duration and should not be performed on the basis of increased department workflow[3]. However, only one article reports on ADP quantity, so the usefulness of the collection of the scan duration to assist in the determination of the ADP has not been fully explored. From the authors' perspective, it is important to determine the ADP to identify the normal clinical practice and understand the trade-off between the A and the scan duration required to maintain diagnostic image quality. Alessio et al. reported the ADP values for ^{18}F-FDG PET/CT and ^{99m}Tc-MDP SPECT/CT scans to provide clear guidelines for clinical practice to ensure the obtainment of sufficient image quality[19]. The authors illustrate that determining the ADP requires the collection of the administered activity and scan duration during the NDRL survey from participant clinical centre, which is easy to perform. The authors conclude that if the ADP value is consistently higher than the reported national ADP values, then the clinical practice should optimise the A, adjust the scanning time or both to ensure that sufficient image quality is obtained[19]. Therefore, future PET/CT and SPECT/CT NDRL methods should report both 75th percentile (DRL) and 50th percentile achievable dose to encourage clinical centres to optimise and improve their clinical practice. NDRL methods should collect data on A and acquisition time to evaluate the value of ADP, as a DRL metric.

All but one of the presented PET/CT and SPECT/CT NDRL methods failed to report the details of CT acquisition protocols[23]. Investigating radiation doses delivered from different CT acquisition protocols aids in dose optimisation[8]. However, the details of the acquisition are important to investigate the differences between NDRLs and to assist with optimisation. The NDRL method should be easy to perform and serve as a guideline to ensure that the median radiation dose metric delivered from clinical centres is equal to or lower than the recommended 75th percentile of the NDRL standard[3, 19]. The reported NDRL values should be used as a way to underpin optimisation strategies. The optimisation process is separate to the DRL process and should be initiated at the level of clinical practice when the median radiation dose quantity of clinical centre exceeds the 75th percentile of NDRL standard without justifiable reason[3, 19]. Optimising CT components associated with PET/CT and SPECT/CT procedures would be achieved by modifying CT acquisition parameters, such as by lowering kVp and mAs values, or selecting a larger pitch ratio without compromising diagnostic image quality[8]. It is practical to report the NDRL standard and collect the CT parameters to understand the details of CT acquisition protocol and variation between all participant centres. Jallow et al. reported the NDRL for $CTDI_{vol}$ and collected all CT acquisition parameters associated with ^{18}F-FDG oncological imaging procedures in United States PET/CT clinical centres[23]. They demonstrated that the 75th percentile of $CTDI_{vol}$ associated with ^{18}F-FDG PET/CT oncological procedures was 9.8 mGy. Their results highlighted a wide range of CT acquisition parameters among participants clinical centres such as tube current, pitch ratio and collimation, which ranged from 20–450 mA, 0.5–2, and from 5–40 mm, respectively[23]. The diversity of CT acquisition parameters indicates there is an opportunity to optimise CT acquisition protocols for ^{18}F-FDG whole-body PET/CT examinations. Thus, it is more practical to report PET/CT and SPECT/CT NDRL methods and report the details of the CT acquisition protocol to assist in the development of dose optimisation strategies[23].

NDRL units for A are either A (MBq) or A per unit of body weight (MBq/kg). The recommended A depends on several factors such as equipment type, patient weight, acquisition protocol and reconstruction method[6, 51]. It is important to illustrate that weight-based A is not appropriate for some SPECT/CT examinations, in which the A is concentrated in a single organ, such as thyroid and sentinel node examinations, as well as pulmonary ventilation and perfusion examination[3]. The methods that NM clinics use to determine A to patients are varied, some use fixed methods or follow international guidelines, while others use weight-based methods[26]. Alessio et al. examined different strategies for A for ^{18}F-FDG whole-body PET/CT and ^{99m}Tc-MDP SPECT bone examinations[19]. They reported no statistical differences in the average A for fixed, range, and weight-based strategies. They also found that PET/CT (n=3) and SPECT/CT (n=1) mobile clinics delivered higher radiation doses than the non-mobile clinics by 30% and 40%, respectively, due to the utilisation of fixed methods for determining A[19]. Oliveria et al. illustrate that adjusted ^{18}F-FDG weight-based strategies greatly varied among two clinics using PET/CT equipment from the same manufacturer and with same scintillation detectors (3.7 MBq.kg^{-1} to 7.4 MBq.kg^{-1}), illustrating a lack of standardisation and a potential to optimise the ^{18}F-FDG dose[26]. Roch et al. claimed that the A recommendations should be determined based on patient weight[25]. Adopting weight-based strategy enables to explore the variations for the A between clinical centres. Thus, NDRL surveys should report the recommended administered strategy based on patient weight (MBq/kg) for all PET/CT and SPECT/CT examinations in order to provide suitable guidelines for clinical centres[25].

The effective dose (E) was also reported for the majority of PET/CT, SPECT/CT, PET, SPECT and CT components associated with PET and SPECT procedures during NDRL surveys (Tables 2 and 3)[15, 18, 22, 24, 27, 29, 30]. The E from PET/CT and SPECT/CT is defined as the sum total of the radiation dose (mSv) from the A and from the CT components allowing

quantification of total radiation exposure (Total E (mSv) = E_{NM} +E_{CT}) and radiation risk[52, 53]. The E method in PET/CT and SPECT/CT is calculated by multiplying each radiation dose by specific conversion coefficients assigned for the A and the DLP value for the CT dose[52]. Some researchers used the Monte Carlo software programme to calculate the E value for CT doses such as CT-Expo software version 2.1 and 2.4 (Medizinische Hochschule Hannover Germany) and ImPACT scan CTDI dosimetry software (version 1.0.4 with the National Radiological Protection Board (NRPB) SR250 dose data)[15, 23, 24, 27]. However, E methods are based on assumptions about patients that are not commonly true due to variation in size and physiology. At the moment, the E methods described seem straightforward; however, the results of E values are prone to a lack of precision. Calculating E for the A requires multiplication by a conversion coefficient taken from the ICRP tables. The result of E from CT varies amongst different CT dosimetry software due to the various methods and algorithms utilised for each software program[54].

Reporting E is the only way to merge the radiation doses into one metric from the total radiation doses delivered from PET/CT and SPECT/CT examinations. The reporting of E from PET/CT and SPECT/CT procedures enables us to understand the variation of radiation doses delivered from each radiation dose component and supports a dose optimisation strategy. However, the ICRP 135 publication illustrates that reporting the E should not be a part of NDRL methods[3]. It is impractical to use E comparisons when a wide range of patients' ages and genders are being compared because it is subjected to large uncertainty[40]. Shrimpton et al explained that E data were excluded from the UK NDRL survey because E has a different purpose than NDRL[55]. The exact method for calculating E is complex and requires collecting extra information about patients' individual biokinetics, physiological and anatomical properties for A and a number of CT parameters such as beam energy and beam filtration[36]. The E is subject to much uncertainty; therefore, it is not yet recommended to be a part of NDRL methods[3].

Further research is required to investigate the role of E in developing dose optimisation strategies.

Recommendations

Based on this extensive review, we suggest the following recommendations:

1. It is recommended that PET/CT and SPECT/CT NDRL methods adopt a non-weight restriction approach and then filter the data acquired for the purpose of international data comparison.
2. A clear description of the administered radiopharmaceutical and scan range for CT components should be provided for each PET/CT and SPECT/CT examination.
3. NDRL methods should assess the usefulness of achievable dose and ADP as a DRL metric for A.
4. It is recommended that NDRLs report the DRLs for PET/CT and SPECT/CT procedures for equipment equipped with or without TOF and CZT technology.
5. Reporting the NDRL with details of CT acquisition parameters will underpin the dose optimisation strategy programme.
6. It is recommended that NDRLs of PET/CT and SPECT/CT report the A per patient weight for each exam.
7. Finally, the E value should not be reported as NDRL metric as it is based on a number of assumptions impacting on its accuracy.

Conclusion

The literature shows differences in methods for establishing DRLs for PET/CT and SPECT/CT examinations. Findings also show variations in reported PET/CT and SPECT/CT DRLs arise from patient characteristics, methods reporting, and progress of the technology. NM professions should report both radiation doses from the A and the CT dose used for different

purposes rather than report a separate NDRL for A or CT dose. Further research should be performed to assist in the international standardisation of data collection and reporting of NDRL PET/CT, with more attention given to SPECT/CT procedures.

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661 Table 1. Criteria for determining study eligibility.

Characteristics	**Criteria**
Study year	Articles published up to October 2017.
Study type	Cohort studies
Population	Adult patients undergoing PET/CT and SPECT/CT examination
Intervention	Adult DRL measurement methods for PET/CT and SPECT/CT examinations
Comparator	Reliability of DRL methods for adult in PET/CT and SPECT/CT examinations Reproducibility of DRL methods for adult in PET/CT and SPECT/CT examinations
Outcomes	PET/CT and SPECT/CT DRL methods for adult patients.

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663 Table 2. Summary of hybrid PET/CT DRL methods.

Authors (Years & Country)	**Procedure**	**Clinical indication**	**Radiotracer**	**Scan range**	**Characteristic of patient sample**	**DRL dosimetry value**		**E (mSv)**		
						A(MBq) [MBq/kg]	**$CTDI_{vol}$ and DLP (mGy) & (mGy.cm)**	**A**	**CT**	**Total**
Kwon et al[15] (KO, 2016)	Whole body	-	^{18}F-FDG	Base of skull-upper thigh	10 per each exam	370 [5.89±1.46]	5.96 and 560	5.89	6.26	12
Etard et al[27] (FR, 2012)	Whole body	-	^{18}F-FDG	At least neck-thigh	20 (50-100 kg)	350 [4.3] 250 [3.5 TOF]	8 and 750	5.7	8.6	14
Iball et al[18] (UK,2017)	Half body	Tumour Infection/ Inflammation	^{18}F-FDG	Base of brain-mid thigh	30 per each exam	-	4.3 and 400	7.6	6.5	14
Roch et al[20] (FR, 2017)	Whole body	-	^{18}F-FDG	-	30 per each exam	350 260 [3.6 TOF]	- -	- -	- -	- -
Watanabe et al[21] (JP, 2016)	Tumour Tumour Tumour Brain - - - -	Tumour Tumour Tumour - - - - -	^{18}F-FDG HP ^{18}F-FDG (Delivery) ^{18}F-FDG HP ^{18}F-FDG (Delivery) ^{15}O-CO_2 g: 2D ^{15}O-O_2 g: 2D ^{15}O-CO g: 2D ^{15}O-CO_2 g: 3D	- - - - - - - -	-	235 [2-5] 252 [2-5] 227 255 7500 4500 3000 2888	- - - - - - - -	- - - - - - - -	- - - - - - - -	- - - - - - - -

664 Table 2. Summary of hybrid PET/CT DRL methods (continued).
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Authors (Years & Country)	**Procedure**	**Clinical indication**	**Radiotracer**	**Scan range**	**Characteristic of patient sample**	**DRL dosimetry value**		**E (mSv)**		
						A (MBq) [MBq/kg]	**$CTDI_{vol}$ and DLP (mGy) & (mGy.cm)**	**A**	**CT**	**Total**
Watanabe et al[21] (JP, 2016)	-	-	^{15}O-O_2 g: 3D	-	-	6600	-	-	-	-
	-	-	^{15}O-CO g: 3D	-	-	7125	-	-	-	-
	Myocardial/ Metabolism	-	^{18}F-FDG H	-	-	221	-	-	-	-
	Myocardial/ Metabolism	-	^{18}F-FDG D	-	-	251	-	-	-	-
	Myocardial/ Perfusion	-	^{13}N-NH3	-	-	718	-	-	-	-
Jallow et al[23] (US,2016)	Oncology	-	^{18}F-FDG	-	2010-14: 35, 65, 76, 42 and 14 cases	-	9.8, 9.8, 10.2, 9.7 and 9.7	-	-	-
Willegaignon et al[22] (BR, 2015)	Oncology/ inflammation	Tumour/ Inflammation	^{18}F-FDG	-	-	370	6.76±1.08	-	-	-
	Brain	-	^{18}F-FDG	-		350	5.11±1.52	-	-	-
	Bone	-	^{18}F-NaF	-		370	7.30±0.30	-	-	-
Alessio et al[19] (USA, 2015)	Whole body	-	^{18}F-FDG	-	1-5 (4.3±1.3) cases	592	-	-	-	-
Oliveria et al[26] (BR, 2013)	^{18}F-FDG PET	Cancer	^{18}F-FDG	-	-	387.7 [5-5.4]	-	-	-	-
Roch et al[25] (FR, 2013)	^{18}F-FDG PET	-	^{18}F-FDG	-	20 (60-80 kg)	350 and 337 [5]	-	-	-	-

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667 Table 2. Summary of hybrid PET/CT DRL methods (continued).

Authors (Years & Country)	**Procedure]**	**Clinical indication**	**Radiotracer**	**Scan range**	**Characteristic of patient sample**	**DRL dosimetry value**		**E (mSv)**		
						A(MBq) [MBq/kg]	**$CTDI_{vol}$ and DLP (mGy) & (mGy.cm)**	**A**	**CT**	**Total**
Botros et al[28] (AU & NZ, 2009)	Whole body	Tumour	^{18}F-FDG	-	20 per exam or facility guidance level for 70-80 kg	385	-	-	-	-
	Brain	-	^{18}F-FDG	-		385	-	-	-	-
	Myocardial Viability	-	^{18}F-FDG			370	-	-	-	
Hart et al[29] (UK, 2005)	Tumours PET	Tumour	^{18}F-FDG	-	-	400	-	7	-	-
Brix et al[30] (DE, 2002)	Oncology	-	^{18}F-FDG	-	-	370 (2D)	-	7	-	-
	Neurology	-				200 (3D)	-	3.8	-	-
	Cardiology	-								
	Other application	-								

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669 Note: TOF= Time of flight, $^{15}O\text{-}CO_2$= 15 Oxygen Carbon dioxide, $^{15}O\text{-}CO_{15}$= Oxygen Carbon monoxide, HP= hospital product,, g= gas, $^{13}N\text{-}NH_3$= N13 ammonia, NaF= Sodium Fluoride,, A.A
670 =administered activity.
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682 Table 3. Summary of hybrid SPECT/CT DRL methods.

Authors (Years & Country)	**Procedure**	**Clinical Indication**	**Radiotracer**	**Characteristic of patient sample**	**DRL dosimetry value**		**E (mSv)**		
					A (MBq) [MBq/kg]	**$CTDI_{vol}$ and DLP (mGy) & (mGy.cm)**	**A**	**CT**	**Total**
Iball et al[18] (UK, 2017)	Bone	Bone*	^{99m}Tc-phosphates	30 per each exam	-	4.9 and 150	3.9	-	-
	Parathyroid	Adenoma	^{99m}Tc-sestamibi		-	5.6 and 170	8.1	1.4	9.5
	Post-thyroid ablation	Post-thyroid Ablation*	^{131}I-iodide		-	5.9 and 210	-	1.5	-
	Tumour MIBG	Tumour MIBG*	^{123}I-MIBG		-	5.5 and 240	5.2	-	-
	Octreotide	Octreotide*	^{111}In-octreotide		-	5.5 and 240	11.9	3.3	15.2
	Myocardial	Myocardial*	^{99m}Tc-sestamibi		-	2.1 and 3.6	7.2* and 6.3	0.9*	8.1
Avramova-Cholakova et al[24] (BG, 2015)	Breast	-	^{99m}Tc-sestamibi and tetrofosmin	$H_{1,2,}$ and $_3$:64, 9 , and 18	700	3 and 100	6.3, 5.9, and 2.8	3.2, 1.7, and 1.5	9.5, 7.6, and 4.3
	Bone	-	^{99m}Tc-MDP	$H_{1,3,}$ and $_4$:42, 35, and 13	600	3 and 200	2.5, 3.4, and 2.9	1.2, 1.8, and 7.2	3.8, 5.1, and 10.1
	Thyroid	-	^{99m}Tc-pertechnetate	H_1:14	74	4 and 170	1	3.6	4.6
	Parathyroid	-	^{99m}Tc-sestamibi	$H_{1,2,}$ and $_3$:7, 10, and 10	120	2.6 and 100	7.4, 6, and 5	4.1, 2.3, and 1	11.5, 8.3, and 2
	Thyroid	Metastasis	^{131}I-iodide	$H_{1,1}$ and $_2$: 12,7, and 10	185	4 and 170	167, 167, and 74	1, 0.5, and 2.4	-
	Lymphatic	-	^{99m}Tc-Nanocoll	H_1 and $_2$:10 and 20	74	4 and 120	0.3 and 0.2	2.8 and 2.1	3.1 and 2.2
	Lung perfusion	-	^{99m}Tc-MAA	$H_{2,3}$, and $_4$: 20, 14, and 19	20	2.6 and 100	1.1, 2, and 2	1.4, 1.3, and 8.5	2.5, 3.3, and 10.5

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Table 3. Summary of hybrid SPECT/CT DRL methods (continued).

Authors (Years & Country)	Procedure	Clinical indication	Radiotracer	Characteristic of patient sample	DRL dosimetry value		E (mSv)		
					A (MBq) [MBq/kg]	$CTDI_{vol}$ and DLP (mGy) & (mGy.cm)	A	CT	Total
Willegaignon et al[22] (BR, 2015)	Brain/ Perfusion	-	^{99m}Tc-ECD	-	1203	-	8.17±1.69	-	-
	Brain/ Tumour	Tumour	^{201}Tl-chloride	-	185	-	43.40±47.8	-	-
Alessio et al[19] (USA, 2015)	Bone		^{99m}Tc-MDP	1-4 (2.2±0.8) cases	999	-	-	-	-
Heart et al[29] (UK, 2005)	Bone	-	^{99m}Tc-MDP	-	800	-	3	-	-
	Lung Perfusion	-	^{99m}Tc-MAA	-	100	-	0.3	-	-
	Myocardial	-	^{99m}Tc- tetrofosmin	-	400	-	3.1	-	-
	Myocardial	-	^{99m}Tc-sestamibi	-	400	-	3.7	-	-
	Myocardial	-	^{201}Tl-chloride	-	80	-	12.9	-	-
	CBF	-	^{99m}Tc-Exam	-	500	-	4.8	-	-

Note MIBG= metaiodobenzylguanidine, *= stress, H= hospital, MAA= macro aggregated albumin, ECD= ethyl cysteinate dimer, EXAM= Exametazime, Bone*= metastatic disease, equivocal uptake on planar studies, characterisation of lytic and sclerotic lesions, localise and characterise site of unexplained pain, localise and characterise site of multifocal pathology, evaluation of new/persistent symptoms following orthopaedic intervention, Post-thyroid ablation*= identify remnant thyroid tissues, and undertake accurate staging, Tumour MIBG*= Neuroendocrine tumour imaging, assessment of disease, suitability for therapy and response, identification of primary tumours and metastases, assessment of post-therapeutic tumour targeting, and assessment of tumour recurrence, Octreotide*= Somatostatin receptor imaging – assessment of disease, suitability for therapy and response, identification of primary tumours and metastases, assessment of post-therapeutic tumour targeting, and assessment of tumour recurrence, Myocardial*= myocardial perfusion imaging and/or viability, and qualitative assessment of coronary calcium, CBF= cerebral blood flow.

699 Table 4. Summary of hybrid NM/CT equipment.

Authors (Years &country)	Modality	Number	Manufacture	Year of installation	Type of detectors	
					Non-TOF	TOF
Kwon et al[15] (KR, 2016)	PET/CT	105	GE discovery (45): Discovery 600 (5), 690 (8), 710 (7), ST (4), STE (12), STE8(1), STE16(6), VCT(2) Philips (18): GXK6 (1), 16POWER (1), TF (4), TF16 (4), TF64 (8). Siemens (41): DUO (2), True Point (1), True point2 (2), True point6 (4), True point16 (2), True point 40 (12), True point64 (1), mCT20 (2), mCT40 (1), mCT 64 (5), mCT 128 (6), mCT X4R (1), mCT FLOW (2) No data (1)	2000-5 2006-10 2011-15 -	BGO (30) GSO (3) LBS (15) LSO (42)	LYSO (14) - - -
Jallow et al[23] (US,2016)	PET/CT	158	GE (81) Philips (20) Siemens (56) Toshiba (1)	2001-2013 2004-2013 2003-2002 2005	- - - -	LYSO (158) - - -
Avramova-Cholakova et al[24] (BU, 2015)	SPECT/CT	4	GE (1): Discovery NM/CT 670 with 16-detector row CT. Siemens (3): Symbia 2T (2) with a 2 detector CT row, Symbia T16 (1) with a 16 detector row CT	- - - -	- -	- -
Willegaignon et al[22] (BR, 2015)	PET/CT SPECT/CT	- -	GE (48%) Elscint (20%) Siemens (17%) Philips (12%) Other (3%)	- - - - -	- - - - -	- - - -
Oliveira et al[26] (BR, 2013)	PET/CT	42	GE (11) Philips(8) Siemens (20)	- - -	BGO (3) GSO (3) LSO (18) Nal (Ti) (2)	LYSO (2) - - -

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701 Table 4. Summary of hybrid NM/CT equipment.

Authors (Years &country)	**Modality**	**Number**	**Manufacture**	**Year of installation**	**Type of detectors**	
					Non-TOF	**TOF**
Hart et al[29] (UK, 2005)	PET/CT SPECT/CT	7% (PET) 75% (SPECT)	GE (4) Siemens (3) GE (45%) Siemens (23%) Philips (25%) Park (0.8%) Toshiba (6%) Mediso (0.4%)	- - - - - - - -	- - - - - - - -	- - - - - - - -
Brix et al[30] (DE, 2002)	PET/CT	-	2 D and 3D PET equipment	- -	- -	- -

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703 Note: GE= General electric, BGO= Bismuth germinate oxide, GSO= Gadolinium oxyorthosilicate, LBS= Lutetium based scintillators, LSO= Lutetium oxyorthosilicate, LYSO= Lutetium yttrium oxyorthosilicate, Nal
704 (TI)= Sodium iodide doped with thallium, and Min= Minutes.

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706 Figure 1. Flow diagram of included and excluded PET/CT and SPECT/CT NDRL studies.

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