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REVIEW ARTICLE
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18F-FDG PET Adults Whole-Body Scan Injected Dose Optimization: A Mini Review

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ABSTRACT

While there is a necessity to have guidelines in order to control the ^{18}F-FDG usage in PET-CT scan exams to protect the patient and the clinical staff, there is another necessity to keep these guidelines up-to-date and according to the recent advances and adaptations of the new PET-CT scanner modalities. Regarding SNMMI, a fixed range of ^{18}F-FDG activity administered to the Whole-body scans in adult patients was established, yet the last update of these guidelines was in 2006. By the same token, the EANM last updated guidelines were in 2015. In this review 27 articles were successfully optimized the FDG injected dose using different techniques after 2015. These articles were analyzed and sorted to check the most common facilities that have been used to reach the optimized amount of FDG. As a result, most of the articles have very common features and each of them had an optimized rate that is under the lower limits the EANM injection guidelines. And due to the common advance techniques, that has been used in these scanners we concluded that its utterly possible to have an exam using a DTP below the guidelines while maintain a reportable image quality. Therefore, international guidelines need to take in count these advance facilities in the upcoming version of their recommendations.

INTRODUCTION

PET imaging is widely used in a wide range of clinical applications, such as the investigation of oncological and neurological illnesses (1, 2). A successful PET/CT procedure should accomplish the clinical goal while keeping the radiation dose as low as reasonably practicable (ALARA)(3). Reducing the radiopharmaceutical ^{18}F-fluorodeoxyglucose (FDG) dosage or its related acquisition time not only can reduce the radiation dose to the patient and the clinical staff, but also can bring economic benefits (4). Patients may experience fewer side effects, such as discomfort or nausea, when a lower dose FDG is used. International guidelines for FDG PET/CT protocols for tumor imaging specify appropriate dose-related parameters. The dosage of injected FDG activity given to the patient is suggested to be within certain limit by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines 370–740 MBq (5).

The European Association of Nuclear Medicine (EANM) regulations, on the other hand, recommend dosage based on subject weight, scanner overlapping percentage, and acquisition time (6, 7). The current EANM guidelines for tumor imaging with ^{18}F-FDG (version 2 in 2015) recommend adapting the administration injection activity quadratically to the body mass, however for practical reasons, the guideline also includes a linear activity-body mass relationship (6). These guidelines ensure that the measured FDG tumor uptake is, within certain limits, independent of the sensitivity of the system used or the center where the study is performed (8). Several studies have investigated the potential FDG dose optimization, such as Mirosaw Dziuk et al. in 2020, who proposed a 25% FDG dose reduction; Elena Prietoa et al. in 2018 proposed a 28% administered dose reduction; Takuro Umeda et al. suggested a 23-42% reduce in the acquisition time is possible; Fred Wickham et al. estimated that 29% less injected dose can be reached using some expressions; and Katia Katsari et al. calculated that 33% less FDG was required. Other authors, however, have proposed a new regimen for dose administration that can reduce the injected dose below the EANM recommendations, like Groot et al. (9-14). The visual detectability quality of low-contrast ^{18}F-FDG characteristics in PET scans is affected by a number of factors, including scanner efficiency, injected activity, uptake time, acquisition time, and patient size. PET equipment and software advancements during the past two decades have resulted in significant improvements in the sensitivity of PET scanner systems (15). PET hardware and software advances include scanners with much larger geometric coverage of the body, quite sensitive and compact silicon photomultiplier light sensors, rapid detectors for time-of-flight PET utilizing conventional scintillation light or other rapid emission levels, and fast electronics blended with computational techniques to better estimate the location, time, as well as energy of an interaction in the detector. Thus, the objective of our review is to discuss several articles that optimized the injected dose of ^{18}F-FDG PET-CT in whole-body adult exams to prove the possibility of performing diagnosable exams below international standards. This is the first review that collects different attempts to optimize the international standards of ^{18}F-FDG injection and its related time per bed position after the last updated SNMMI and EANM guidelines.

METHODS

The purpose of this research is to provide evidence of the possibility of performing ^{18}FDG PET-CT scan exams with a lower prescribed dose than the guidelines of SNMMI and EANM, depending on the up-to-date PET-CT facilities. For data collection, Scopus, PubMed, and Google Scholar were used. In order to achieve meaningful findings, the keywords "^{18}F-FDG dose optimization," "^{18}F-FDG PET-CT dose reduction," "minimizing the ^{18}F-FDG injected dose in the PET-CT scan," "FDG acquisition time optimization," and "reducing time per bed position for ^{18}F-FDG PET-CT" were chosen. From these outcomes, the following criteria for exclusion have been chosen: pediatrics dose optimization, PET-MRI dose optimization, and articles that focus on CT radiation dose reduction without minimizing the FDG dose. Only the first ten pages of results were used (sorted by relevance, with ten articles per page). Additionally, duplicate articles were filtered, and articles that had PET-MRI dose optimization in context (in the title, abstract, or conclusion) were excluded. Since the search keywords were synonyms, duplicates had to be removed. Papers that lack a clear focus on ^{18}F-FDG administered dose or time optimization in the abstract, title, or conclusion also were eliminated. The data timeframe was set to meet the last update of ^{18}F-FDG guidelines by EANM in 2015 to 2022-Jun. The articles that successfully reduced the time per bed position were considered successful attempts at FDG dose reduction. Hence, a reduction in acquisition time of 25% (from 2 minutes to 1.5 minutes) can immediately translate into a reduction in dosage of 25% (from 3.0 to 2.25 MBq/kg) (16). All 27 collected articles were manually clustered based on the optimized FDG dose or time per bed position, while acceptable image quality for diagnosis is maintained, in whole-body adult PET-CT scan exams. The following information was extracted: the first author's name and publication year; the PET-CT modality; the scanner sensitivity; the axial field of view; the algorithm used; the type of detector; and the optimization rate of dose and time. Information was extracted from these clusters and reported in the Table l. Then the lowest possible optimized DTP that can be reached by each article was considered.

RESULTS

The summary Table 1 shows approximately 23 articles for which we were able to report their lowest

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optimized rate. It is also worth to be mentioned that most of the articles used several injected doses, which led to one or several optimized doses. In the summary Table 1, explore the studies that had utilized very highly sensitive PET devices in their studies (>170 cps/MBq), all of which were using the Time of flight (TOF) and Point Spread Function (PSF) options together (17-22). In addition, almost more than half of the PET scanners that were included in our literature were utilizing both the Time of flight and Point Spread Function technology for positron emission tomographic images reconstruction (17-31). Also optimization of reconstruction algorithm, using of using new Bayesian penalized-likelihood reconstruction algorithm (Q.clear) (1, 16-22, 24-27, 31-40) could show their effect on injection dose optimization. Furthermore, As It shows that the scanner detector type, like lutetium-yttrium oxyorthosilicate (LYSO) and Lutetium oxyorthosilicate (LSO) were the most frequent scanners were evaluated in studies. SiPM detectors also due to its higher capability in image quality improvement has been widely researched. we have found that most of the PET scanner's sensitivity values mentioned in our study were between 9 and 16 cps/kBq (1, 18, 20, 23-25, 30-32, 34, 36, 39-41). However, the new generated scanner sensitivity was about 176 cps/kBq (17-22, 26). It was also demonstrated that all of the studies used scanners with a large axial field of view, beginning at 153 mm and including 24 out of 31 PET scanners with a longer FOV greater than 190 mm.

DISCUSSION

The EANM proceeded a guideline for administrating the ^{18}F-FDG in 2015 (6). The injected dose of ^{18}F-FDG and the time per bed position calculations is varied depending on the PET-CT overlaps and the patients' weights. Based on the guidelines–based on phantom experimentations, hypothetical estimations and retrospective studies on highly diverse populations–the injected activity of ^{18}F-FDG ought to be 3.5-7 MBq/kg (6, 8, 42-45). Nevertheless, it is mentioned that PET-CT scanner sensitivity and the new technology facilities can play an important role in reducing the FDG injection dose or the time per bed position. As a result, several studies decided to optimized the ^{18}F-FDG inject dose to find out the lowest dose possible depending on their PET-CT scanner facilities. Several factors proofed to have a significant effect on the image quality and therefor it can reduce the injected dose or lowering the acquisition time. The frequent advance algorithm usage was noticeable due to its impact on imaging quality. For example, iterative methods such as OSEM are currently the standard reconstruction technique for almost any PET scanner and will most likely remain the method of choice in the near future. Hence, image reconstruction and image quality could be substantially improved (46). About 22 out of 31 scanner that have been involved in our study used the OSEM as their preferable algorithm to reach the lowest possible optimized DTP in their PET-CT exams. The Point Spread Function (PSF) information measured in an enormous range of positions in the field of view (FOV) is integrated into reconstructed techniques. As a result, the PSF correction is anticipated to enhance spatial resolution while decreasing distortions (47). On the other hand, the Time of Flight (TOF) would include the time information to correctly identify the localization of annihilation points along the line-of-responses (LORs). Consequently, TOF data is believed to lessen the noise and to boost the contrast (48, 49). The utility of TOF information in strengthening image quality in overweight patients was investigated utilizing large diameter phantoms (50, 51). The utilization of TOF is well-known to improve the signal-to-noise ratio (SNR) in PET Imaging studies (52). Research findings have shown that effectiveness of lesion detection with TOF was exactly equivalent to that of non-TOF lesion detection, where the image acquisition duration for the TOF data had been shrunk (51, 53). A Prime example, the study by Kadrmas et al. indicated that lesion detection accuracy evaluated using the same scanner as in his study he compared between non-TOF and TOF images, where the image acquisition time for the TOF information had already been reduced by forty percent (53). According to one study, TOF information can minimize acquired counts while preserving picture quality and commonly used computation metrics (54). In addition, Taniguch et al. concluded that OSEM, PSF and TOF improved the PET images in his study (55). According to the Table 1 the number of scanners that had the TOF, PSF and OSEM is great indeed and that refer to how effective can be using one or more of these algorithms in image quality which can give us more flexibility to use injected dose or time lower than the standard guidelines. It is well known that detector's technology is improving rapidly and significantly

each year with regard to energy and timing resolution due to companies' competitions to take the lead in the medical imaging market. One other fact is that PET scan clinical utilization has been altered from a modality primarily used for basic and clinical studies into clinical routine (accelerated by the combination with CT). Since 2000, the majority of PET scans have been related to oncology, and these scans typically cover a large portion of the body. Several other types of PET scanners have a total body PET devices that have superior quality (10–40× greater sensitivity), and there is a pretty obvious direct application for this detector's technology (56). The new PET detectors utilize materials that is efficient in photoelectric conversion of the annihilation photons and shortening decay time of the scintillation light, which is a key requirement for high counting rates and better PET images (57, 58). Digital PET detector technology with silicon photomultipliers (SiPM) had also helped to improve timing, energy, spatial resolution, and effective time-of-flight (TOF) sensitivity (59-62). As a result of this technology, scanning is faster and there is less injected activity (39, 63). According to the summary Table 1, in this review there were about 13 scanners had utilized the SiPM technology. Solid-state digital PET detectors use a novel combination of lutetium-based scintillator crystal arrays with a silicon photomultiplier (SiPM), which improves intrinsic sensitivity and temporal resolution (64). The summary Table1, indicates that the majority of scanners in our study had the Lutetium oxyorthosilicate (LSO) scintillator crystals and lutetium-yttrium oxyorthosilicate (LYSO) crystals as they represent the detectors of 21 out of 31 PET scanners in this study. While some companies, such as Siemens and Philips, use only L(Y)SO for their PET systems, GE Healthcare maintains a line of PET/CT scanners with Bismuth germanium oxide (BGO) detectors (1, 16, 34-36, 40, 65). The FOV in turn, played a significant role in dose optimization, according to the principle that says ; as we lengthen the scanner, more line-of-response (LORs) emitted by the patient will strike the detector ring, as detailed by Eriksson et al.(66). By raising the axial length to 150 cm, the geometric sensitivity of a 1-m-long source can be increased above seventy-five percent. A study has identified an improve in sensitivity and Noise Equivalent Count Ratio (NECR) in the PET/CT is because of its extended axial field of view (AFOV). According to the reported spatial resolution, time resolution, and sensitivity, scanners with an extended AFOV ,like the Biograph Vision PET/CT make them competitive new devices in the class of PET (67). The increased sensitivity provided by the Biograph TruePoint PET/CT with TrueV's extended axial coverage enables a reduction in either scan time or injected dose without compromising diagnostic image quality (68). The current PET systems have limited sensitivity due to their scanner solid angle coverage, which is mainly affected by the axial length of the scanner in common cylindrical scanners(69). Additionally, the small ring diameter has a significant effect on sensitivity; however, lower ring diameter can be only applied in dedicated brain and breast scanners and could provide higher sensitivity than conventional whole body scanners (70) and therefore need lower injected dose. Further dose optimization of these dedicated scanners may be reviewed as part of our future work. The summary Table 1, showing that 24 out 31 PET-CT scanners in 24 out of 27 article had an extended axial FOV over 190 mm in this literature in which authors have successfully optimized the ^{18}FDG dose below the international limits (1, 16-27, 29-31, 33, 35, 36, 39, 41, 71). The mentioned advances demonstrated the ability to further reduce ^{18}F-FDG activity, which is highly desirable in clinical routine to keep radiation exposure for patients and hospital staff as low as reasonably achievable (72, 73). Because of these facilities' variations in PET-CT scanners, the sensitivity of the scanners is different. And since the scanner sensitivity is playing an important role in PET image quality, our study proofed that as the administrated DTP were optimized greatly in the studies that used higher sensitive devices to produce an optimized DTP lower that the International guidelines. All of the studies mentioned could be attributed to current advances in the PET/CT clinical setting and the use of novel PET/CT advanced technologies, which enable improved scanner sensitivity and thus less administered activity for appropriate image quality (74). The EANM guidelines, on the other hand, admitted that higher sensitivity PET/CT systems can lower the dose or improve scan performance (6). Nonetheless, the current administrated activity of ^{18}F-FDG is calculated using the patient's weight, scanner overlap, and time per bed position (6). Typically, about 3 MBq/kg bodyweight of ^{18}F-FDG are injected when using a time per bed position of 3 min

(DTP of 9 MBq/kg.min) (75). The summary Table 1 indicates that almost all of the mentioned articles were successful in reducing the administered ^{18}F-FDG PET-CT level below the international standard of nine DTP MBq/kg.min. One of the study limitations was that three articles used more than one PET-CT scanner in their methods to reach an optimized dose, which means different scanner sensitivities were used in the same article, while the author did not mention by which device the optimized dose had been reached (20 ,18 ,1). Finally, by using either theoretical or practical application methods, all of the articles achieved either a shorter time per bed position or a lower injected dose than the international guidelines.

CONCLUSION

Due to the success that these articles had after optimizing the injected dose and acquisition time below the international standards while maintaining diagnosable ^{18}F-FDG PET-CT images, we recommend that the international standards (EANM and SNMMI) for ^{18}F-FDG administration in whole-body adult exams be modified and adjusted. The future guidelines should be more specific according to the scanner type and its facilities.

Disclosure of potential conflicts of interest:

The authors declare that they have no conflict of interest.

Table 1: a summary table of each article included in the review with details.

Cite	Scanner Used	The optimized rate	PET-CT Detector type	Used algorithm	Axial FOV in cm	PET-CT Sensitivity cps/KBq
(23)	Biograph mCT	FDG dose of 0.05 mCi/kg at continuous bed motion rate of 1.1 mm/sec.	LSO	ordinary Poisson iterative with attenuation correction TOF +PSF	21.6	9.6
(39)	Biograph Vision	Scan duration or activity administration could be reduced by a factor of 3	LSO+ SiPM	ordinary Poisson ordered +OSEM TOF	26.1	16.4
(30)	Biograph mCT	FDG dose was reduced to 2.5 MBq/kg at 1.5 min per bed position	LSO	SAFIRE iterative data reconstruction TOF+PSF	22	9.6
(41)	Biograph mCT	From 3 min per bed position and 3 MBq/kg, the injected FDG was reduced by 66 MBq per patient	LSO	TrueX (UltraHD-PET) TOF	22	10.0
(31)	Biograph mCT	FDG reduction lead to radiation dose reduction of 28.7%.	LSO	OSEM TOF+PSF	21.8	9.6
(29)	Vision 600 Edge digital	reduction of acquisition time or activity can be reduced as 75%	LSO+SiPM	TrueX TOF +PSF	26.3	16.4
(27)	Digital Biograph Vision	Scan time duration or injected activity can be reduced threefold.	LSO + SiPM	OSEM TOF+PSF	26.3	16.4
(71)	Biograph TruePoint	Qualitatively	LSO	OSEM PSF	21.6	7.6
(25)	Biograph Vision 600	Injected FDG of 3 MBq/kg at one min per bed position	LSO + SiPM	OSEM TOF+PSF	26.3	16.4
(38)	VEREOS Philips Digital	This study paved the way for half-duration PET scans	LYSO + SiPM	OSEM PSF	16.4	22
(40)	Discovery 600	overall reduced in acquisition time by 23–42%	BGO	OSEM PSF	15.3	9.6
(37)	Discovery D-690	0.8 MBq/kg using a 3-min-per-bed-position	LYSO	OSEM	15.7	7.5

(36)	Discovery ST 8	The Scan time in this study was 2.9 minutes, A 27.6% shorter.	BGO	OSEM	19.4	9.3
(32)	Discovery MIDR	The injected FDG was optimize to 1.85 MBq/kg	LBS + SiPM	Q.Clear TOF	20	13.5
(16)	Discovery IQ	FDG dose can be reduced by up to 25%	BGO	GE SharpIR + Q.Clear	26	22.8
(1)	A-Discovery IQ B-Discovery ST-16 C-Discovery ST-4	FDG dose were reduced by one-third	A-BGO B- BGO C-BGO	A-OSEM B-VPHID C-VPHID SubtlePET™	A- 26 B-15.7 C-15.7	A- 22.8 B- 9.12 C- 9.3
(28)	Discovery 710	Qualitatively	LBS	VUE Point iterative TOF+PSF	15.7	10
(35)	Discovery IQ	Effective dose reduction to 3.62 MBq/kg at 2 min per bed position	BGO	VUE Point HD + Q. Clear	26	20.1
(34)	Discovery ST	3–4 MBq/kg body weight at 3 min per bed position	BGO	OSEM+ FORE-Iterative	15.7	9.3
(24)	Discovery MIDR	Propose using a DTP of 6	LSO + SiPM	OSEM+BSREM + Q. Clear A-TOF B- TOF+PSF	20	13
(18)	A-uMI780 B- uEXPLORER	Total-body PET/CT with half-dose is possible (1.85 MBq/kg at 2 min per bed position)	A-LYSO B-LYSO + SiPM	A-OSEM B-OSEM TOF+PSF	B-30 A-194	A-16 B-176
(20)	A-uMI780 B- uEXPLORER	FDG of 3.7 MBq/ kg is possible at 30–45 s acquisition time	A-LYSO B- LYSO + SiPM	A- OSEM B- OSEM TOF+PSF	A-30 B-194	A- 16 B- 176
(19)	uEXPLORER	Injected FDG reduction by 69.2% compared with that in the weight-based regimen of 3.7 MBq/kg.	LYSO + SiPM	OSEM TOF+PSF	194	176
(26)	uEXPLORER	Qualitatively	LYSO + SiPM	OSEM TOF+PSF	194	176
(21)	uEXPLORER	Ultra-low FDG activity injection (0.37 MBq/kg) in total-body PET/CT with 8 min acquisition time	LYSO + SiPM	OSEM TOF+PSF	194	176
(22)	uEXPLORER	Total-body PET/CT with half-dose (1.85 MBq/kg) FDG and 2-min acquisition time	LYSO + SiPM	OSEM TOF+PSF	194	176
(17)	uEXPLORER,	DTP of 14.01, 9.34, and 4.67 MBq min.kg^{-1} is possible	LYSO + SiPM	OSEM TOF+PSF	194	176

List of Abbreviation

ALARA	As low as reasonably achievable
FDG	18F-fluorodeoxyglucose
SNMMI	Society of Nuclear Medicine and Molecular Imaging
EANM	The European Association of Nuclear Medicine
DTP	Dose time product
FOV	The field of view

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AFOV	The axial field of view
OSEM	Ordered subset expectation maximization algorithm
Q.Clear	Bayesian penalized-likelihood Reconstruction algorithm
LORs	Line-of-responses
NECR	Noise equivalent count ratio
PSF	Point Spread Function
TOF	Time of flight
LYSO	Lutetium-yttrium oxyorthosilicate
LSO	Lutetium oxyorthosilicate
SNR	Signal to noise ratio
SiPM	Silicon photomultipliers
FDA	U.S. Food and Drug Administration
NN	The nearest neighbour algorithm
U-net	Convolutional neural network
BGO	Bismuth germanium oxide
PennPET	An extended field-of-view PET scanner
SUV	Standard uptake value
LBS	Lutetium-based scintillator

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