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Impacts of time interval on 18F-FDG uptake for PET/CT in normal organs

A systematic review

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Abstract

Background: To perform a systematic review of the effect of time interval on 2-deoxy-2-[18F] fluoro-D-glucose (18F-FDG) uptake in normal organs.

Methods: PubMed, EMBASE, Ovid, and Cochrane databases were searched to identity all potential eligible literature. The study characteristics and relevant data were extracted and analyzed. We adopted the effect size (ES) and the coefficient of determination (R^2) to best measure the magnitude of the relation between time interval and 18F-FDG uptake in normal organs.

Results: Seven articles and 860 participants were included. The time interval on liver and mediastinal blood pool were relatively medium (R^2=0.01–0.03, ES = –0.57 and –0.60) but noticeable (R^2 = 0.06, ES = –0.68 and –0.39), respectively. The uptake of 18F-FDG on cerebellum, spleen, bone marrow, muscle, bowel, and adipose remains to be verified as the rare studies. In addition, other factors such as body mass index and blood glucose level appeared to be important which also affect 18F-FDG uptake in normal organs.

Conclusion: The impact of time interval on SUVs in liver and mediastinal blood pool were relatively medium but clinically noticeable. More studies need to be done to solve the relation between the SUVs of other organs and time interval.

Abbreviations: 18F-FDG = 2-Deoxy-2-[18F]fluoro-D-glucose, ES = effect size, PET/CT = positron emission tomography/computed tomography, SUV = standardized uptake value.

Keywords: impact, normal organs, PET/CT, time interval

1. Introduction

Integrated positron emission tomography/computed tomography (PET/CT) is increasingly used in diagnosis, staging, therapy assessment, and follow-up of cancer patients.[1] In clinical practice, we evaluated the 18F-FDG images by qualitatively using visual comparison of the metabolism in lesions relative to normal tissues or semi-quantitatively by standardized uptake values.[2,3] There are many factors such as weight, blood glucose level, and time interval affecting the SUV on normal organs.[4]

18F-FDG uptake in normal tissues is used as the reference standard when assessing tumor treatment.[5] Until now, there are no clear consensus on the impact of time interval on the 18F-FDG uptake though some studies have found that the time interval had some influence on SUVs in some degree. According to the guideline of EANM, the recommended interval between FDG administration and the start of scanning is 60 minutes with an acceptable range of 55–75 minutes while the other suggested the time should be within 50–70 minutes after tracer injection.[6,7] Additionally, time interval was not control easily because of different aims of evaluating the disease in clinical trials. To increase the diagnostic accuracy, delayed FDG PET imaging has been processed and helped in differentiate malignancy from benign lesions.[8,9] Knowledge of the impact of time interval on the SUV of normal tissues is crucial for interpreting an FDG PET images, however, as far as concerned, there is no valid information on this phenomenon.

After many years of practical use of PET/CT, to what extent different time interval contributes to 18F-FDG uptake in normal organs has not been determined. The purpose of our study was to evaluate the impacts of time interval on 18F-FDG uptake in normal tissues.

2. Methods

2.1. Study design

We followed the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.[10] We conducted a search on PubMed, EMBASE, Web of Science, and Cochrane Library until October 2017 for studies reporting the association between the time interval and the uptake of 18F-FDG on normal organs. For the search, we used a combination of 4 themes of Key words: (PET/CT OR PET-CT) AND (standardized uptake value OR SUV) AND (normal OR healthy) AND (uptake interval OR time interval). Reference lists of relevant articles were also reviewed to identify further studies. Languages were restricted to English. It is not necessary to achieve an ethical approval because this is a meta-analysis.

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2.2. Study selection

The study selection process was performed independently by 2 reviewers, with any disagreements being discussed. Studies were eligible for inclusion if they met the following criteria: be a cohort study or cross-sectional study; investigate the association between influence factors including time interval and the uptake of 18F-FDG. We excluded according to studies in which 18F-FDG-PET was performed only CT (not PET/CT) and studies with others radiopharmaceuticals (not 18F-FDG).

2.3. Data extraction

Two researchers independently extracted relevant data from the eligible studies and disagreements were resolved by consensus or determined by a third author. For each study, the following data were extracted: authors, year of publication, country, samples, median ages, study design, SUV, time between 18F-FDG administration and scanning, reference standard, methods, results, and main conclusions.

2.4. Statistical analysis

We examined the relationship between maximum and mean standard uptake value (SUVmax/SUVmean) and time interval. We also evaluated other factors affecting SUV to identify potential confounding variables that could affect the relation of time interval on 18F-FDG uptake. The data from the included studies were seem not to be homogeneous and the effect of time interval on SUV was evaluated by 2 statistics: the effect size (ES) and the coefficient of determination (R^2). We can conclude the effect size by the difference between the mean SUVmax/mean of the early phase group verse the mean SUVmax/mean of delayed-phase group. The effect size were put into 5 grades: very small (<0.2), small (0.2–0.5), medium (0.5–0.8), large (0.8–1.2), and very large (1.2–2).[11] In addition, there is no validated tool to assess the risk of bias among cross-sectional studies.[12] Due to these limitations, we only make a system review between time interval and SUV instead of a meta-analysis.

3. Results

3.1. Literature search

Figure 1 showed the flowchart which summarized the process of study screen and selection. Overall, our literature search yielded 95 results, after exclusion of 21 by title or abstract and 53 duplicated studies; 7 met the qualified standard for evaluation.

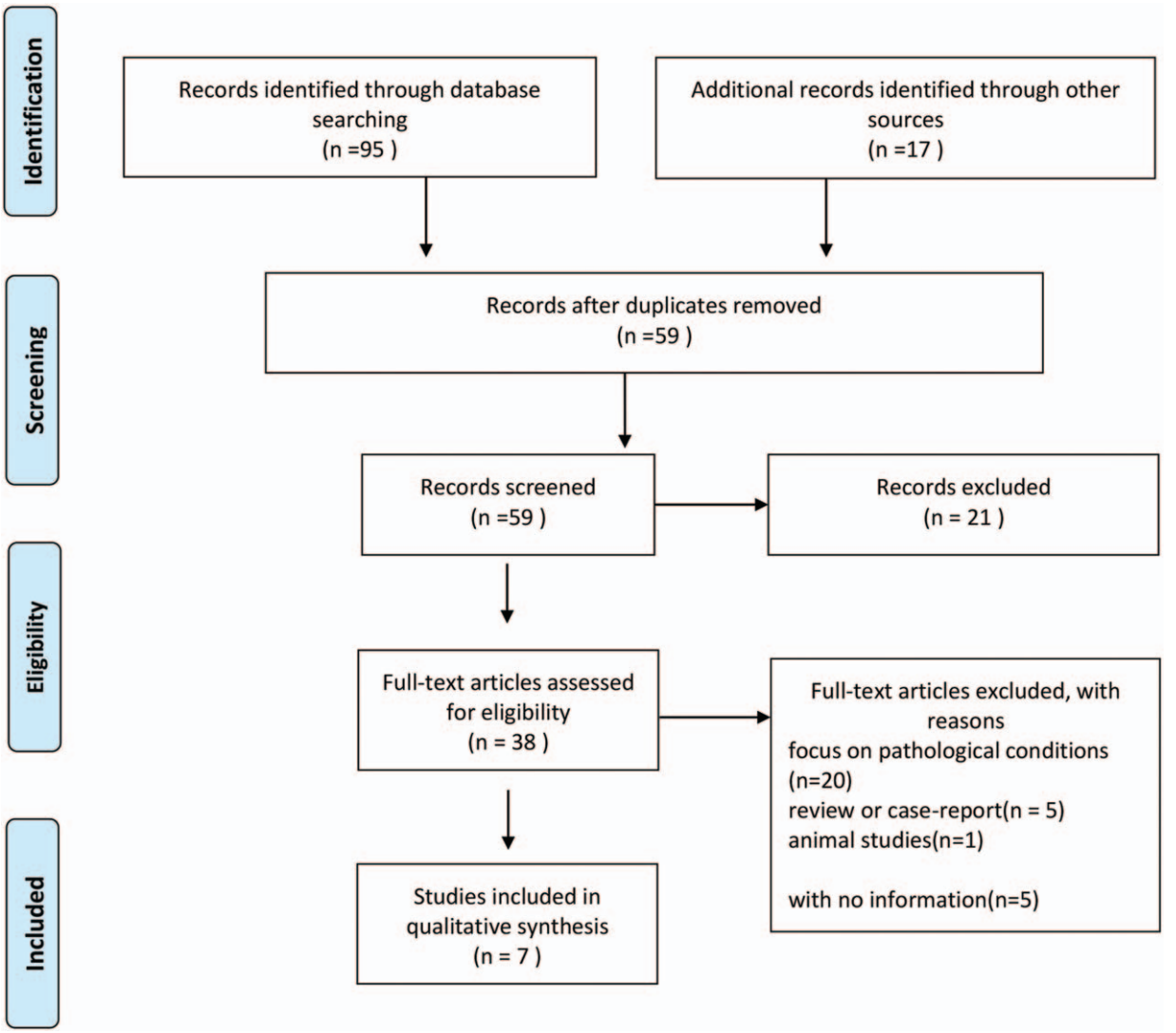

Figure 1. Flowchart of article selection.

Table 1

Study characteristics.

Study	Study design	Sample (n)	Fasting duration	FDG dose (range or mean ± SD), MBq	Uptake interval (range)	Organs affected by uptake interval (magnitude)	Not affected by uptake interval	Factors affecting SUV (organ)	Factors not affecting SUV
Malladi et al 2012, USA	R	Oncological patients (557)	4–6 h	462.5 ± 99.9 MBq	77.4 ± 18.6 min	Mediastinal (R^2 = 0.06), Liver (R^2 = 0.01)	—	Age, gender, BMI, glycemia, uptake interval	FDG dose, IV contrast, ethnicity
Kuruva et al 2012, India	P	Oncological patients (88)	6 h	N/A	75.92 ± 19.75 (51−160) min	liver (N/A)	mediastinal	Weight uptake interval	Age, gender, glycemia, DM
Mahmud et al 2015, Malaysia		Oncological patients (51)	6 h	327 ± 35.63 MBq	80.05 ± 55.57 min	Liver (R^2 = 0.03)	—	BMI, Age, Incubation period	FDG dose
Bennett B et al 2008, USA	R	Oncological patients (99)	N/A	6.7 MBq/kg	60 verse 180 min	Cerebellum (ES = 0.61), Spleen (ES = 0.22), Bone marrow (ES = 0.33), Muscle (ES = 0.34), Mediastinal (ES = −0.39), Adipose	Lung; liver	Uptake interval	N/A
Isabel et al 2013, spain	P	Oncological patients (15)	>6 h	7 MBq/kg	60 verse 180 min	Mediastinal (ES = -0.68)	N/A	Uptake interval	N/A
Akira et al 2011 japan	R	Healthy patients (39)	>5 h	3 MBq/kg	50 verse 100 min	Bowl (ES = 0.31), Liver (ES = −0.60)	N/A	Uptake interval	N/A
Eric et al 2011, France		Oncological patients (16)	6 h	358 ± 80 MBq	72 ± 12 verse 159 ± 20 min	Liver (ES = −0.57)	N/A	Uptake interval	N/A

? N/A = unclear, ↑ = positive correlation, ↓ = negative correlation, BG = blood glucose, BM = bone marrow, BMI = body mass index, DM = diabetes, ES = effect size, MSK = musculoskeletal, N/A = not available, P = prospective, R = retrospective, R^2 = coefficient of determination, SD = standard deviation.

In addition, a manual search of the reference lists within the retrieved articles did not yield any potential related studies on the electronic database. Finally, 7 articles met the inclusion criteria and were included.

3.2. Study characteristics

A summary of basic characteristics of individual study was presented in Table 1. Among them, 2 were conducted in United States, and each one in India, Malaysia, Spain, France, and Japan. The included articles comprised a total of 860 participants (mean, 58.74), most patients were referred for PET/CT due to all kinds of indications. Therein 2 were prospective cohort studies and 3 were retrospectively evaluated. Two evaluated the effect of different uptake interval on SUV measurements in liver and mediastinal.[13,14] Two separately evaluated the liver[15,16] and only 1 in mediastinal, bowel, and the whole body separately.[17–19] Uptake interval were recorded between the scanning and injection of 18F-FDG in all studies. Only 4 studies were performed by stratification according to uptake interval for subgroup comparison.[15,17–19]

3.3. Study quality

We can conclude the quality of the selected studies in Table 1. The designation of "not applicable" (NA) was used when the response to the item was negative or the item was not included in the study design. Among our selected studies, different sampling stratification was observed (e.g., some used an uptake interval <60 minutes or >180 min, whereas others didn't adopt the identical stratification), some studies chose only one or 2 tissues to analyses (e.g, liver or mediastinal blood pool) and a consistent statistical summary measurement (e.g., effect size) could not draw to identify the effect of uptake interval on SUVs. Therefore, we only processed a system review instead of Meta-analysis to evaluate the impact of uptake interval on SUVs.

3.4. Imaging parameters

There are various differences in imaging parameters among selected articles. Three articles used the injected dose per body weight (MBq/kg) as the unit of 18F-FDG dosage, but some articles chose mean 18F-FDG dosages which ranged consistently (327–462 MBq) and Kuruva et al[13] did not specify mean 18F-FDG dose.

Most of them, patients fasted for approximately 6 hours before 18F-FDG administration and PET/CT imaging. One fasting duration was 5 hours and the remaining one fasting time could not be indicated.[17] In addition, the blood glucose level among the articles are varied and the unit also is different. But except for one paper including patients are diabetes, the rest could be assumed to be normal according to existing guidelines. For these studies, PET/CT scanners were also different. Three reports used Siemens's PET/CT scanners (Siemens Medical Solutions, Erlangen, Germany): Biograph 64 TruePoint, Biograph LSO DUO, and Pico 3D.[16,18,19] Three used General Electric's PET/CT scanners (GE Healthcare, Waukesha, WI): Discovery ST, Discovery STE.[14,15,17] In addition, there also one which did not specify the used canner.[13]

3.5. Synthesis of results

This review including 7 studies evaluated the effect of uptake interval on 18F-FDG uptakes in 2 separate statistical approaches. Four studies sought significant difference in SUV or SUL between groups classified by uptake time (e.g., 60 minutes verse 180 min). So we can use effect size (ES) to assess objectively the effect of uptake interval in the early phase and delayed phase. Another 3 studies calculated the correlation between uptake interval and 18F-FDG uptake by Pearson's coefficients (r). For this case, we chose the R^2 values to calculate the association of the variables. Table 2 showed the results of some tissues on the association between uptake interval and SUV/SUL. The degree of this association and other factors whether or not affecting 18F-FDG uptake are shown in Table 1.

3.6. Effect of uptake interval on the liver

There are 5 authors reporting a significant effect of uptake interval on 18F-FDG uptake in the liver.[13–17] Among these, 3 adopted group analysis which PET imaging text performed at either early phase (50–60 minutes) or delayed phase (100–180

Table 2

Organ-specific analysis of the association between uptake interval and SUVmax/mean.

	Malladi et al 2012, USA	Bennett B et al 2008, USA	Kuruva et al 2012, India	Mahmud et al 2015, Malaysia	Isabel et al 2013, spain	Akira et al 2011 japan	Eric et al 2011, France
Cerebellum		↑					
Liver	↓	–	↓	↓		↓	↓
Blood pool	↓	↓	—		↓		
Muscle		↑					
Bone marrow		↑					
Spleen		↑					
Lung		–					
Bowel						↓	
Adipose		↓					

↑ = positive correlation, ↓ = negative correlation, — = no association.

minutes) and one were examined with multivariable regression. The uptake interval on liver are relative medium ($R^2 = 0.01$–0.03, ES = −0.57 and −0.60) with a progressive decrease with increasing uptake time. Kuruva et al reported similar finding based on multivariate analysis. Of note, there is one article which found no association between the uptake interval and FDG uptake based on one-way ANOVA.[17] In summary, 18F-FDG uptake in the liver is affected by uptake interval, it cannot be ignored as the degree of this effect is relatively medium.

3.7. Effect of uptake interval on the mediastinal blood pool

Three studies demonstrated a small-to-moderate negative association between mediastinal blood pool and uptake interval.[14,16,17] In addition, all of them used different statistical analysis to evaluate the impact of uptake interval on mediastinal blood pool 18F-FDG uptake ($R^2 = 0.06$, ES = −0.68 and −0.39). However, Kuruva et al showed that mediastinal blood pool 18F-FDG uptakes were not affected by any factors through multivariate analysis. Thus, we should keep the effect of time interval on the mediastinal blood pool in mind when therapy response is evaluated by PET/CT.

3.8. Effect of uptake interval on other tissues

One studies reported a physiological FDG uptake in the colon from the early to the delayed phase in PET/CT imaging (ES = 0.31).[19] In addition, Chin et al found that relation between uptake interval and cerebellum (ES = 0.61), spleen (ES = 0.22), bone marrow (ES = 0.33), muscle (ES = −0.34), and adipose (ES = −0.27). The 18F-FDG of lung were not influenced by time interval.[17]

3.9. Influence of other factors on 18F-FDG uptake

Many factors such as BGL, BMI, age, gender, and weight other than uptake interval were showed to affect 18F-FDG uptake.[24] Most studies including multivariate analyses have found that BGL has an important impact on brain.[20,21] With the BGL increasing, the uptake of 18F-FDG on brain is decreased. Compared to liver and mediastinal, although BGL has a small effect which seem to be ignored as clinical references.[22] Besides, 4 articles investigated the relation of BMI to SUV showed that BMI has an important effect on uptake of 18F-FDG.[14,16,20,21] However, there is no association between BMI and the heart in a multivariate analysis, so the uptake cannot be affected by the dose of 18F-FDG.[23]

4. Discussion

In summary, we systematically evaluated the evidence regarding the relationship between time interval and 18F-FDG uptake in normal organs. We have found that the time interval was relatively medium but noticeable on the liver ($R^2 = 0.01$–0.03, ES = −0.57 and −0.60) and mediastinal blood pool ($R^2 = 0.06$, ES = −0.68 and −0.39) with decreasing SUV with longer time. According to the rare studies on the impact in other organs, we cannot draw a consistent conclusion and further studies need to be done. In addition, some other factors such as body mass index and blood glucose levels were also found that have effect on 18F-FDG uptake; thus, these results should be taken into account when we evaluated the effects of time interval on the 18F-FDG uptake in different organs.

Compared to age, sex, and BMI, time interval may be easy to change in view of the difference among diseases and preparation of patients in clinical trials. Because of this variation, the recommended time interval of the PET Response Criteria in Solid Tumors (PERCIST) is 60 minutes with an acceptable range of 55–75 minutes. Moreover, another guideline on the PET scan suggests the start of scanning at 50–70 minutes after tracer injection. When a patient had repeating FDG PET/CT study, particularly in the assessment of therapy response, it is essential to keep time interval within 10 minutes or 15 minutes.[6,7] According to the varied time interval in clinical trials, the effect on quantitative and qualitative comparisons is very indispensable which therapy response made between the tumor FDG and background uptake. Tumor FDG uptake is seems to increase along with longer FDG time interval while the background uptake would decrease. This mechanism may be complex and one hypothesis may explain the fact that liver is filled with glucose-6-phosphatase resulting in continuous glycolysis and decrease in FDG retention and the mediastinal blood pool activity is thought to decrease because of the clear of FDG by the kidneys over time.[24,25] Based on this phenomenon, we take delayed-phase image to better display the lesions for some special disease. PERCIST also emphasized that liver should be normal to be used as a reference for the assessment of therapy response, in addition, the absolute or relative difference in SUVs between 2 studies is < 0.3 or 20% in serial studies.

Given the lack of evidence and literatures, we cannot found a convincing conclusion on the relationship between time interval and the SUV of cerebellum, lung, spleen, bone marrow, muscle, bowel and adipose. Although rare study separately found that time interval has positive effect on the SUV of cerebellum, lung, spleen, bone marrow, muscle, bowel and adipose. Thus, further

studies should focus on and find better background tissues, such as lung, which is easier to draw ROI than mediastinal blood pool and is less affected by time interval.

For other technological factors, such as image acquisition, reconstruction parameters, matrix size and difference on readers, has proved to affect the uptake of 18F-FDG.[26] To reduce these uncertainties, similar facility and procedure should be taken when repeating PET/CT for the assessment of therapy response. We also can take advantage of the computer science to create an automatic algorithm alike the novel autocorrecting procedure used in cardiovascular system in MRI and ultrasound.[27,28]

The limitation of our review included the amount and study designs of papers, the differences of the statistical reporting on the relationship between time interval and FDG uptake among studies, and the blood glucose level, FDG dose injected and fasting duration are considerably heterogeneous across the studies. Though these limitations, our findings are likely applied to a large number patient population.

5. Conclusion

The impact of time interval on SUVs in liver and mediastinal blood pool were relatively small but clinically noticeable. More studies need to be done to solve the relation between the SUVs of other organs and time interval.

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