Meta-Analyses on Technical Aspects of PET

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14.1 Introduction

In literature, there are few meta-analyses that have addressed technical and methodological issues concerning positron emission tomography (PET) imaging despite their important role in determining the quality of the diagnostic results [1–19].

14.2 Factors Affecting ^{18}F -FDG Uptake

The factors that may affect fluorine-18 fluorodeoxyglucose (^{18}F -FDG) uptake of normal tissues/organs and tumour lesions have been explored by three studies.

Wang et al. [1] demonstrated that the impact of time interval on standardized uptake value (SUV) in liver and mediastinal blood pool was relatively medium but clinically noticeable. Due to the rare studies, this relationship remains to be verified for other organs (cerebellum, spleen, bone marrow, muscle, bowel and adipose tissue).

Nevertheless, other factors such as body mass index and blood glucose level (BGL) appeared to be important in determining ^{18}F -FDG uptake in normal organs.

The effect of BGL on ^{18}F -FDG uptake and SUV has been more extensively explored by Eskian et al. [2] who demonstrated a correlation between increased BGLs and increased SUV_{max} and SUV_{mean} values in liver and blood pool. Conversely, an increase of BGL is significantly associated to lower SUV_{max} and SUV_{mean} in brain and muscle while both SUV values in tumours seemed to be affected, with significant reduction, only by BGL >200 mg/dl. The authors concluded suggesting that in patients with BGL lower than 200 mg/dl no interventions are needed for lowering BGL, unless the liver is the organ of interest. Nevertheless, new studies are warranted to evaluate sensitivity and specificity of ^{18}F -FDG PET for diagnosis of malignant lesions in patients with hyperglycaemia.

The uptake of ^{18}F -FDG in brown adipose tissue (BAT) is another finding that may affect the detection of tumour lesions. Hou et al. [3] demonstrated that gender, season and age are risk factors for ^{18}F -FDG uptake in BAT. In particular, the ^{18}F -FDG uptake rate was 2.16 times in females as that in males, 8.67 times in the minors as that in the adults and 1.94 times in winter as that in summer.

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14.3 Repeatability of the Quantitative Measurements

PET is widely used in oncology for the response assessment to treatment by the quantitative measurements of tracer uptake of the tumour lesions. For this purpose, the repeatability of these measurements in metabolic imaging is pivotal and needs to be established. Two studies dealt with the repeatability of the SUV estimation in tumour lesions [4, 5].

De Langen et al. [4] demonstrated that in ^{18}F -FDG PET imaging SUVmean had better repeatability performance than SUVmax. For serial PET scans, a combination of 20% as well as 1.2 SUVmean units was most appropriate threshold to identify a significant metabolic change in tumoural lesions. Nevertheless, both measures showed poor repeatability for lesions with low ^{18}F -FDG uptake since test-retest variability is affected by the level of ^{18}F -FDG uptake while tumour volume had minimal influence on repeatability. The authors recommend to report the evaluation of biologic effects in PET by using a combination of minimal relative and absolute changes of SUV.

The same group also analysed the response evaluation using ^{18}F -Fluorothymidine (^{18}F -FLT) [5]. In this case, the best repeatability was obtained using SUVpeak. Differences $\geq 25\%$ in ^{18}F -FLT SUV measurements likely represented a true change in tumour uptake. Nevertheless, larger differences are required for FLT metrics comprising volume estimates when no lesion selection criteria are applied.

The partial volume effect is another factor that may hamper accurate quantification of radiopharmaceutical uptake by tumour lesions leading to underestimations of SUV values and possibly compromising the lesion detection. A meta-analysis [6] investigated the clinical impact of the partial volume effect correction factor in oncological PET studies and in particular the potential benefit in its application for diagnosis, staging, prognostication and response assessment concluding that the accumulated evidence does not support routine application of partial volume correction in standard clinical PET practice.

14.4 Dual-Time-Point Imaging

A second late acquisition after conventional ^{18}F -FDG PET/CT imaging (dual-time-point technique) has been suggested to discriminate between inflammatory and neoplastic lesions. This approach is based on the evidence that in inflammatory lesions the ^{18}F -FDG uptake is characterized by a progressive washout after an initial trapping, while in tumour tissues, in particular before treatment, the uptake of the tracer increases over time. Two meta-analyses addressed this issue: both showed comparable performance between standard single-time-point and dual-time-point ^{18}F -FDG PET imaging in diagnosing pulmonary nodules [7] and in detecting lymph nodal metastases [8]. The results of the studies do not support the routine use of an additional late acquisition for these two clinical purposes.

14.5 Correlation Between Proliferation Markers (Ki-67) and Tracer Uptake in Tumours

Although ^{18}F -FDG is not a tumour-specific agent, several studies showed that ^{18}F -FDG uptake may be an index of biological aggressiveness of the disease. Nevertheless, whether ^{18}F -FDG PET imaging can be a marker of tumour cell proliferation remains controversial. Deng et al. [9] analysed pooled data from clinical studies focused on this issue. The results demonstrated a moderate positive correlation between ^{18}F -FDG uptake and tumour cell proliferation marker Ki-67 (combined correlation coefficient = 0.44) and suggested that ^{18}F -FDG SUV may be used as an indicator of the tumour proliferation and invasiveness. A subgroup analysis based on different tumour types showed varied degrees of correlation. The correlation was highly significant in thymic epithelial tumours; significant in gastrointestinal stromal tumours (GIST); moderate in lung, breast, bone and soft tissue, pancreatic, oral, thoracic, uterine and ovary cancers; average in brain, oesophageal and colorectal cancers; and poor in head and neck, thyroid, gastric and malignant melanoma tumours.

The correlation between ^{18}F -FLT uptake and Ki-67 was also investigated. Chalkidou A et al. [10] found sufficient data to support a strong ^{18}F -FLT/Ki-67 correlation only for brain, lung and breast cancer. The authors highlighted the importance of the methodology used to measure Ki-67 expression: the correlation was significant and independent of cancer type only when using Ki-67 average measurements, or measuring Ki-67 maximum expression on whole surgical samples.

14.6 Correlation Between ^{18}F -FDG SUVmax and ADC Values in Tumour Tissues

Apparent diffusion coefficient (ADC) is a parameter obtained by diffusion-weighted magnetic resonance imaging (MRI), reflecting the brownian movement of water molecules. The ADC value has been shown to link with the cell density, microvascular circulation and membrane integrity of a tumour tissue. Two meta-analyses [10, 11] examined the potential relationship between ^{18}F -FDG SUV that characterize the metabolic activity of tumour cells and ADC. Both studies found inverse correlation between ADC and SUV in patients with cancer. This inverse correlation, which was generally weak, appeared higher in the brain tumour, cervix carcinoma and pancreas cancer. However, larger prospective studies are warranted to validate these preliminary findings in different cancer types.

14.7 Diagnostic Performance of Hybrid Imaging in Oncology

After the introduction in the last years of hybrid scanners, many experiences indicated that the integration of functional and morphological imaging (hybrid imaging) provides additional diagnostic information useful in different clinical settings and particularly in oncology.

In a meta-analysis published by Gao et al. in 2013 [13], pooled data from comparative studies revealed that integrated PET/CT has higher sen-

sitivity (0.95 vs 0.85) and similar specificity (0.96 vs 0.95) with respect to PET alone in the detection of distant metastases. Analogous results were obtained comparing integrated PET/CT with CT alone (sensitivity 0.97 vs 0.80 and specificity 0.97 vs 0.94, respectively), confirming the additional value of the PET/CT hybrid imaging in tumour staging.

More recently published data suggested a complementary role of ^{18}F -FDG PET/CT and MRI in oncological patients. Miles et al. [14] compared these two imaging modalities in patients with suspected residual disease or recurrent tumours. PET demonstrated greater sensitivity for detecting lymph nodal recurrence, whereas MRI was more effective than PET/CT in the detection of skeletal and hepatic recurrence. A review of studies assessing therapeutic impact of PET/MRI suggested a greater likelihood for change in clinical management when PET/MRI was used for assessment of suspected residual or recurrent disease rather than tumour staging. Supplementing the evidence-base data for ^{18}F -FDG PET/MRI with studies that compared the components of this hybrid technology separately, ^{18}F -FDG PET/MRI is likely to be clinically effective for the investigation of patients with suspected residual or recurrent cancers.

Xu et al. [15] demonstrated that ^{18}F -FDG PET/CT has similar patient-based sensitivity (0.85 versus 0.85) and specificity (0.96 versus 0.97) to MRI in the detection of distant metastases. Similar lesion-based performance was also estimated (PET/CT sensitivity and specificity: 0.85 and 0.90 and MRI sensitivity and specificity: 0.88 and 0.89). The analysis of a small number of studies indicated that the combined use of these two modalities may have higher patient-based sensitivity (0.89) than PET/CT (0.82) and whole body MRI (0.81) alone, suggesting that the combined use of these two modalities may provide more benefit than PET/CT and MRI alone.

Finally, Shen et al. [16] after analysing the results of 38 studies that involved 753 patients and 4234 lesions concluded that PET/MRI has excellent diagnostic potential for the overall detection of malignancies in cancer patients. On a per-patient level, the pooled sensitivity and

specificity were 0.93 and 0.92, respectively. On a per-lesion level, the corresponding estimates were 0.90 and 0.95, respectively.

14.8 Varia

The ^{18}F -FDG PET/CT imaging has been defined by several authors as more accurate than standard radiological imaging in evaluating the response to treatment in oncological patients, in particular when a residual mass is still detectable. Kim et al. [17] compared the tumour response assessment according to the metabolic criteria developed by the European Organization for Research and Treatment of Cancer (EORTC) and morphologic criteria (RECIST1.1.) in patients with malignant solid tumours. The pooled analysis of 181 patients recruited from seven studies demonstrated a moderate agreement of tumour responses between the RECIST and EORTC criteria ($k = 0.493$). The level of agreement was not affected by the anti-cancer treatments (chemotherapy or targeted therapy). A disagreement was found in 66 of 181 patients (36.5%). Tumour response was upgraded in 54 patients and downgraded in 12 when adopting the EORTC criteria. The estimated overall response rates were significantly different between the two criteria (52.5% by the EORTC vs. 29.8% by the RECIST, $p < 0.0001$). The conclusions confirmed that the metabolic findings are more sensitive than the morphologic criteria to detect tumour response to the treatment.

The PET/CT imaging with radiolabelled choline is a reliable tool for the detection and localization of recurrent disease in patients with prostate carcinoma. A meta-analysis by von Eyben et al. [18] investigated whether the use of different tracers, ^{11}C -choline (^{11}C -Cho) and ^{18}F -fluorocholine (^{18}F -FCH), may provide different diagnostic performance. The detection rates of metastatic sites in studies with ^{11}C -Cho and ^{18}F -FCH did not differ significantly. The radiation activity of ^{11}C -Cho and ^{18}F -FCH injected was not significantly associated with the detection rate of extra-prostatic lesions. The authors concluded that the detection of metastatic lesions in patients with biochemical recurrence (PSA levels of 1–10 g/ml) was clinically relevant when

performed by PET/CT with radiolabelled choline regardless of the radiotracer injected.

The introduction of hybrid medical imaging technology has transformed the practice of diagnostic nuclear medicine and nowadays PET/CT and single photon emission computed tomography/computed tomography (SPECT/CT) have wide acceptance for many clinical investigations. A concern with PET/CT and SPECT/CT imaging is the combined radiation doses from both radiopharmaceutical and X-ray CT components. Therefore, it is imperative to implement a radiation dose optimization process to protect patients from unwarranted high radiation burdens. Alkhybari et al. [19] systematically reviewed data published in literature to determine the variations in reported national diagnostic reference levels (NDRL) methodology and values for adult PET/CT and SPECT/CT procedures. Discrepancies were found between the methodologies applied to establish and report both PET/CT and SPECT/CT NDRLs. In particular, the authors remarked the opportunity for hybrid imaging to report both radiation doses from the radioactivity injected and the CT dose rather than a separate NDRL. They concluded that further researches should be focused on reporting more NDRLs for hybrid examinations to collect enough data to establish a robust NDRL standard for the CT portion in PET/CT and SPECT/CT examinations.

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