Review Article

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The Use of PET-CT in Rheumatology

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Abstract: Positron emission tomography (PET) is a sensitive imaging tool that gives quantitative measure of underlying inflammation. Computed tomography (CT) scan used in combination with PET further helps to delineate the anatomical structure. PET-CT can be helpful for the early diagnosis of rheumatic diseases by pattern recognition, but its role in disease monitoring still needs further evaluation. It is not a fast track solution for all because of different sensitivity and specificity to different diseases, relative high cost, and radiation exposure to the patients.

Keywords: PET-CT, inflammatory diseases

1 Background and technical aspects of PET-CT

Positron emission tomography–computed tomography (PET-CT) is the fusion of functional and anatomic scan that acquired almost simultaneously. It helps us to visualize the form and activity of potential diseases within the body. It is now a popular nuclear imaging modality for the evaluation of cancer, fever or inflammation of unknown origin. The differential diagnosis sometimes includes the rheumatic disorders. It is based on the fact that the glucose transporters are up regulated on cell membrane secondary to the hypoxic drive in the highly proliferative cells such as tumor or aggregated inflammatory cells. The increase in metabolism of these cells can be reflected by the increased uptake of radiolabeled glucose such as $^{18}$fluorine-2-fluoro-2-deoxy-d-glucose ($^{18}$F-FDG) [1].

Inside the machine, there is a PET portion which is physically mounted together with the CT system. PET images are fitted with various crystals called scintillators (bismuth germanium oxide, lutetium oxyorthosilicate, and cerium-doped gadolium oxyorthosilicate). These scintillators are used to detect the gamma rays emitted from those foci that concentrated with the radiolabeled glucose (Figure 1). They will convert gamma rays to light signals and followed by electric signals that can be displayed on a monitor. However, photons originated from structures deeper in the body are more attenuated than those originating closer to the surface. This attenuation can leads to false interpretation. In order to correct this, the CT scan can generate an attenuation map or coefficients that can be used to correct this attenuation effect. Once scaled, they can be applied to the emission data to obtain the attenuation-corrected image. Apart from improving the image quality, this correction process is also essential.

Figure 1: Positrons emitted from positron-emitting radionuclide (e.g., $^{18}$F-FDG) annihilate with electrons and emit gamma ray, which is detected by scintillators in PET system (http://www.hamamatsu.com/eu/en/technology/innovation/pet/index.html).

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for quantification that generates standardized uptake values (SUV). Abnormal PET activity should also be interpreted by comparing with background organ activity such as liver. There are slight variations among different centers because of different FDG activity used, different injection time, different size and site of the lesion(s) under investigation [2]. In general, the cut-off of SUV of >2.5 (g/ml) would be regarded as significant.

Usually, the CT scan is done after the PET scan. Some centers will perform contrast-enhanced CT scan focus only on the part of that showed abnormal uptake(s) in the PET scan as to reduce the overall radiation exposure. CT provides additional anatomical details and thus combination of PET and CT offers better accuracy. For example, the sensitivity of a solitary lung lesion by CT alone and PET alone was 74%, respectively, while the combination of two scans increased the sensitivity up to 93% [3].

2 Potential use of PET-CT in rheumatic conditions

2.1 Large vessel vasculitis (LVV)

PET-CT is useful for early diagnosis of large vessel vasculitis (LVV) (Figure 2 and 3). Muto et al. evaluated the use of PET-CT for elderly with inflammation of unknown origin [4]. About 10.5% of them were diagnosed to have LVV, while most of them did not have specific symptoms at presentation. Patients with LVV were also found to have significant higher aortic wall SUV compared with the controls. In the systematic review that included 21 studies (413 patients, 299 controls), FDG-PET had a pooled sensitivity at 90% and a pooled specificity at 98% for giant-cell arteritis (GCA). In the same review that included 7 studies and 191 patients, the pooled sensitivity and specificity were 87% and 73%, respectively, for Takayasu’s arteritis (TA) [5]. Another systematic review by Treglia et al. also suggested that PET-CT was superior over conventional imaging methods in early diagnosis of LVV [6]. It is particularly useful in diagnosing non-cranial GCA or GCA with negative temporal biopsy.

However, the value of disease monitoring by PET-CT in LVV was not yet well established. Moreover, there were some different findings between GCA and TA. Blockmans et al. performed a prospective study on the use of PET in 35 patients with biopsy-proven GCA. PET scans were performed at the point of diagnosis before any treatment and 3 and 6 months after treatment. FDG uptake decreased substantially and paralleled to the decrease in inflammation parameters from diagnosis to 3 months of therapy, but there was no further decrease at 6 months. And the difference of FDG in those relapsed compared to those remained in remission was not significant [7]. The persistent FDG uptake might be due to vascular remodeling, atherosclerosis, and partial disease activity. Therefore, PET had limited value in assessing disease activity over time in GCA. On the other hand, FDG uptake correlated with clinical disease activity and markers of inflammation in TA. And the maximum SUV was significantly higher in patients relapsing despite treatment than those who in remission [8]. But its use for follow-up of patients with TA was limited by accumulating radiation risk, which is a particular concern as patients are younger.

2.2 Small vessel vasculitis

The role of PET-CT in antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis was once questioned as its spatial limitation was only around 4 mm in diameter for vessels. A recent retrospective review by Michael J. Kemna et al. suggested it was in fact useful especially when biochemical parameters were inconclusive [9]. Although it could not differentiate active vasculitis activity from infection, it helped to choose the site for biopsy for further evaluation. They reported a case of cryptococcal myositis in ANCA-associated vasculitis during the intensive immunosuppressive treatment. It was first detected by PET-CT scan and subsequently confirmed by biopsy and culture. Another review by Soussan et al. suggested that it is more sensitive for granulomatous...
polyangiitis compared with microscopic polyangiitis and eosinophilic granulomatous polyangiitis [10]. But glomerulonephritis and vasculitis activity on skin, nerve, and eyes could be missed in PET scan.

2.3 Inflammatory myopathy

The sensitivity of PET for inflammatory myopathy as reflected by FDG uptake at muscle was only 33–66% [11,12]. It is inferior as a diagnostic tool when compared with electromyography, muscle biopsy, and magnetic resonance imaging (MRI), but it has the additional advantage of detecting underlying malignancy and interstitial lung disease (Figures 4 and 5) [11]. Risk of malignancy is the highest in the first 3 years of diagnosis. From a prospective study on 55 patients with recent diagnosis of myositis, the overall predictive value of tumor screening by a single PET-CT scan was as good as that of the conventional cancer-screening package (which included physical examination, blood tests for tumor markers, CT thorax and abdomen with contrast and gynecological examination for women) [13].

2.4 Adult onset Still’s disease (AOSD)

PET-CT showed high SUV in bone marrow (100%), spleen (90.9%), lymph nodes (80.0%), and joints (75.0%) in adult onset Still’s disease (AOSD) [14]. Less commonly, high uptakes could also be seen in pericardium, pleura, salivary glands, eyelids, muscle, and major blood vessels. The pattern of SUV helps to guide the diagnosis of AOSD when combined with clinical features. Although PET-CT
cannot differentiate AOSD from lymphoma, it aided to choose the appropriate site for biopsy, for example, lymph nodes and bone marrow [15]. SUV would be reduced after successful treatment. The SUV of spleen was reported to be correlated with serum lactate dehydrogenase and reflected disease activity [14].

2.5 Relapsing polychondritis (RPC)

Relapsing polychondritis (RPC) is rare, and its early diagnosis is difficult. But in case of RPC, FDG accumulation would be shown at cartilage areas including tracheobronchial trees, costal cartilage, joints, larynx, nasal cavity, paranasal sinuses, and auricles [16]. It might reveal nasal or bronchial inflammation even before the airway symptoms. This specific pattern of uptake helps the early diagnosis of RPC and also helps to differentiate disease relapse from other causes of fever in patients on high-dose immunosuppressive therapy [17].

2.6 IgG4-related disease (IgG4-RD)

IgG4-related disease (IgG4-RD) is an immune-mediated inflammatory disorder involving multiple organs. It is a clinical–pathological diagnosis, and thus it is important to allocate the inflammatory lesions for biopsy and to rule out malignancy. More than 90% of patients showed multiorgan involvement in PET-CT. And PET-CT was shown to be more sensitive than ultrasonography (USG) or CT alone [18]. The pattern of pancreas, salivary glands, retroperitoneal region, and vascular wall involvement would prone the diagnosis to IgG4-RD rather than metastasis and guide the biopsy site(s) for further confirmation. PET-CT also has a role in disease monitoring. It could detect active disease in those with normal C-reactive protein, which was common in IgG4-RD. The disappearance of FDG uptake correlated with treatment response [19].

2.7 Polymyalgia rheumatica (PMR)

PET is sensitive in detecting synovitis and bursitis at shoulders and hips [20]. Yamashita et al. found that uptakes at ischial tuberosities, greater trochanters, and lumbar spinous process were commonly seen in polymyalgia rheumatica (PMR). Positive results at two of these three sites would be even more specific than uptakes just at shoulders or hips joints for diagnosing PMR without compromising its sensitivity [21]. It could also help to differentiate PMR from elderly onset rheumatoid arthritis (RA) by pattern recognition. Uptakes at ischial tuberosities and interspinous process were common for PMR but not elderly onset RA, while uptake at wrists were common for RA but not PMR [22].

2.8 Rheumatoid arthritis (RA)

Beckers et al. reported that the sensitivity of PET on active inflamed joints, which were defined by clinically swollen tender joints with positive ultrasound (USG) doppler signals, in established RA was up to 90% [23]. The SUV correlated with the clinical severity in terms of disease activity score 28 [24]. There were significant differences in SUV between the active inflamed joints and the joints in remission [25]. The recent advance in PET scan for the detection of arthritis was using macrophage tracer 11C-(R)-PK11195 to detect subclinical arthritis in RA. It was reported to be more sensitive than MRI in detecting subclinical disease activity and predicting the risk of flare in patients with clinical remission [26]. The advantage of PET scan over other imaging modalities is that it scans all the joints in one session, including the high-risk lesion at atlantoaxial joint [25]. It also helps to differentiate RA from other connective tissue diseases by pattern of distribution [27].
2.9 Spondyloarthopathy (SpA)

PET is useful to detect enthesitis. Taniguchi et al. found that the maximum SUVs at the entheses of lumbar spinous process, pubic symphysis, and ischial tuberosities were statistically higher in spondyloarthopathy (SpA) when compared with RA [28]. It was also sensitive to pick up sacroiliitis in active AS when using subjects with mechanical low back pain as control. The sensitivity of PET for sacroiliitis was up to 94% in the patients with grade 3 sacroiliitis by X-ray [29]. High SUV in sacroiliac joints helps to differentiate SpA from seronegative RA and PMR [30]. SUV decreased after successful treatment and correlated with clinical severity.

2.10 Limitations of PET-CT

Cancer detection by PET-CT was generally sensitive for lung, lymphoma, melanoma, colorectal cancers, and head and neck tumors, whereas the evidence in the detection of gynecological cancers was sparse [31]. Low sensitivity was observed for carcinoma of stomach (37.9%) [32] and extrahepatic cholangiocarcinoma (60%) [33]. It could be false reassuring in some cases. Furthermore, the use for cancer screening in general population was still under debate because many benign lesions such as supraclavicular fat pads, nodular goiter, and benign prostat hypertrophy could also be shown as high uptakes. It could lead to unnecessary and potentially invasive investigations with extra cost, risks, and anxiety to patients [34].

PET-CT is one of the expensive imaging modalities. It is only available in few tertiary public hospitals in Hong Kong for staging of lung cancer and lymphoma. For other indications, it still needs to be paid by patients or to be done in private settings.

Apart from cost, there was also concern on radiation exposure. The radiation from PET-CT is 13.5–32 mSV depending on different protocols. It is approximate to 675–1,600 chest X-rays. Estimated cancer incidence induced by radiation is 0.0048% per mSV, on an average, taking into account and that younger age will have higher cumulative risk. One Hong Kong study suggested that the associated lifetime cancer incidence for patients who are 20 years of age was estimated to be up to 0.622%. This is not negligible from the view of public [36]. Thus, ordering a PET-CT should be clinically justified.

3 Conclusion

PET-CT is useful for diagnosing the rheumatic disease especially when the presentation, serology, and clinical pattern are inconclusive. It has the potential advantage of including the whole body in one scan and being sensitive to detect certain types of malignancy. However, it is still expensive and its role in disease monitoring is controversial.

References


