Role of FDG-PET/CT in the evaluation of infectious and inflammatory disease

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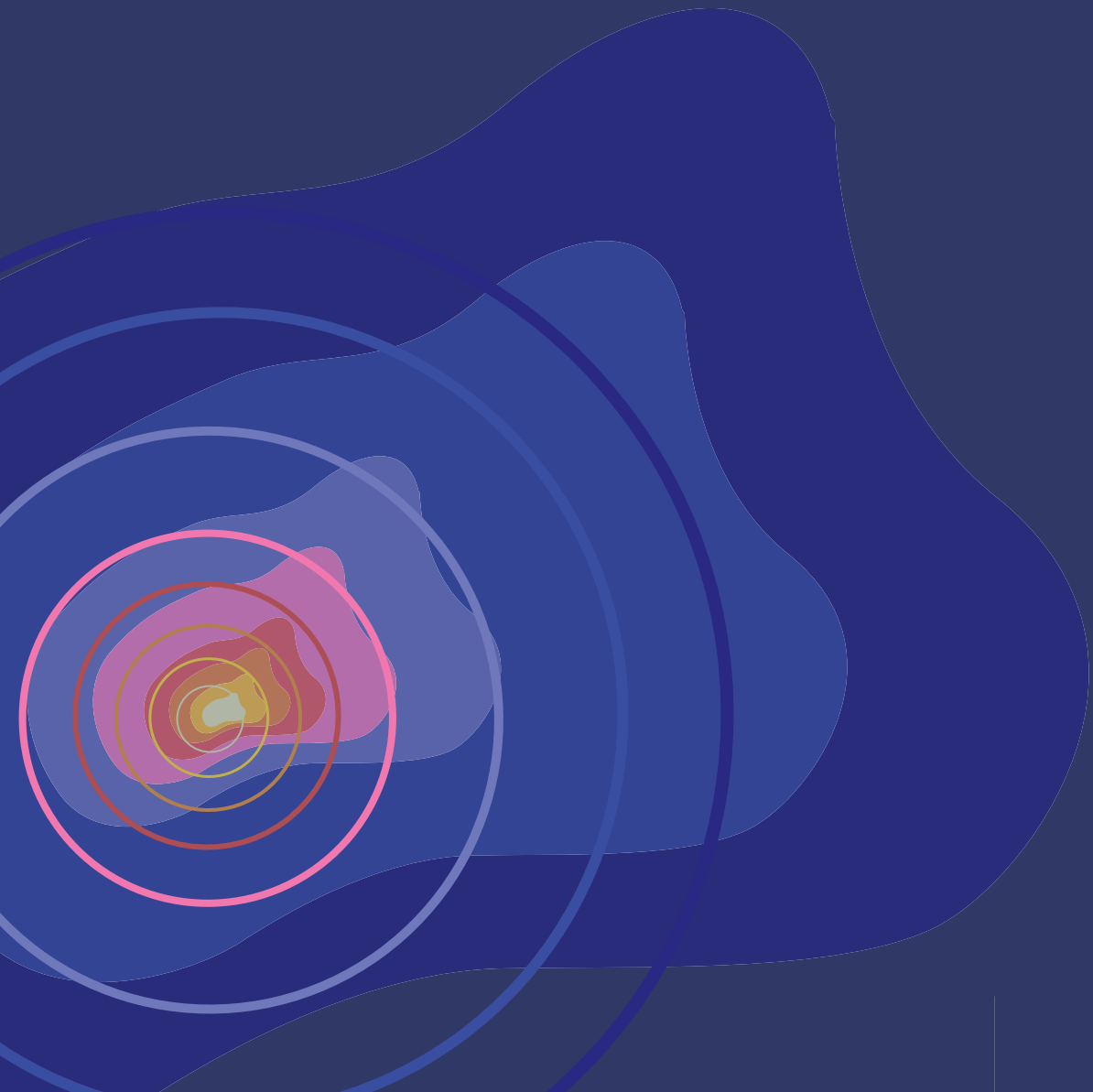
CHAPTER 12

Summary, general discussion and conclusion



SUMMARY

In **Chapter 1**, an introduction is given about the physics behind Positron Emission Tomography (PET) and an explanation about why this technique can be applied in diagnosing infectious and inflammatory disease using Fluorine-18 labeled glucose (^{18}F-FDG). As most infectious and inflammatory processes attract white blood cells and other inflammatory cells which consume more glucose than surrounding tissue, these diseases can often be visualized on FDG-PET/CT. An outline of the thesis is given as well.
Chapter 2 comprises a descriptive study about the use of PET/CT for personalized management of infectious diseases. This chapter can be regarded as a more in-depth introduction to the thesis, as many relevant diseases are discussed. These include the use of FDG-PET/CT in bloodstream infection of unknown origin, infective endocarditis, vascular graft infection, spondylodiscitis, and cyst infections. Upcoming technological advances such as total body PET/CT and infection-specific radiotracers are discussed as well.
Chapter 3 describes a retrospective study about factors affecting the diagnostic yield of FDG-PET/CT in patients with a bloodstream infection. In this study, 185 patients were included with a bloodstream infection who underwent FDG-PET/CT to determine the focus of infection.
In 120 out of 185 patients (65%), the infection focus could be identified on FDG-PET/CT, with a high sensitivity (80.2%) and specificity (79.6%). FDG-PET/CT was less likely to detect the infection focus in patients who were treated with antibiotics for more than 7 days. Between 0 and 7 days of antibiotic treatment, an infection focus was found in 71% of patients. In patients who were treated with antibiotics for 8 to 14 days, the infection focus was found in 52% of cases. Finally, in patients being treated with antibiotics for more than 22 days, the infection focus was found in only 38% of patients. The odds of detecting an infection focus on FDG-PET/CT was also lower in patients with blood cultures positive for Enterococci.
One of the diseases highlighted in this thesis is Autosomal Dominant Polycystic Kidney Disease (ADPKD). This is a disease where patients have progressive cyst development in their kidneys and often their liver as well, ultimately leading to kidney and/or liver failure. Approximately half of these patients develop a cyst infection at some point, but these are very difficult to diagnose with conventional imaging. **Chapter 4** describes a retrospective study which included 30 patients with ADPKD who underwent FDG-PET/CT for the evaluation of a potential cyst infection. In 24 out of our 30 patients, the infection focus was found on FDG-PET/CT. In 19 of those cases, a cyst infection was found. This resulted in a sensitivity of 89% and specificity of 75% for diagnosing cyst infection on FDG-PET/CT. In 63% of patients, FDG-PET/CT also resulted in a change of antibiotic regimen, for example switching to fluoroquinolones, which are more lipophilic than other antibiotics, allowing them to cross cystic walls and treating these infections.
Chapter 5 concerns a pictorial essay on FDG-PET/CT for the evaluation of cyst infection. The FDG-PET/CT images of five interesting patients are discussed, including two true positive cases, one true negative case, one false positive case, and one false negative case. The clinical

indications for performing FDG-PET/CT in cyst infection and reasons for false positive or false negative results are discussed, such as renal malignancy. The treatment consequences of the FDG-PET/CT scan are discussed as well.

Chapter 6 entails a case study including three patients with Lemierre syndrome who underwent FDG-PET/CT. This is a relatively rare syndrome where patients with a pharyngeal infection develop septicemia and internal jugular vein thrombosis, followed by septic emboli. Fusobacterium necrophorum is usually the causative pathogen, but other pathogens are also possible. The conventional imaging of the included patients is compared to the FDG-PET/CT images, along with the treatment consequences of FDG-PET/CT and patient outcomes.

Chapter 7 presents a retrospective study on the use of FDG-PET/CT in intensive care patients with bloodstream infection. 30 intensive care patients were included, who underwent FDG-PET/CT to determine the focus of their bloodstream infection. In 21 patients, an infection focus was found, which led to changes in clinical management, such as percutaneous drainage or surgery, in 14 patients. FDG-PET/CT reached a sensitivity of 91% and specificity of 88% for identifying the infection focus. PET image quality, based on a three-point Likert scale, was significantly associated with detecting the infection focus. The most common causes for poor image quality were inadequate preparation for FDG-PET/CT (for example, not stopping all intravenous glucose administration at least six hours before FDG-PET/CT, which can be challenging if patients receive multiple intravenous solutions through multiple pumps), and kidney failure, leading to reduced background clearance of FDG. Because intensive care patients have to be constantly monitored, reducing scanning time with total body PET/CT systems would greatly benefit the use of FDG-PET/CT in intensive care patients, also in terms of logistics. No adverse events were reported in the patient cohort.

Chapter 8 describes a retrospective quantitative study about the clinical implications of increased FDG uptake in the bone marrow and spleen on FDG-PET/CT in patients with bacteremia. The study was conducted because this 'hypermetabolism' of the bone marrow and spleen can be noted in some patients, without a clear explanation. 145 patients were included, from whom several quantitative measures were taken in the bone marrow, liver, and spleen. The strongest statistically significant factors associated with high FDG uptake in the bone marrow were a higher CRP (due to a higher inflammatory response), younger age (because of more hematopoietically active red marrow), and a cardiovascular infection focus such as endocarditis or vascular graft infection.

Chapter 9 displays a retrospective study on the role of FDG-PET/CT in children with fever of unknown origin. This was defined as fever for more than 8 days, where no probable cause could be established despite history taking, physical examination, and laboratory work-up. 110 children with fever of unknown origin were included. In 68 children, the definitive cause of fever was eventually found, and in 53 children this was based on the FDG-PET/CT result. The causes included a wide range of diagnoses, of which the most important ones were endocarditis, systemic juvenile idiopathic arthritis, inflammatory bowel disorder, cholangitis,

and post-transplant lymphoproliferative disease. FDG-PET/CT reached a sensitivity of 86% and specificity of 79% for detecting the cause of fever. A higher CRP and lower leukocyte count were associated with a higher odds of detecting the cause of fever on FDG-PET/CT.

Chapter 10 highlights a retrospective study on the importance of glucose management before FDG-PET/CT in patients with bacteremia of unknown origin. The research hypothesis was that a higher serum glucose would lead to a lower odds of detecting an infection focus on FDG-PET/CT, because of direct competition between FDG and serum glucose at glucose binding sites of infection foci. 322 patients with bacteremia of unknown origin were included, who underwent FDG-PET/T to identify the source of infection. In patients with a serum glucose between 3.0 and 7.9 mmol/L, the true positive detection rate of FDG-PET/CT varied between 61-65%. In patients with a serum glucose between 8.0 and 10.9 mmol/L, the detection rate decreased to 30-38%. Finally, in patients with a serum glucose above 11.0 mmol/L, the detection rate was only 17%. Current PET/CT guidelines in infection imaging recommend an upper glucose threshold of 11.0 mmol/L. However, the results indicate that a lower glucose threshold before FDG-PET/CT imaging for infection should be maintained.

Chapter 11 presents a review on the limitations and pitfalls of FDG-PET/CT imaging in infection and inflammation. The general limitations of FDG-PET/CT are discussed, such as the non-specificity of FDG for infection and inflammation (especially directly post-operatively when patients exhibit post-surgical inflammation). Additionally, the need to synthesize ^{18}F-FDG daily due to its half-life of 110 minutes, the patient preparation time, including fasting for at least 6 hours or even 24 hours with cardiac imaging, and cessation of all intravenous glucose and insulin therapy in time are discussed. More specific limitations are highlighted as well, including increased FDG uptake of the colon when patients use metformin, increased FDG avidity of the gastro-intestinal tract due to peristalsis, increased FDG avidity of the ovaries and endometrium during ovulation or menstruation, decreased background clearance of FDG due to kidney failure, FDG accumulation in the urinary tract due to FDG excretion, and challenges with imaging of moving organs such as the lungs or heart. Several solutions for these limitations are discussed as well, such as performing ECG-gated or respiratory-gated PET/CT, dietary precautions, and proper insulin management before FDG-PET/CT in case of hyperglycemia. Taking all these limitations and possible solutions into account may lead to a higher sensitivity and specificity of FDG-PET/CT for the imaging of infection and inflammatory disease.

DISCUSSION

Current applications of PET/CT in infectious and inflammatory disease

Over the past decades, PET/CT has acquired an increasingly important role in the management of many infectious and inflammatory diseases[1,2]. For example, FDG-PET/CT is now routinely performed in patients with high risk Staphylococcus aureus bacteremia to identify the focus of infection or potential septic infection foci, in suspected vascular graft infection, in suspected endocarditis, and suspected infection of foreign bodies such as artificial hips or knees[3]. More and more hospitals and policy makers have included the use of FDG-PET/CT in their standard diagnostic protocols and flowcharts for (suspected) infectious and inflammatory disease[4]. This can be attributed to accumulating evidence showing the use of FDG-PET/CT is cost effective in many infectious diseases, and yields higher sensitivity and specificity compared to other diagnostic examinations[5]. As PET/CT can be applied to numerous other diseases (metastatic spread in cancer and response to chemotherapy, cardiac metabolism after myocardial infarction), and healthcare manufacturers offer many types of PET/CT machines, more and more hospitals nowadays own PET/CT scanners to be able to perform these FDG-PET/CT examinations themselves, or have contracts with more specialized hospitals where patients can be referred to for PET/CT . Especially considering the ageing population and an increasing prevalence of patients with vascular grafts, hip and knee replacements, implantable cardioverter-defibrillators, immunocompromised status after organ transplantation or use of immunosuppressive drugs, FDG-PET/CT will continue to play a key role in the management of infectious disease[6]. Currently, it is the only imaging modality that can offer whole-body evaluation within an hour and exclude or confirm a wide range of differential diagnoses in patients who present with an infectious profile and multiple potential sources of infection, without the need for invasive procedures such as punctures or biopsies, and even before anatomic changes such as abscess formation have occurred[7].

While FDG-PET/CT shows a high diagnostic value in numerous infectious and inflammatory diseases, it also has its disadvantages, as has been previously described in this thesis[8]. The most important disadvantage of using FDG as a radiotracer in PET/CT, is that glucose is the main fuel source of the human body and occurs in virtually every cell. FDG-PET/CT is aimed at detecting elevated glucose utilization anywhere in the body. Because many processes and diseases can cause elevated glucose uptake, it can sometimes be difficult to distinguish between infection and sterile inflammation of foreign bodies like vascular stents or artificial hips, and distinguish physiological postoperative changes from infection[9]. However, FDG uptake patterns can be used to distinguish between the two, where diffuse FDG uptake is more associated with sterile inflammation, and focal FDG avidity with infection[10].
FDG-PET/CT is currently less suitable in an acute setting where patients may present septic, as patients have to fast for 4-6 hours before FDG-PET/CT, and FDG-PET/CT is usually only

performing during business hours because it is a more advanced exam requiring synthesis and proper handling of the radiotracer FDG, requiring special training of healthcare providers[11,12]. These factors also limit the capacity for FDG-PET/CT in most hospitals. While it is not possible to overcome all of these limitations, there are several developments that will further improve the diagnostic value of FDG-PET/CT in infectious and inflammatory disease.

FUTURE APPLICATIONS OF PET/CT

Infection specific radiotracers

As elevated FDG uptake is not specific for infection, it would be very interesting to perform PET/CT with more infection-specific radiotracers. Multiple studies have been performed or are still being performed to discover new radiotracers with a higher specificity for infection. Patients with a suspected foreign body infection such as an artificial hip or vascular graft, could be imaged with radiolabeled antibodies against the known or suspected bacterial strain. For example, antibodies against Staphylococcus aureus could be labeled with Zirkonium-89, and increased uptake of the foreign material could provide a high specificity for infection with Staphylococcus aureus[13,14]. Metabolic properties of bacteria could also be utilized. For example, sorbitol labeled with ^{18}F could be used to detect Enterobacteriaceae, which could show the focus of infection in patients with an Escherichia coli bacteremia[15]. When foreign bodies such as artificial hips or heart valves show elevated FDG uptake, surgeons may still be hesitant to replace or remove these items, as FDG uptake is not 100% specific for infection.
When nuclear medicine physicians can say with almost certainty that foreign bodies are infected with bacteria due to infection-specific tracers, and may even define the extent of the infection, the multidisciplinary decision-making process around prosthetic infections will become much easier. Infection-specific tracers could also benefit patients in their immediate postoperative phase. For example, after laparotomy, there may be free fluid and gas throughout the abdomen, which could indicate leakage of anastomoses or infection. As surgeries also cause inflammatory and regenerative responses, elevated FDG uptake in postoperative patients does not necessarily indicate infection[16]. However, infection-specific tracers would allow a definitive distinction, enabling better decision-making whether to perform a relaparotomy or not. Therefore, further development of these tracers could have major clinical implications in future medicine.

Total Body PET/CT

Currently, most hospitals use PET/CT systems with a 20-25 cm wide detector ring. To image the whole body, the table of the PET/CT is shifted through the detector ring 20 cm a time. With a 3 minute per bed position, performing whole-body PET/CT takes up to 20-30 minutes. As FDG is administered intravenously, it is distributed through the whole body. With a 20 cm

wide detector ring, most emitted high-energy photons scatter outside the detector ring, and less than 1% of the photons are actually recorded[17].

Thanks to technological advancements, new PET/CT systems are being developed with a considerably longer field of view. Total body PET/CT systems can have an extended field of view of up to 200 cm instead of 20 cm. During scanning, the patient will be placed in this 200 cm tube covered by PET detectors (or slightly shorter tube length, depending on the model), which will significantly decrease photon scattering outside the field of view. For a 200 cm total body PET/CT system, this could theoretically increase sensitivity by a factor of 40 compared to whole-body scans on current PET/CT systems, with similar scanning time and FDG dosage. Alternatively, it could also decrease scanning time by a factor of 40 to 15–30 s with similar sensitivity and FDG dosage, or decrease FDG dosage by a factor of 40 to 0.2 mSv (equivalent to 2 chest X-rays) while maintaining similar sensitivity and scanning time[18]. For infectious disease, it would be possible to detect much smaller metastatic infection foci, to detect low-grade infections with only a limited number of bacterial cells involved, increase the possibilities of follow-up PET/CT imaging to monitor treatment response, and increase the number of infection-specific radiotracers that can be effectively used in PET imaging. Severely ill patients can be scanned very rapidly, and due to shorter scanning time, the capacity of performing PET/CT will significantly increase[8]. Due to a lower radiation burden, the use of total body PET/CT is also more suitable in (young) children. Additionally, the shorter scanning time also renders the need for general anesthesia during the scanning procedure of children less likely.

GENERAL CONCLUSION

FDG-PET/CT is an incredibly valuable tool in diagnosing patients with complex infectious and inflammatory diseases. While most infections, such as urinary tract infections or pneumonia, can often easily be diagnosed with conventional diagnostics, FDG-PET/CT really distinguishes itself in more complex patients with an inflammatory or infectious profile without a clear focus, or with suspected foreign body infection. Because FDG-PET/CT can be performed to image the whole body, it can easily rule out many differential diagnoses at once or detect potential septic infection foci. This enables physicians to diagnose patients earlier, and can prevent multiple invasive procedures for patients such as biopsies or surgery. Performing FDG-PET/CT in selected patients, such as in patients with Staphylococcus aureus bacteremia, has also proven cost-effective. The main limitation of FDG-PET/CT is the non-specificity of elevated FDG uptake for infection. However, different uptake patterns can help discriminate sterile inflammation from infection more and more, and new infection-specific tracers are under development. The latest total body PET/CT machines offer an incredible upgrade in patient scanning time and image resolution, with decreased radiation dosage. PET/CT has established its role in the management of infections and inflammatory diseases, and will likely start playing an increasingly important role in the coming future.

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