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REVIEW ARTICLE

# Research Progress of [$^{68}$Ga]Citrate PET's Utility in Infection and Inflammation Imaging: a Review

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**Abstract**

Imaging diagnosis of infection and inflammation has been challenging for many years. Infection imaging agents commonly used in nuclear medicine, such as [$^{67}$Ga]citrate, 2-deoxy-2-[$^{18}$F]fluoro-D-glucose ([$^{18}$F]FDG), and radionuclide-labeled leukocytes, have their own shortcomings. Identification of a tracer with considerable economic benefit, high specificity, and low radiation dose has become clinically urgent. In the twenty-first century, with the increasing availability of positron emission tomography (PET) devices and the commercialization of Ge-68/Ga-68 generators, the study of [$^{68}$Ga]citrate applications for infection and inflammation has increased and shown good potential. In this report, the research progress that supports [$^{68}$Ga]citrate PET's applications various infectious diseases and inflammation is reviewed.

**Key Words:** [$^{68}$Ga]citrate PET, Infection, Inflammation, Utility

## Introduction

At present, non-invasive diagnosis of infection and inflammation remains a challenge, and early identification and locating of lesions are important for timely diagnosis and treatment. Traditional imaging techniques, such as X-ray, computed tomography (CT), and ultrasound, are first-line imaging methods for identifying and locating infection and inflammation [1, 2]. However, these methods rely solely on anatomical changes to indicate local information, which are often undetectable in the early stages of disease due to the minimal anatomical change [3]. Magnetic resonance imaging (MRI) provides detailed anatomical information, which is very sensitive and useful in evaluating patients who have not undergone surgery, but it is of limited value in the presence of metal implants and in the identification of postoperative edema and infection [4]. Inflammatory parameters such as C-reactive protein, erythrocyte sedimentation rate, and white blood cell count are helpful, but they lack sensitivity and specificity [5].

In the field of nuclear medicine, reliable and sensitive imaging methods are being sought for early and sensitive diagnosis of infection and inflammation. Currently, markers such as [$^{67}$Ga]citrate, radiolabeled leukocyte, and 2-deoxy-2-[$^{18}$F]fluoro-D-glucose ([$^{18}$F]FDG) are used for the diagnosis of infection and inflammation [6], but these compounds have some limitations.

Single-photon emission computed tomography (SPECT) using [$^{67}$Ga]citrate is the oldest nuclear medicine method for imaging infection and inflammation, and has been widely used in the diagnosis of many diseases since 1971, such as fever of unknown origin, severe lymphocytic inflammation, autoimmune inflammation, idiopathic pulmonary fibrosis, chronic pancreatitis, chronic bronchial asthma, and sarcoidosis [5, 7–9]. Gallium is absorbed by infectious and inflammatory tissues both due to increased capillary permeability and because it binds to ferritin in leukocytes [2]. Over time, the [$^{67}$Ga]citrate SPECT scan has developed into a mature technology, which provides a multi-functional

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imaging tool for nuclear medicine physicians and can be used in a wide range of clinical applications. Although [$^{67}$Ga]citrate imaging has been recognized as a practical and accurate method, it still has many disadvantages. Firstly, Ga-67 is expensive because it must be manufactured through a cyclotron. Secondly, its half-life ($T_{1/2}$ = 78.3 h) is long and the waiting time after injection is at least 48–72 h [1]. Therefore, the diagnostic process is long and confers a relatively large radiation dose to the patient. Thirdly, the quality and resolution of the image are reduced by limited injection activity, multiple energy peaks of Ga-67 (90 keV, 180 keV, and 300 keV), and liver and intestinal activity [1, 2, 5].

Radionuclide-labeled leukocyte scintigraphy (LS) has advanced clinical disease diagnosis. LS is now the first choice nuclear medical examination method for the sensitive and specific diagnosis of infections, excluding spinal infections [10, 11]. Commonly used tracers for *in vitro* leukocyte labeling include [$^{111}$In]oxine and [$^{99}$Tc]exametazime [12]. Although LS is the radionuclide gold standard for the majority of infections [13], there are limitations to its use. In most cases, LS can sensitively identify neutrophil-mediated inflammatory processes as the majority of labeled leukocytes are neutrophils [12, 13]. It is less useful for diseases in which the cellular responses do not involve neutrophils, including opportunistic infections, mycobacterial infections, and sarcoidosis [12]. Secondly, LS is less sensitive to chronic infections, which may be due to a reduced number of neutrophils in cases of chronic inflammation [13]. It may therefore be unsuitable for imaging chronic inflammation. Thirdly, leukocytes accumulate at both inflammatory sites and in the bone marrow. Differentiating between the two using LS is challenging [10]. In addition, leukocyte labeling is time-consuming and requires direct blood contact, heightening the risk of contamination [11]. It also requires at least 2000 white blood cells per ml to obtain satisfactory images [12]. This may not be feasible in leukopenia patients and children. Moreover, patients using antibiotics have a reduced sensitivity to the procedure [14].

[$^{18}$F]FDG positron emission tomography (PET) is considered a promising imaging method for the diagnosis of infection and inflammation that provides more accurate information than traditional nuclear medicine [15]. Although [$^{18}$F]FDG PET is a sensitive imaging modality, it has some limitations. Infection or inflammatory diseases in normal organs and tissues with high FDG metabolism or excretion may not be detectable with [$^{18}$F]FDG PET [1, 15]. Furthermore, lesions with high metabolic activity may indicate not only infection and inflammation, but also repair and cancer [1]. Moreover, [$^{18}$F]FDG PET may be falsely positive in patients with uninfected or loosened bone implants [1, 15]. In addition, [$^{18}$F]FDG has been reported to not distinguish between bone infection and the inflammatory process of early normal bone healing, which represents a high level of cellular metabolism and glucose consumption and, thus, mimics the uptake of [$^{18}$F]FDG during infection [3, 15].

Optimal radionuclide probes for infection/inflammation imaging should target the cells expressed solely during infection or inflammation, permitting separation infection from aseptic inflammation [1]. The procedure should be highly sensitive and specific, economical, readily available, have reasonable radiation dosimetry, and elicit a minimal immune response [1, 16]. A strong ability to distinguish between infections and tumors is also desirable. The probes should be stable so to permit long-term imaging with no accumulation in non-inflamed tissue [16, 17]. They should also be rapidly cleared and provide high contrast and stability [16, 17]. However, identifying radiopharmaceuticals that distinguish infection from aseptic inflammation with these advantages remains a major challenge. In recent years, a variety of nuclear imaging agents have been developed, including radiolabeled antibacterial drugs, cytokines, monoclonal antibodies, and nucleoside analogues [18, 19]. However, these tracers have not been employed in routine clinical practice.

In the twenty-first century, with the increased availability of PET devices, interest in the use of PET radiopharmaceuticals for infection and inflammation imaging has increased. The radionuclide Ga-68 is positron-emitting, produced by a generator, and suitable for PET imaging. Compared with [$^{18}$F]FDG, Ga-68 does not require a cyclotron, and its radiation burden is lower. However, as the positron emission energy of Ga-68 (2.91 MeV) is higher than F-18 (0.64 MeV), its spatial resolution is lower than F-18 [3]. Both [$^{67}$Ga]citrate and [$^{68}$Ga]citrate have similar chemical properties [8]; however, [$^{68}$Ga]citrate has many advantages over SPECT-based [$^{67}$Ga]citrate for the diagnosis of infection and inflammation. Firstly, Ga-68 is a short-lived positron-emitting radionuclide with a short half-life and a decay mode (90 %, 10 % electron capture) suitable for PET imaging [1]. Secondly, Ga-68 is obtained from a Ge-68/Ga-68 generator system that can be used for a 6–12-month period, which is easy to produce and of low cost [1]. Thirdly, patients can be given high dose of tracer because its physical half-life is much shorter than Ga-67, and the imaging process is fast and convenient [2, 20, 21]. Finally, [$^{68}$Ga]citrate PET has high spatial resolution and sensitivity that can be used to quantitatively evaluate the accumulation of tracer, and its imaging quality is superior to that of [$^{67}$Ga]citrate SPECT [2]. Therefore, [$^{68}$Ga]citrate PET is likely to be as useful as [$^{67}$Ga]citrate SPECT in infection and inflammation imaging and avoids most of the shortcomings of [$^{67}$Ga]citrate SPECT. The use of [$^{68}$Ga]citrate has long been neglected after the development of the Ga-68 generator, which may be due to the fact that the half-life of [$^{68}$Ga]citrate is very short and most of the images of [$^{68}$Ga]citrate are obtained far beyond the physical half-life [8, 9]. However, after a small number of clinical trials, infection, and inflammation imaging with [$^{68}$Ga]citrate began to attract attention. Currently, the Ge-68/Ga-68 generator is gradually being adopted commercially, and preclinical tests and clinical trials of [$^{68}$Ga]citrate PET are

also increasing. Existing studies have demonstrated that [68Ga]citrate PET has good prospects for application to skeletal muscle infection and inflammation, abdominal infection, inflammatory bowel disease (IBD), tuberculosis (TB), atherosclerosis (AS), and contagious disease, which provide new opportunities for clinical diagnosis of infection and inflammation. In addition, [68Ga]citrate PET has been found to have the potential for distinguishing between bone infection and aseptic inflammation. It can also be applied to the planning of surgery and the detection of therapeutic effect in patients with bone infection. Research progress of [68Ga]citrate PET for imaging during infection and inflammation are shown in Table 1. Although there are few relevant studies at present, this approach may be put into clinical use in the future, so it is reviewed here.

## Uptake Mechanism of [68Ga]Citrate

Gallium is a transition metal of group B, which is similar to iron ions in terms of charge and atomic radius [16, 22]. However, unlike iron, Gallium cannot be reduced *in vivo*, so gallium still binds to iron transporters and cannot interact with protoporphyrin IX to form heme [23]. The uptake mechanism of [68Ga]citrate *in vivo* is not completely clear, but current studies suggest that several factors contribute. Partial uptake is caused by increased capillary permeability in the lesion [24]. In addition, [68Ga]citrate is mostly bound to transferrin after injection and then enters the cell through the transferrin receptor, thereby accumulating in inflammatory foci [16, 25, 26]. Furthermore, [68Ga]citrate can bind to ferritin in bacteria and to lactoferrin in neutrophils or be directly absorbed by siderophores that have high affinity for gallium and thereby be freely distributed in circulating blood [3, 26].

## Biodistribution of [68Ga]Citrate

Excretion of Ga-68 occurs primarily in the gastrointestinal tract. Several studies have shown that [68Ga]citrate PET can detect lesions within 30 min after injection and uptake of lesions is increased from 30 to 60 min [27]. At 120 min, the quality of the images deteriorates significantly; consequently, the target background ratio is not conducive for interpretation [28]. Therefore, the image quality of [68Ga]citrate PET is best at 60 min after injection. During the study period, the activity of the mediastinal blood pool, liver, spleen, and bone marrow were significant, whereas the activity of soft tissue was low, and no intestinal activity was observed [27]. In addition, there was sustained high vascular activity in the thigh region [27]. Because of the high background activity in the chest and upper abdomen, [68Ga]citrate PET may be most suitable for imaging the lower abdomen and extremities [27].

## Applications of [68Ga]Citrate PET to Infection and Inflammation Imaging

### *Musculoskeletal System*

Infection and inflammation of the musculoskeletal system are one of the most challenging pathologies in orthopedics. Traditional imaging methods, such as X-ray, CT, MRI, and conventional nuclear medicine, have limitations, especially in the absence of substantial anatomical changes [3]. The gold standard for PET imaging is [18F]FDG, which provides systemic information and has high sensitivity and specificity for bone infection and inflammation [29, 30]. However, [18F]FDG PET can be falsely positive when differentiating aseptic inflammation from bone infection. To improve the accuracy of diagnosis and differential diagnosis, high expectations have been placed on the study of novel tracers for infections. So far, no new infectious imaging agent has been widely used in clinical practice, and related applications are still being investigated through a wide range of studies. Preliminary data has confirmed that [68Ga]citrate PET has good potential for application to the diagnosis of bone infection with reliable negative predictive value and overall accuracy and can successfully distinguish infection from aseptic inflammation.

In 2010, Nanni *et al.* [31] first evaluated the accuracy of [68Ga]citrate PET/CT for the diagnosis of bone infection. The researchers performed [68Ga]citrate PET/CT scans on 31 patients who were suspected of bone infection, including 18 cases of acute osteomyelitis, 9 cases of intervertebral disc inflammation, and 4 cases of chronic osteomyelitis. The average injection dose was 4.5 MBq, and imaging was performed 60 min after injection. A total of 40 [68Ga]citrate PET/CT results were obtained, and all patients underwent biopsy. Finally, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated by combining with MRI, CT, LS, biopsy results, and follow-up data. The results were 23 true positive scans, 4 false positive scans, and 13 true negative scans, and no obvious tracer uptake was found in uninfected bone implants. The final sensitivity was 100 %, specificity was 76 %, positive predictive value was 85 %, negative predictive value was 100 %, and overall accuracy was 90 %. The results of this study are satisfactory and support the role of [68Ga]citrate for the diagnosis of bone infection: (1) [68Ga]citrate PET/CT scan has good diagnostic performance, and no false positives were reported (Fig. 1), and (2) [68Ga]citrate PET/CT scan can be used to evaluate the efficacy of antibiotic therapy and can contribute to preoperative planning of surgery, which may improve the prognosis of patients with bone infection. However, the study has some limitations, including the small number of patients included in the study and no control group.

In 2015, Nielsen *et al.* [32] studied the diagnostic value of [68Ga]citrate, [18F]FDG, and other tracers in a porcine hematogenous osteomyelitis model. The researchers

**Table 1.** Research progress of [$^{68}$Ga]citrate PET for imaging during infection and inflammation

| Authors | Year | Setting | Modality | Application | Main finding of [$^{68}$Ga]citrate | Ref. |
|---|---|---|---|---|---|---|
| Rizzello *et al.* | 2009 | C | [$^{68}$Ga]citrate PET | IBD | Increased uptake of [$^{68}$Ga]citrate in the descending colon in a patient with IBD | [36] |
| Nanni *et al.* | 2010 | C | [$^{68}$Ga]citrate PET/CT | Osteomyelitis and diskitis | The sensitivity, specificity, positive predictive value, negative predictive value, and total accuracy of [$^{68}$Ga]citrate PET/CT in the diagnosis of bone infection were 100 %, 76 %, 85 %, 100 %, and 90 %, respectively | [31] |
| Kumar *et al.* | 2012 | PC/C | [$^{68}$Ga]citrate PET | *Staphylococcus aureus* infection in rats and intra-abdominal infection in a patient | [$^{68}$Ga]citrate detects *Staphylococcus aureus* infection in rats and an intra-abdominal infection in patients | [27] |
| Vorster *et al.* | 2014 | C | [$^{68}$Ga]citrate PET/CT | Malignant lesion, TB, and benign lung lesions | [$^{68}$Ga]citrate PET detects malignant pulmonary tumors and is applicable as a tracer with negative predictive values in pulmonary disease | [28] |
| Thackeray *et al.* | 2015 | PC | [$^{68}$Ga]citrate PET<br>[$^{18}$F]FDG PET<br>[$^{68}$Ga]DOTATATE PET | Myocardial inflammation after myocardial infarction | [$^{68}$Ga]citrate obscures specific accumulation in inflammatory tissue | [44] |
| Nielsen *et al.* | 2015 | PC | [$^{68}$Ga]citrate PET<br>[$^{18}$F]FDG PET<br>[$^{11}$C]PK11195 PET<br>[$^{11}$C]methionine PET<br>[$^{111}$In]leukocytes SPECT | *Staphylococcus aureus* osteomyelitis | [$^{68}$Ga]citrate may be useful for the diagnosis of soft issue lesions | [32] |
| Afzelius *et al.* | 2016 | PC | [$^{68}$Ga]citrate PET<br>[$^{18}$F]FDG PET<br>[$^{11}$C]PK11195 PET<br>[$^{11}$C]methionine PET | *Staphylococcus aureus* infection | [$^{68}$Ga]citrate accumulated to a lesser extent in infectious foci | [1] |
| Mirzaei *et al.* | 2016 | PC | [$^{68}$Ga]citrate PET/CT | Turpentine oil–induced inflammation | [$^{68}$Ga]citrate PET/CT can identify the inflammatory site of animal models in 60~80 min | [8] |
| Fuchigami *et al.* | 2017 | PC | [$^{68}$Ga]citrate PET/CT | SFTSV-infected mice | [$^{68}$Ga]citrate could visualize the inflammation induced by SFTSV infection | [5] |
| Jødal *et al.* | 2017 | PC | [$^{68}$Ga]citrate PET<br>[$^{18}$F]FDG PET<br>[$^{11}$C]methionine PET<br>[$^{11}$C]Donepezil PET | Porcine osteomyelitis | [$^{68}$Ga]citrate was not useful for the imaging of osteomyelitis | [45] |
| Salomäki *et al.* | 2017 | C | [$^{68}$Ga]citrate PET/CT<br>[$^{18}$F]FDG PET/CT | *Staphylococcus aureus* bacteraemia | [$^{68}$Ga]citrate PET/CT was comparable to [$^{18}$F]FDG PET/CT for the detection of osteomyelitis, while [$^{18}$F]FDG was favorable for the diagnosis of soft tissue infections | [26] |
| Lankinen *et al.* | 2018 | PC | [$^{68}$Ga]citrate PET/CT<br>[$^{68}$Ga]chloride PET/CT | *Staphylococcus aureus* osteomyelitis | [$^{68}$Ga]citrate was superior to [$^{68}$Ga]chloride for PET imaging of postoperative osteomyelitis | [3] |
| Tseng *et al.* | 2019 | C | [$^{68}$Ga]citrate PET/CT<br>[$^{18}$F]FDG PET/CT | Prosthetic joint infections | [$^{68}$Ga]citrate PET/CT can be used as a supplement to [$^{18}$F]FDG PET/CT for the diagnosis of artificial joint infections. It was characterized by high specificity and could distinguish infection status from aseptic inflammation | [34] |
| Segard *et al.* | 2019 | C | [$^{68}$Ga]citrate PET/CT<br>[$^{67}$Ga]citrate PET/CT | Joint infection and pyrexia of unknown origin | The sensitivity and specificity of [$^{68}$Ga]citrate PET/CT during the diagnosis of bone and joint infection or pyrexia of unknown origin were consistently lower than with [$^{67}$Ga]citrate scintigraphy | [43] |
| Vorster *et al.* | 2019 | C | [$^{68}$Ga]citrate PET/CT | TB | [$^{68}$Ga]citrate PET can distinguish active and inactive TB lesions | [38] |

inoculated *Staphylococcus aureus* into the right femoral artery of pigs. Seven days later, PET/CT scans were performed. The results showed that [$^{18}$F]FDG was better than [$^{68}$Ga]citrate and several other tracers in osteomyelitis model, whereas [$^{68}$Ga]citrate was better than [$^{18}$F]FDG for the diagnosis of soft tissue lesions. However, a subsequent study contradicts the conclusions of Nielsen *et al*. In 2017, Salomäki *et al.* [26] researched the potential of [$^{68}$Ga]citrate PET/CT and [$^{18}$F]FDG PET/CT for detection of *Staphylococcus aureus* bacteremia. They performed [$^{18}$F]FDG and [$^{68}$Ga]citrate PET/CT in 4 patients with *Staphylococcus aureus* bacteremia (including 3 cases of intervertebral

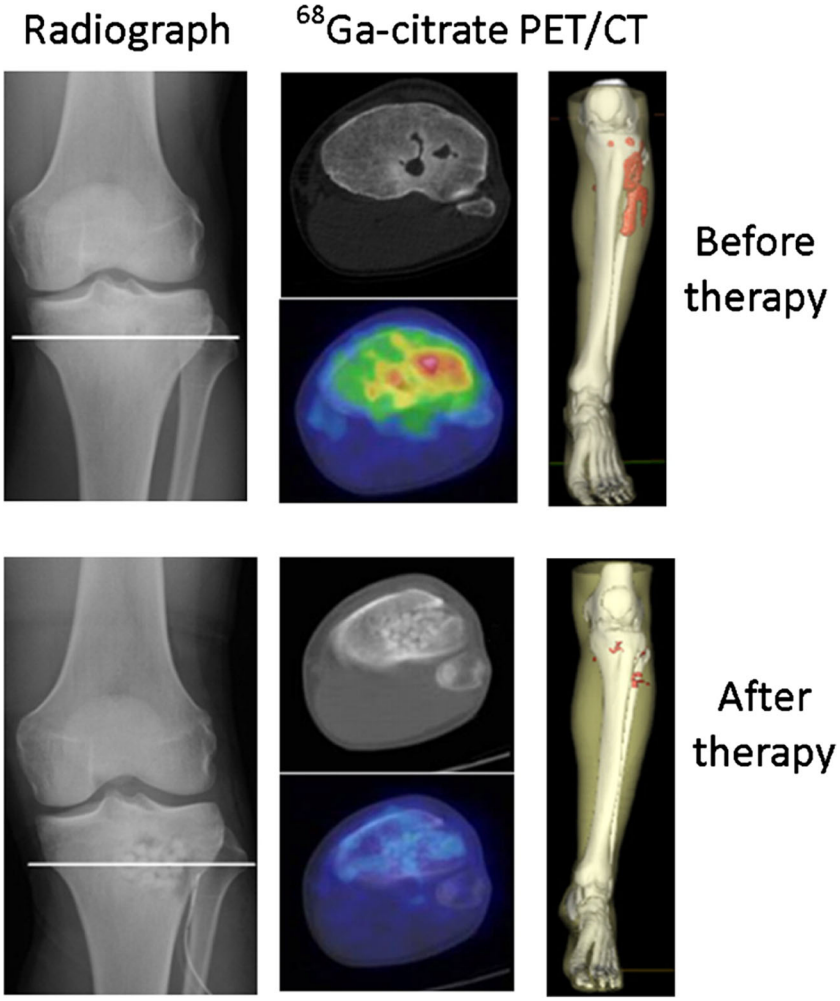


**Fig. 1.** [$^{68}$Ga]citrate PET/CT images of a patient with acute osteomyelitis before and after operation. Significant uptake of the left fibula was observed prior to therapy. No obvious uptake after therapy was observed. This research was originally published in JNM. From Cristina *et al.* [31].

discitis and 1 case of toe osteomyelitis). The final results showed that [$^{68}$Ga]citrate PET/CT was comparable to [$^{18}$F]FDG PET/CT for the detection of osteomyelitis, whereas [$^{68}$Ga]citrate PET/CT was only visible or completely invisible for soft tissue infections. Soft tissue lesions could not be clearly detected by [$^{68}$Ga]citrate PET/CT.

The results of these two studies were significantly different, primarily regarding the soft tissue lesions detected by [$^{68}$Ga]citrate. The different dosage of [$^{68}$Ga]citrate in two studies could have caused the divergent results. In the blood pool, [$^{68}$Ga]citrate has a high background activity, and Salomäki *et al.* believed that the use of high doses of tracers may have influenced the lack of detection of soft tissue lesions. However, if the dose of tracer is reduced properly, the background activity of the blood pool may decrease enough to show the soft tissue infection [26]. There are some interesting findings in Salomäki's study. In one patient, [$^{68}$Ga]citrate (but not [$^{18}$F]FDG) uptake was observed in the inferior vena cava (IVC); later, ultrasound confirmed IVC thrombosis. This finding may be related to the aggregation of tracer proximal to the stenosed thrombus, and more comprehensive studies are needed to explain the differences between the [$^{68}$Ga]citrate and [$^{18}$F]FDG findings. In addition, [$^{68}$Ga]citrate PET/CT unexpectedly detected 3 cases of AS, which may be either a coincidence or a potential application; further research is needed to determine its importance. Another important finding of Salomäki's study was that the uptake of [$^{18}$F]FDG, but not [$^{68}$Ga]citrate, was significantly enhanced in uninfected healing bone. This finding is not incidental. As early as 2005, Makinen *et al.* [33] found that in healed bone, the uptake of [$^{18}$F]FDG was significantly enhanced but the uptake of Ga-68 was not obvious. The difference between the two studies is that Makinen *et al.* used Ga-68 without the precursor citrate. The physical and chemical properties do not differ greatly between Ga-68 and [$^{68}$Ga]citrate; however, Ga-68 chelated with citrate can bind more to ferritin in the blood and

thereby better display the lesion [22]. Although there is relatively little clinical evidence, current research results support the hypothesis that [68Ga]citrate may perform better than [18F]FDG to confirm healing osteomyelitis and to distinguish the physiological inflammatory process of normal bone healing from bone infection. This may have important clinical implications by reducing the incidence of false positive images in patients with bone healing after surgery and trauma.

Subsequently, a prospective study by Tseng *et al.* [34] further validated the role of [68Ga]citrate and [18F]FDG in differentiating aseptic inflammation from infection. Thirty-four patients with clinically confirmed or suspected artificial hip/knee joint infections were included in the study; all underwent [68Ga]citrate PET/CT and [18F]FDG PET/CT imaging. The positive criteria were the uptake of abnormal radioactive tracer at the bone-prosthesis interface and/or the soft tissue around the prosthesis. Altogether, 26 patients (76 %) were diagnosed as infected. The results showed that the sensitivity, specificity, and accuracy of [68Ga]citrate PET/CT and [18F]FDG PET/CT were 92 %, 88 %, and 91 % and 100 %, 38 %, and 85 %, respectively. Of note, the metabolic volume (MV) of infected prostheses was significantly higher than that of uninfected prosthesis on [68Ga]citrate PET/CT scan ($P < 0.05$), but their MVs did not differ significantly on [18F]FDG PET/CT. This study showed that [68Ga]citrate PET/CT had significantly higher specificity than [18F]FDG PET/CT (88 % *versus* 38 %, respectively), whereas [18F]FDG PET/CT imaging had superior sensitivity, which suggested that [68Ga]citrate PET/CT can be complementary to [18F]FDG PET/CT in the detection of prosthetic joint infection (Fig. 2). This study also demonstrated that [68Ga]citrate PET/CT can successfully distinguish prosthetic infection from aseptic inflammation, which has important clinical significance for early and differential diagnosis of prosthetic joint infection after joint replacement. In addition, this study found that [18F]FDG PET/CT had an advantage in diagnosing sinus tract infections or cold abscesses, whereas [68Ga]citrate PET/CT was more effective in identifying bone remodeling associated with fracture and osteolysis. However, this study has important limitations. First, radiotracer uptake at the bone-prosthesis interface and/or the soft tissue around the prosthesis was the positive criterion for diagnosis, which may lead to differences in the study results. The sample size of the study was small, and the conclusions may not be generalizable. Furthermore, the researchers did not evaluate the effects of attenuation correction and non-attenuation correction, which may cause some problems for PET scanning. In the future, larger sample size studies will be needed to confirm the diagnostic performance of [68Ga]citrate PET/CT.

We performed a prospective study of [68Ga]citrate PET/CT imaging in patients with bone infections or osteoarthritis. As shown in Fig. 3, [68Ga]citrate PET/CT performed well in these patients.

## *Gastrointestinal Applications*

Studies have shown that [68Ga]citrate has no physiological uptake in the intestinal tract, so it has a potential role for detecting intestinal lesions. Recent reports have also revealed a role for [68Ga]citrate PET for the diagnosis of IBD and abdominal infection. Because these were primarily case reports, this application will need to be evaluated in larger studies.

## *IBD*

In the past, [67Ga]citrate PET has been applied to the diagnosis of IBD, so it is not surprising that [68Ga]citrate PET is useful for diagnosing IBD [35]. In 2009, Rizzello *et al.* [36] described the application of [68Ga]citrate PET to patients with IBD in a study of [68Ga]citrate synthesis and quality control. They injected a patient with 130 MBq of [68Ga]citrate and performed PET imaging 90 min after the injection. Increased uptake in the descending colon was observed, which was consistent with the site of inflammation confirmed postoperatively. This study suggests that [68Ga]citrate PET may be useful in imaging diagnosis of IBD, but this still needs to be validated in further studies.

## *Abdominal Cavity Infection*

In 2012, Kumar *et al.* [27] performed [68Ga]citrate PET scans of patients with abdominal infection after appendectomy. Their research demonstrated that lesions can be detected within 30 min after injection of [68Ga]citrate and that the intensity of tracer uptake in the lesions increased from 30 to 60 min after injection (Fig. 4). In this study, [68Ga]citrate PET was used in the diagnosis of patients with abdominal infections for the first time, and the results highlighted another possible clinical role of [68Ga]citrate PET for imaging infections.

## *Respiratory System*

Worldwide, millions of people suffer from various infectious and inflammatory diseases of the lung yearly. However, these pathogenic processes are difficult to clarify due to their complex development processes and multiple pathogenic factors [37]. Chest X-ray and high-resolution CT display only anatomical information but do not provide information about disease activity [37]. Lung biopsy is the gold standard but is invasive. Therefore, development of a non-invasive technique to assess the evolution of lung disease is urgently needed. For evaluating lung malignancies and systemic metastases, [18F]FDG PET is the best imaging method; however, the diagnosis of pulmonary infectious diseases is still limited and expensive. For decades, [67Ga]citrate has been used for lung inflammation and infection imaging.

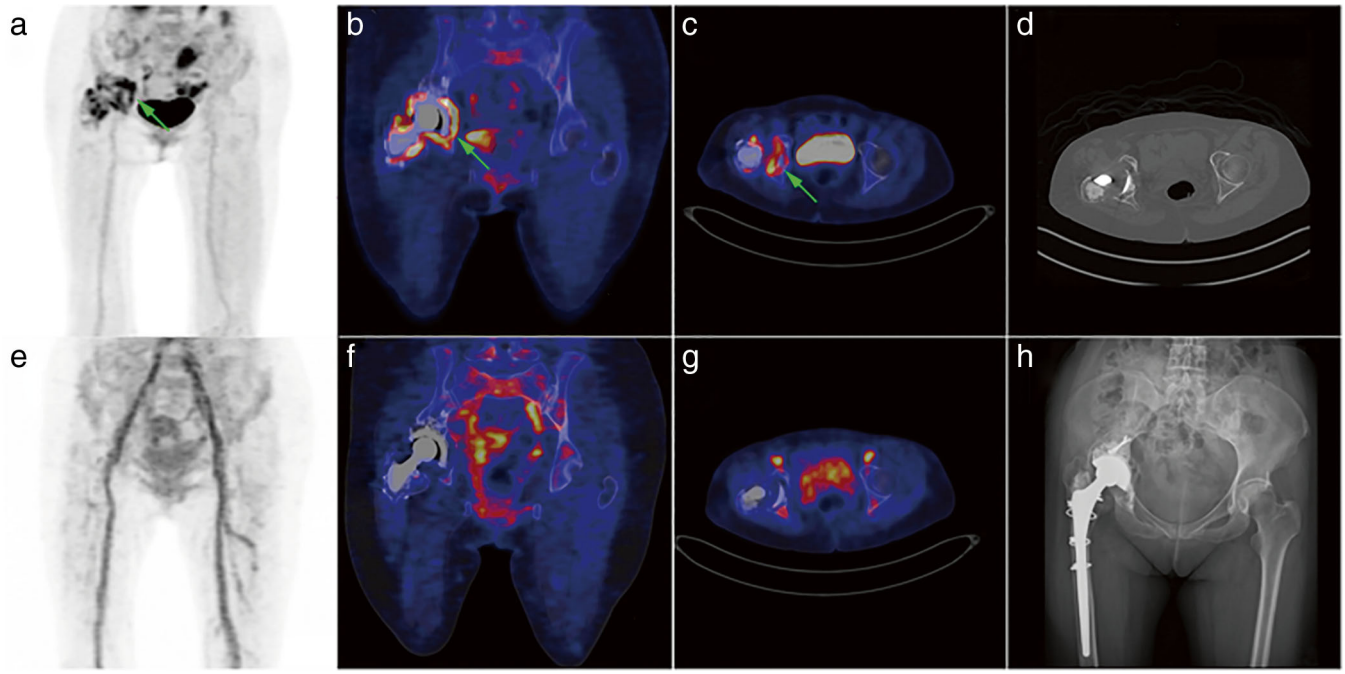


**Fig. 2.** Imaging findings of [$^{18}$F]FDG PET/CT and [$^{68}$Ga]citrate PET/CT in a patient with a history of right total hip arthroplasty performed 16 years prior to imaging. [$^{18}$F]FDG PET/CT showed increased uptake around the prosthesis (**a**–**d**, green arrows), while [$^{68}$Ga]citrate PET/CT had no obvious tracer uptake (**e**–**g**). Cup loosening with synovial hypertrophy and clear joint fluid were observed during surgery. This confirmed [$^{18}$F]FDG PET/CT false positives. Adapted from Tseng *et al.* [34] (this article is distributed under the terms of the creative commons attribution 4.0 international license: http://creativecommons.org/licenses/by/4.0/).

Compared with [$^{67}$Ga]citrate, [$^{68}$Ga]citrate has the advantages of greater simplicity and rapidity, shorter half-life, and lower radiation dose. Therefore, [$^{68}$Ga]citrate PET is expected to perform better than [$^{67}$Ga]citrate for pulmonary infection and inflammation imaging.

### *TB*

In 2019, Vorster *et al.* [38] referred to their preliminary study that evaluated the use of [$^{68}$Ga]citrate PET for the diagnosis of TB. The study found that many pulmonary lesions visible on CT had significant uptake of [$^{68}$Ga]citrate, but some lesions did not uptake of [$^{68}$Ga]citrate. The final pathology confirmed that the lesions with no obvious uptake of [$^{68}$Ga]citrate were inactive TB lesions. Most patients (77 %) presented with extrapulmonary invasion based on [$^{68}$Ga]citrate PET, including invasion of lymph nodes, pleura, bone, the spleen, and the gastrointestinal tract. The researchers suggested that [$^{68}$Ga]citrate PET can provide a method to distinguish between active and inactive lesions and that it is superior to CT for detecting extrapulmonary involvement. At present, distinguishing active pulmonary TB from inactive pulmonary TB is difficult by imaging, and more large-scale trials are needed to verify the value of [$^{68}$Ga]citrate PET for pulmonary TB.

### *Indeterminate Pulmonary Lesion*

The differentiation of benign and malignant pulmonary lesions is still a difficult problem, and solving this problem using traditional imaging methods is difficult [28]. Although [$^{18}$F]FDG PET/CT is currently the optimal imaging modality for the diagnosis of pulmonary malignancy, it is difficult to differentiate malignant from benign lesions in some cases, and the lesion still needs to be confirmed by bronchoscopy and biopsy [39]. Compared with [$^{18}$F]FDG, the normal biodistribution of [$^{68}$Ga]citrate does not include any pulmonary uptake and has an advantage in dosage [28, 36]. In 2014, Vorster *et al.* [28] first used [$^{68}$Ga]citrate PET to image the pathology of patients' lungs. They studied 40 patients with diverse lung pathology, including malignant lesions (14 cases), TB (12 cases), and other benign pulmonary lesions (fibrosis, sarcoidosis, and infectious or inflammatory lesions) (10 cases); the diagnoses of 27 patients were confirmed by histology. The diagnoses of the other patients were confirmed by the results of clinical or biochemical examinations. The study showed that the uptake of [$^{68}$Ga]citrate was significantly increased in malignant lesions; the uptake of [$^{68}$Ga]citrate in benign lesions, such as infection and sarcoidosis, was slightly increased, but still lower than in malignant lesions ($P < 0.05$); the tracer accumulation was very low or absent in lesions with

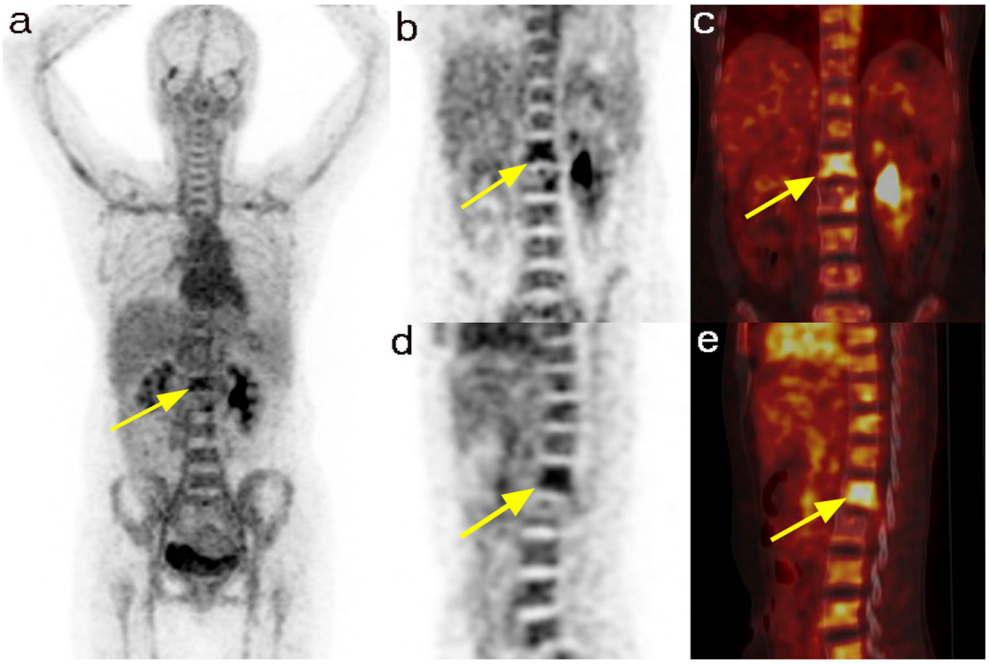


**Fig. 3.** The patient was a 32-year-old woman with an 8-month history of lower back pain. **a** Diffuse uptake of the first lumbar vertebrae was observed on maximum-intensity projection [$^{68}$Ga]citrate PET image, **b** coronal PET image, **c** coronal fused PET/CT image, **d** sagittal PET image, and **e** sagittal fused PET/CT image. Postoperative examinations showed spinal TB, consistent with the imaging findings.

significant changes on CT images but without malignant, infectious, or inflammatory changes on histologic examination (Fig. 5). The results revealed that (1) the accumulation of tracer in all pulmonary malignant lesions was increasing and higher in the intensity than in benign lesions, which confirmed that [$^{68}$Ga]citrate PET may have the potential to detect malignant pulmonary tumors, and (2) [$^{68}$Ga]citrate may be used as a tracer with good negative predictive value in pulmonary disease. Therefore, for the patient without obvious uptake of [$^{68}$Ga]citrate, the physician can recommend follow-up and adopt an observation strategy and thereby avoid unnecessary invasive examinations [28]. The researchers suggested that the increased uptake of tracer in malignant lesions may be due to the fact that malignant lesions are often associated with chronic anemia, which can result in diffuse increase of [$^{68}$Ga]citrate uptake in the bone marrow and spleen. This increased uptake of tracer may also be attributed to the increased expression of transferrin [28, 40].

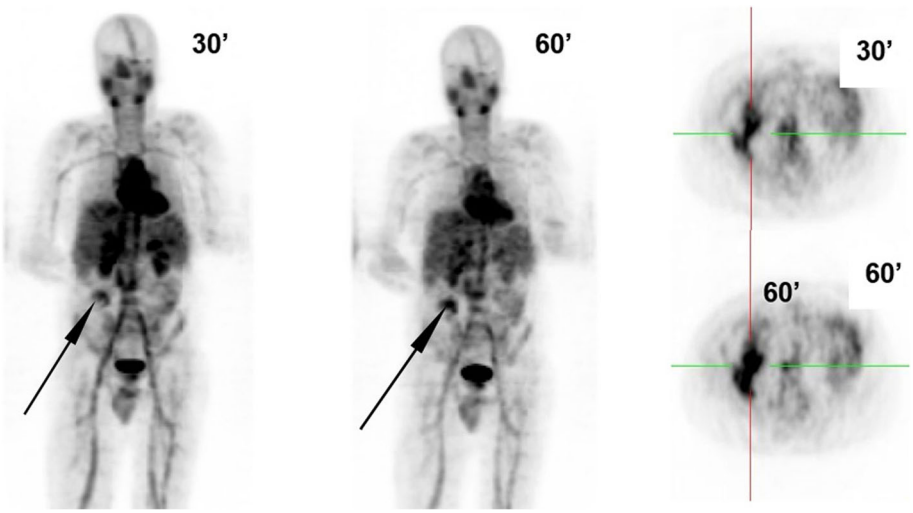


**Fig. 4.** [$^{68}$Ga]citrate PET imaging in patients with intraperitoneal infection. Adapted from Kumar *et al.* [27].

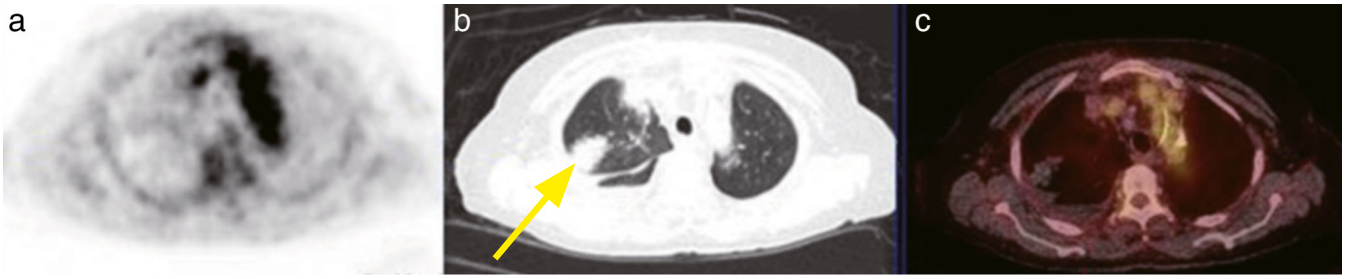


**Fig. 5.** A 71-year-old female presented with a right upper lung mass with pleural effusion on axial CT images (**b**). Axial [$^{68}$Ga]citrate PET image (**a**) and fused PET/CT image (**c**) showed no obvious uptake of these lesions. Histological examination showed no malignant or inflammatory cells. Adapted from Mariza *et al.* [28].

## *Cardiovascular System: AS*

AS is a chronic inflammatory disease of the arterial wall characterized by monocyte infiltration of the subcutaneous space and differentiation into macrophages. Because vulnerable plaques usually contain a large number of activated macrophages, imaging of macrophages may provide a useful tool for the assessment of vulnerable plaques [22]. In 2017, Salomäki *et al.* [26] accidentally found that [$^{68}$Ga]citrate detected 3 cases of AS in a study of [$^{68}$Ga]citrate PET/CT detection of infectious foci of *Staphylococcus aureus* bacteremia. The discovery could be a coincidence, but it is more likely to suggest a potential application. Although [$^{68}$Ga]citrate has not been used in the study of AS, there is a positive correlation between expression of transferrin receptor and macrophage infiltration in atherosclerotic lesions [22]. At present, the accepted uptake mechanism of [$^{68}$Ga]citrate is that it binds to transferrin in plasma and then converts to a gallium-transferrin complex and enters cells that express the transferrin receptor [28]. In patients with AS, [$^{68}$Ga]citrate is likely to bind to the transferrin receptor at the lesion site, resulting in a high uptake by the lesion on PET/CT. Extensive research is still needed to determine the feasibility of [$^{68}$Ga]citrate PET for detection of AS.

## *Contagious Disease*

In 2017, Fuchigami *et al.* [5] used [$^{68}$Ga]citrate to observe the lesions of mice in a small animal PET/CT study of mice infected with leishmaniasis and severe fever associated with thrombocytopenia syndrome virus (SFTSV). Leishmaniasis is a vector-borne disease caused by a protozoan belonging to

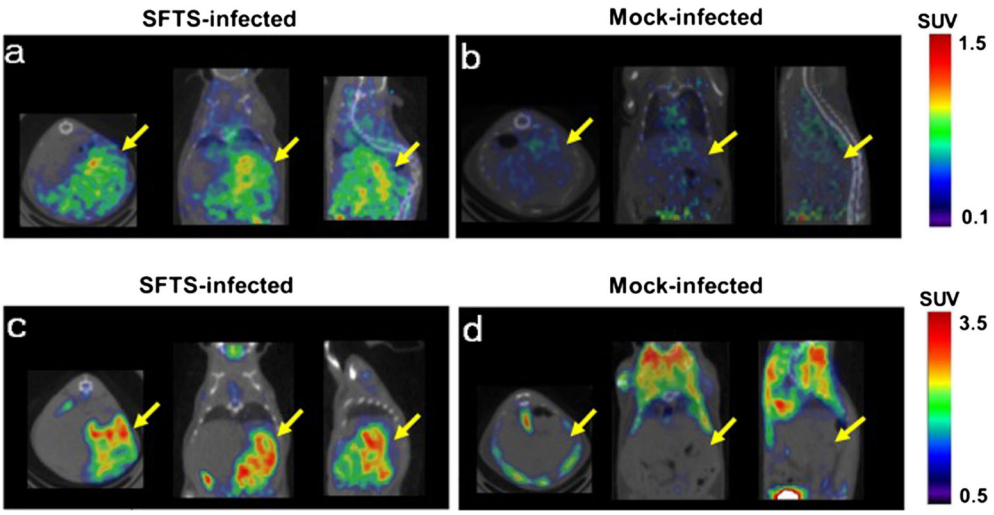


**Fig. 6.** [$^{68}$Ga]citrate and [$^{18}$F]FDG PET/CT imaging in SFTSV-infected and mock-infected mice. Accumulation of [$^{68}$Ga]citrate was observed in the gastrointestinal tracts of SFTSV-infected mice (**a**), but the gastrointestinal activity of mock-infected mice was low (**b**). [$^{18}$F]FDG was visible in the GI tracts of SFTSV-infected mice (**c**), but no obvious signal was observed in mock-infected mice (**d**). The accumulation of [$^{68}$Ga]citrate was similar to [$^{18}$F]FDG, indicating it shows an inflammatory response to SFTSV infection. Adapted from Fuchigami *et al.* [5] (Direct link https://pubs.acs.org/doi/10.1021/acsomega.7b00147).

the genus Leishmania. Its symptoms range from self-healing skin lesions to fatal visceral diseases [41]. SFTSV infection can cause a variety of symptoms, including fever, myalgia, gastrointestinal symptoms, and regional lymphadenopathy [9, 42]. The results of the study showed that [$^{68}$Ga]citrate PET imaging could recognize lesions caused by leishmaniasis; in the gastrointestinal tract of mice infected with SFTSV, it also showed an obvious uptake signal of [$^{68}$Ga]citrate (Fig. 6). Therefore, [$^{68}$Ga]citrate PET/CT may be a useful imaging tool for the detection of leishmaniasis and SFTSV infection that can be used to detect the site of infection, investigate the disease progression and monitor the effect of treatment [5]. Fortunately, Ga-68 production does not require an expensive cyclotron; this economic advantage is particularly important in developing countries that are prone to the spread of tropical infectious diseases.

## Limitation of [$^{68}$Ga]Citrate PET Imaging

[$^{68}$Ga]citrate as an infection and inflammation tracer that has the advantage of a simple and rapid diagnosis process, lack of scanning contraindications, short half-life, and low radiation doses. Its limitations, however, cannot be ignored. Firstly, [$^{68}$Ga]citrate is a non-specific radiotracer that accumulates in inflammatory sites through increased capillary permeability and transferrin binding. As there are many pathophysiological overlaps between infection and aseptic inflammation, distinguishing them with [$^{68}$Ga]citrate is challenging [14].

Secondly, [$^{68}$Ga]citrate accumulates in malignant tumor tissue, which may be related to increased transferrin expression. This makes [$^{68}$Ga]citrate unable to distinguish infection from tumors. In addition, while the short half-life of [$^{68}$Ga]citrate is advantageous from a dosimetry perspective, it may be detrimental to the sensitivity of infection detection, particularly for low-grade infections that require delayed imaging. Because early imaging reflects the non-specific uptake caused by increased blood flow at the infected/inflammatory site, more specific binding is achieved through delayed imaging [43].

Furthermore, [$^{68}$Ga]citrate PET has been shown to possess high blood pool activity and great background interference, which may compromise its clinical application. It may also be unsuitable for the detection of the soft tissue lesions.

To-date, [$^{68}$Ga]citrate has been shown to have value in displaying AS [26]. However, [$^{68}$Ga]citrate accumulation in atherosclerotic arteries is considered a limiting factor when detecting metastatic intravascular infections [26].

## Conclusion

This article reviewed the application of [$^{68}$Ga]citrate PET to many infectious and inflammatory diseases. The advantages [$^{68}$Ga]citrate include lower cost, short physical half-life, and low radiation dose. Although not used clinically yet, current research shows that the use of this tracer in inflammation and infection of the musculoskeletal, gastrointestinal, respiratory, and cardiovascular is promising. In the musculoskeletal system, [$^{68}$Ga]citrate is highly sensitive with no false negatives and is thus preferred [$^{18}$F]FDG when distinguishing the physiological inflammatory processes of normal bone healing from bone infection; moreover, it is valuable for evaluating the curative effect of antibiotic therapy and planning surgery. In addition, [$^{68}$Ga]citrate PET shows good potential for application to abdominal infection and IBD. The study of [$^{68}$Ga]citrate PET for diagnosis of TB activity and differential diagnosis of pulmonary indeterminate lesions has shown great application value, which needs to be verified by further research. Studies have also shown that [$^{68}$Ga]citrate PET has some potential for application to AS and contagious disease. However, currently related studies are few, and the limitations of [$^{68}$Ga]citrate as a non-specific inflammatory tracer cannot be ignored. Further research is required to assess its value for disease diagnostics.

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**Compliance with Ethical Standards**

*Conflict of Interest*

The authors declare that they have no conflict of interest.

## References

1. Afzelius P, Nielsen OL, Alstrup AK, Bender D, Leifsson PS, Jensen SB, Schønheyder HC (2016) Biodistribution of the radionuclides $^{18}$F-FDG, $^{11}$C-methionine, $^{11}$C-PK11195, and $^{68}$Ga-citrate in domestic juvenile female pigs and morphological and molecular imaging of the tracers in hematogenously disseminated Staphylococcus aureus lesions. Am J Nucl Med Mol Imaging 6:42–58
2. Abbasi R, Abu-Zayyad T, Belov K et al (2012) Gallium-labelled peptides for imaging of inflammation. Eur J Nucl Med Mol Imaging 39:68–77
3. Lankinen P, Noponen T, Autio A, Luoto P, Frantzèn J, Löyttyniemi E, Hakanen AJ, Aro HT, Roivainen A (2018) A comparative 68Ga-citrate and $^{68}$Ga-chloride PET/CT imaging of Staphylococcus aureus osteomyelitis in the rat tibia. Contrast Media Mol Imaging. 2018:1–10. https://doi.org/10.1155/2018/9892604
4. Ledermann HP, Kaim A, Bongartz G, Steinbrich W (2000) Pitfalls and limitations of magnetic resonance imaging in chronic posttraumatic osteomyelitis. Eur Radiol 10:1815–1823
5. Fuchigami T, Ono H, Oyadomari K, Iwatake M, Hayasaka D, Akbari M, Yui K, Nishi K, Kudo T, Yoshida S, Haratake M, Nakayama M (2017) Development of a $^{68}$Ge/ $^{68}$Ga generator system using polysaccharide polymers and its application in PET imaging of tropical infectious diseases. Acs Omega 2:1400–1407
6. Connolly CM, Donohoe KJ (2017) Nuclear medicine imaging of infection. Semin Roentgenol 52:114–119
7. Oyen WJG, Boerman OC, Laken CJVD et al (1996) The uptake mechanisms of inflammation-and infection-localizing agents. Eur J Nucl Med 23:459–465
8. Mirzaei A, Jalilian AR, Akhlaghi M et al (2016) Production of $^{68}$Ga-citrate based on a SnO2 generator for short-term turpentine oil-induced inflammation imaging in rats. Curr Radiopharm 9:208–214
9. Aghanejad A, Jalilian AR, Ardaneh K, Bolourinovin F, Yousefnia H, Samani AB (2015) Preparation and quality control of $^{68}$Ga-citrate for PET applications. Asia Ocean J Nucl Med Biol 3:99–106

10. Noriega-Álvarez E, Pimienta GAM, Segura AMB et al (2017) Utility of 8 h and time decay-corrected acquisition scintigraphy with in-vitro labeled white blood cells for the diagnosis of osteoarticular infection. Nucl Med Commun 38:500–508
11. Liberatore M, Calandri E, Ciccariello G, Fioravanti M, Megna V, Rampin L, Marzola MC, Zerizer I, al-Nahhas A, Rubello D (2010) The labeled-leukocyte scan in the study of abdominal abscesses. Mol Imaging Biol 12:563–569
12. Napoleone P, Elena L, Brunella R et al (2006) Nuclear medicine imaging of bone infections. Nucl Med Commun 27:633–644
13. Palestro CJ, Love C, Miller TT (2010) Diagnostic imaging tests and microbial infections. Cell Microbiol 9:2323–2333
14. Love C, Tomas MB, Marwin SE, Pugliese PV, Palestro CJ (2001) Role of nuclear medicine in diagnosis of the infected joint replacement. Radiographics 21:1229–1238
15. Sillat T, Parkkinen M, Lindahl J, Mustonen A, Mäkinen TJ, Madanat R, Koskinen SK (2019) Fibular head avulsion fractures accompanying operative treated medial tibial plateau fractures. Skelet Radiol. DOI: https://doi.org/10.1007/s00256-019-03191-3
16. Kumar V, Boddeti DK (2013) 68Ga-radiopharmaceuticals for PET imaging of infection and inflammation. Recent Results Cancer Res 194:189–219
17. Petrik M, Umlaufova E, Raclavsky V, Palyzova A, Havlicek V, Haas H, Novy Z, Dolezal D, Hajduch M, Decristoforo C (2018) Imaging of Pseudomonas aeruginosa infection with Ga-68 labelled pyoverdine for positron emission tomography. Sci Rep 8:15698
18. Jain SK (2017) The promise of molecular imaging in the study and treatment of infectious diseases. Mol Imaging Biol 19:341–347
19. Lawal I, Zeevaart JR, Ebenhan T, Ankrah A, Vorster M, Kruger HG, Govender T, Sathekge M (2017) Metabolic imaging of infection. J Nucl Med 58:1727–1732
20. Roivainen A, Tolvanen T, Salomäki S, Lendvai G, Velikyan I, Numminen P, Välilä M, Sipilä H, Bergström M, Härkönen P, Lönnberg H, Långström B (2004) $^{68}$Ga-labeled oligonucleotides for in vivo imaging with PET. J Nucl Med 45:347–355
21. Kumar V, Boddeti DK, Evans SG, Roesch F, Howman-Giles R (2011) Potential use of $^{68}$Ga-apo-transferrin as a PET imaging agent for detecting Staphylococcus aureus infection. Nucl Med Biol 38:393–398
22. Silvola JM, Laitinen I, Sipilä HJ et al (2011) Uptake of $^{68}$gallium in atherosclerotic plaques in LDLR$^{-/-}$ApoB$^{100/100}$ mice. EJNMMI Res 1:14. https://doi.org/10.1186/2191-219X-1-14
23. Jensen SB, Nielsen KM, Dennis M et al (2013) Fast and simple one-step preparation of $^{68}$Ga citrate for routine clinical PET. Nucl Med Commun 34:806–812
24. El-Maghraby TAF, Moustafa HM, Pauwels EKJ (2006) Nuclear medicine methods for evaluation of skeletal infection among other diagnostic modalities. Q J Nucl Med Mol Imaging 50:167–192
25. Chianelli M, Mather SJ, Martin-Comin J et al (1997) Radiopharmaceuticals for the study of inflammatory processes: a review. Nucl Med Commun 18:437–455
26. Salomäki SP, Kemppainen J, Hohenthal U, Luoto P, Eskola O, Nuutila P, Seppänen M, Pirilä L, Oksi J, Roivainen A (2017) Head-to-head comparison of $^{68}$Ga-citrate and $^{18}$F-FDG PET/CT for detection of infectious foci in patients with *Staphylococcus aureus Bacteraemia*. Contrast Media Mol Imaging 2017:1–8. https://doi.org/10.1155/2017/3179607
27. Kumar V, Boddeti DK, Evans SG et al (2012) $^{68}$Ga-citrate-PET for diagnostic imaging of infection in rats and for intra-abdominal infection in a patient. Curr Radiopharm 5:71–75
28. Vorster M, Maes A, Jacobs A, Malefahlo S, Pottel H, van de Wiele C, Sathekge MM (2014) Evaluating the possible role of $^{68}$Ga-citrate PET/CT in the characterization of indeterminate lung lesions. Ann Nucl Med 28:523–530
29. Kwee TC, Kwee RM, Alavi A (2008) FDG-PET for diagnosing prosthetic joint infection: systematic review and metaanalysis. Eur J Nucl Med Mol Imaging 35:2122–2132
30. Zoccali C, Teori G, Salducca N (2009) The role of FDG-PET in distinguishing between septic and aseptic loosening in hip prosthesis: a review of literature. Int Orthop 33:1–5
31. Cristina N, Costantino E, Luca B et al (2010) $^{68}$Ga-citrate PET/CT for evaluating patients with infections of the bone: preliminary results. J Nucl Med 51:1932–1936
32. Nielsen OL, Afzelius P, Bender D, Schønheyder HC, Leifsson PS, Nielsen KM, Larsen JO, Jensen SB, Alstrup AK (2015) Comparison of autologous $^{111}$In-leukocytes, $^{18}$F-FDG, $^{11}$C-methionine, $^{11}$C-PK11195 and $^{68}$Ga-citrate for diagnostic nuclear imaging in a juvenile porcine haematogenous staphylococcus aureus osteomyelitis model. Am J Nucl Med Mol Imaging 5:169–182
33. Mäkinen TJ, Lankinen P, Pöyhönen T, Jalava J, Aro HT, Roivainen A (2005) Comparison of $^{18}$F-FDG and $^{68}$Ga PET imaging in the assessment of experimental osteomyelitis due to *Staphylococcus aureus*. Eur J Nucl Med Mol Imaging 32:1259–1268
34. Tseng JR, Chang YH, Yang LY, Wu CT, Chen SY, Wan CH, Hsiao IT, Yen TC (2019) Potential usefulness of $^{68}$Ga-citrate PET/CT in detecting infected lower limb prostheses. EJNMMI Res 9:2. https://doi.org/10.1186/s13550-018-0468-3
35. Vorster M, Buscombe J, Saad Z, Sathekge M (2018) Past and future of Ga-citrate for infection and inflammation imaging. Curr Pharm Des 24:787–794
36. Anna R, Donato DP, Filippo L et al (2009) Synthesis and quality control of $^{68}$Ga citrate for routine clinical PET. Nucl Med Commun 30:542–545
37. Akiko H, Joji Y, Tomoteru Y et al (2012) PET imaging of lung inflammation with [$^{18}$F]FEDAC, a radioligand for translocator protein (18 kDa). PLoS One 7:e45065
38. Vorster M, Maes A, van de Wiele C, Sathekge M (2019) $^{68}$Ga-citrate PET/CT in tuberculosis: a pilot study. Q J Nucl Med Mol Imaging 63:48–55
39. Lin YY, Chen JH, Ding HJ et al (2012) Potential value of dual-time-point $^{18}$F-FDG PET compared with initial single-time-point imaging in differentiating malignant from benign pulmonary nodules: a systematic review and meta-analysis. Nucl Med Commun 33:1011–1018
40. Wang SJ, Gao C (2010) Advancement of the study on iron metabolism and regulation in tumor cells. Chin J Cancer 29:451–455
41. Begoña MM, Rogelio LV (2013) Therapeutic options for old world cutaneous leishmaniasis and new world cutaneous and mucocutaneous leishmaniasis. Drugs 73:1889–1920
42. Lei XY, Liu MM, Yu XJ (2015) Severe fever with thrombocytopenia syndrome and its pathogen SFTSV. Microbes Infect 17:149–154
43. Segard T, Morandeau LM, Dunne ML, Robinson JO, Murray RJ, Geelhoed EA, Francis RJ (2019) Comparison between Gallium-68 citrate PET-CT and Gallium-67 citrate scintigraphy for infection imaging. Intern Med J. DOI: https://doi.org/10.1111/imj.14231
44. Thackeray JT, Bankstahl JP, Wang Y, Korf-Klingebiel M, Walte A, Wittneben A, Wollert KC, Bengel FM (2015) Targeting post-infarct inflammation by PET imaging: comparison of $^{68}$Ga-citrate and $^{68}$Ga-DOTATATE with 18 F-FDG in a mouse model. Eur J Nucl Med Mol Imaging 42:317–327
45. Jødal L, Jensen SB, Nielsen OL, Afzelius P, Borghammer P, Alstrup AKO, Hansen SB (2017) Kinetic modelling of infection tracers [$^{18}$F]FDG, [$^{68}$Ga]Ga-citrate, [$^{11}$C]methionine, and [$^{11}$C]donepezil in a porcine osteomyelitis model. Contrast Media Mol Imaging 2017:1–18