

# Gallium-67 Scintigraphy in the Era of Positron Emission Tomography and Computed Tomography

## Tertiary centre experience

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### تصوير الجسم باستخدام مسح الغاليوم-67 في عصر التصوير المقطعي بالإصدار البوزيتروني والتصوير المقطعي

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**ABSTRACT: Objectives:** Although  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) has largely replaced the use of gallium-67 ( $^{67}\text{Ga}$ ) scintigraphy in the evaluation and follow-up of lymphoma patients,  $^{67}\text{Ga}$  scans are still of value, particularly in countries where no PET/CT service is available. The current study presents the experience of a tertiary care centre using  $^{67}\text{Ga}$  scintigraphy for the evaluation of lymphomas and infections. **Methods:** A retrospective review was conducted of all  $^{67}\text{Ga}$  scans performed between 2007 and 2011 at the Royal Hospital in Muscat, Oman. Images and reports of  $^{67}\text{Ga}$  scans were compared to clinical and radiological follow-up data including CT and PET/CT scans and biopsies when available. **Results:** A total of 74 patients were referred for  $^{67}\text{Ga}$  scintigraphy during this period with 12 patients excluded due to lack of follow-up data, resulting in 62 patients. Among these patients, 90  $^{67}\text{Ga}$  scans were performed, including 59 for lymphoma, 29 for infection and two for sarcoidosis assessment. Of the infection assessment scans, 22 were performed to assess pyrexia of unknown origin and seven for follow-up after known infections. Sensitivity and specificity were found to be 80% and 88%, respectively, for the lymphoma assessment scans. For the infection assessment scans, sensitivity and specificity were reported to be 80% and 100%, respectively. **Conclusion:** Results from this study were consistent with other reported rates of  $^{67}\text{Ga}$  scan sensitivity and specificity in the evaluation of lymphomas and infections. This indicates that  $^{67}\text{Ga}$  scintigraphy is a useful tool for these types of evaluations when PET/CT services are not available.

**Keywords:** Gallium-67-Citrate; Gallium Radioisotopes; Fluorodeoxyglucose F18; Scintigraphy; Lymphoma; Infection; Fever of Unknown Origin; Oman.

**الملخص:** الهدف: على الرغم من أن التصوير المقطعي بالإصدار البوزيتروني/التصوير المقطعي  $^{18}\text{F}$ -fluorodeoxyglucose قد حل إلى حد كبير محل مسح الجسم باستخدام الغاليوم-67 ( $^{67}\text{Ga}$ ) في تقييم ومتابعة مرضى سرطان الغدد الليمفاوية، إلا أن مسح  $^{67}\text{Ga}$  لا يزال ذي قيمة، ولا سيما في البلدان التي تكون فيها خدمة PET/CT غير متاحة. تقدم الدراسة الحالية تجربة مركز رعاية ثلاثية في استخدام مسوحات  $^{67}\text{Ga}$  لتقييم الأورام الليمفاوية والالتهابات. الطريقة: أجري استعراض بأثر رجعي لجميع الحالات التي أجري لها مسح  $^{67}\text{Ga}$  بين عامي 2007 و 2011 في المستشفى السلطاني في مسقط، سلطنة عمان. وتمت مقارنة صور وتقارير مسح  $^{67}\text{Ga}$  لبيانات المتابعة السريرية وتقارير الأشعة المقطعية وتقارير التصوير المقطعي بالإصدار البوزيتروني ونتائج الخزعات عندما تكون متاحة. النتائج: تم تحويل ما مجموعه 74 مريضا لمسح الجسم باستخدام  $^{67}\text{Ga}$  خلال هذه الفترة. تم استبعاد 12 مريضا نظرا لعدم وجود بيانات المتابعة، فكان المجموع المتبقي 62 مريضا أجري لهم ما مجموعه 90 مسحا باستخدام  $^{67}\text{Ga}$ ، بما في ذلك 59 مسحا لسرطان الغدد الليمفاوية، 29 مسحا للعدوى واثنان لتقييم مرض الساركويد. أوضحت النتائج أن الحساسية والخصوصية لمسح  $^{67}\text{Ga}$  لتقييم سرطان الغدد الليمفاوية كان 88% و 80% على التوالي، و 100% و 80% لمسح تقييم العدوى على التوالي. الخلاصة: كانت نتائج هذه الدراسة تتفق مع الدراسات الأخرى التي أجريت لنفس الغرض. وهذا يدل على أن مسح الجسم باستخدام  $^{67}\text{Ga}$  هو أداة مفيدة لهذه الأنواع من التقييمات في المناطق التي لا تتوفر فيها خدمات.

**مفتاح الكلمات:** الغاليوم-67 - سبترت: النظائر المشعة للغاليوم؛ فلورايد-18 فلوروديوكسيجلوكوز؛ مسح الجسم؛ سرطان الغدد الليمفاوية؛ عدوى؛ حمى غير معروفة المنشأ؛ سلطنة عمان.

#### ADVANCES IN KNOWLEDGE

- Results of the current study confirmed that the sensitivity and specificity of gallium-67 ( $^{67}\text{Ga}$ ) scintigraphy in this tertiary centre were consistent with those reported in the international literature.

#### APPLICATION TO PATIENT CARE

-  $^{67}\text{Ga}$  scintigraphy can help in localising the foci of infection. Scans can also show positive findings in patients with neoplastic disease

*presenting with pyrexia of unknown origin. Follow-up  $^{67}\text{Ga}$  scans can be performed to assess the response to treatment or resolution of the infective process.*

*- Despite current hybrid and molecular imaging services provided by combined  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography and computed tomography, this study demonstrated that  $^{67}\text{Ga}$  scintigraphy remains a useful tool for the evaluation and follow-up of patients with lymphoma.*

**T**HE CLINICAL IMPACT AND COST-EFFECTIVENESS of combined  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET) and computed tomography (CT) is well documented in the literature and this technology has a wide range of applications in both benign diseases and oncology.<sup>1</sup> Additionally, the role of PET/CT in the diagnosis and management of lymphomas has been well established for more than a decade.<sup>2</sup> Non-PET radiotracers that were previously used for the evaluation of lymphomas and infections are now seldom utilised in current practice. However, despite the advances this technology has brought to patient management, some centres still lack PET/CT facilities. In other institutions where PET/CT is available, not all PET radiotracers are accessible or approved for clinical practice. Hence, the old radiotracers used in nuclear medicine still exist and play a role in today's modern practice.

One of the most commonly used radioisotopes in tumour imaging, as well as in the imaging of infection and inflammation, is gallium-67 citrate ( $^{67}\text{Ga}$ ).<sup>3</sup> This group IIIA metal has been used for decades for the imaging of various solid neoplasms, particularly lymphomas, and in the investigation of acute inflammatory conditions. It is also used to assess infections and to identify the site of disease in patients with pyrexia of unknown origin (PUO).<sup>4</sup>  $^{67}\text{Ga}$  is produced by cyclotron and has a half-life of 78.26 hours and energy abundances of 93 kilo electron volts ([keV] 40%), 184 keV (20%), 300 keV (17%) or 393 keV (5%). For medical radiology purposes,  $^{67}\text{Ga}$  is provided in the form of a sterile solution of gallium citrate.<sup>3,5,6</sup> The human body reacts to  $^{67}\text{Ga}$  similarly to the way that it handles ferric iron. Gallium III ions bind to transferrin glycoproteins, leukocyte lactoferrin, bacterial siderophores, inflammatory proteins and cell membranes in neutrophils and become concentrated in areas of inflammation and rapid cell division.<sup>3,7</sup>

This retrospective study aimed to evaluate the use of  $^{67}\text{Ga}$  in a tertiary care hospital over a period of five years and compare outcomes with available clinical and radiological follow-up data, including CT and PET/CT scans and biopsies.

## Methods

This retrospective review included all  $^{67}\text{Ga}$  scintigraphy scans performed in the Department of Nuclear Medicine at the Royal Hospital, Muscat, Oman, from 2007–2011. Only patients who were referred to this department and with follow-up appointments at the Royal Hospital were included in the study.

At the Royal Hospital,  $^{67}\text{Ga}$  scans were performed by nuclear medicine technologists with a Siemens E-Cam Dual-Head Variable Angle Gamma Camera (Siemens Medical Solutions USA Inc., Malvern, Pennsylvania, USA). Adult patients undergoing  $^{67}\text{Ga}$  scintigraphy received a dose of 180 megabecquerels (MBq) while the dose for child patients was calculated by multiplying their weight in kg by 180 MBq and dividing the total by 70 kg.<sup>8</sup> All patients with excessive bowel activity were given laxatives and scanned one or two days afterward. Whole body imaging for lymphoma patients was performed 48 hours after the  $^{67}\text{Ga}$  injection using both detectors with a matrix size of 256 x 1,024 pixels. However, patients with PUO or infections were imaged 24 hours after the injection. Additional imaging was performed after 48 hours or later, if deemed necessary.

Spot views of the chest and abdomen were acquired with both detectors with a matrix size of 256 x 256 pixels. Imaging was halted either after five minutes had elapsed or if 500 kilo counts had been obtained. The whole process usually took 30–45 minutes, although sometimes longer if single photon emission CT images were also required.

The  $^{67}\text{Ga}$  images and reports were compared to subsequent clinical and radiological follow-up data, including CT and PET/CT scans and biopsies, if available. These data were collected from hospital records retrospectively.

This study was approved by the Research & Ethical Committee at the Royal Hospital (#MESRC 17/2014).

## Results

A total of 74 patients were referred to the Department of Nuclear Medicine at the Royal Hospital for  $^{67}\text{Ga}$  scintigraphy between 2007 and 2011; however, 12

**Table 1:** Comparison of the findings of gallium-67 scintigraphy lymphoma assessment scans to subsequent clinical and radiological follow-up data (N = 59)

Scan type	Result				Total
	True-positive	False-positive	True-negative	False-negative	
Baseline	5	0	0	1	6
Mid-therapy	3	0	6	1	10
Post-therapy	11	5	24	3	43
<b>Total</b>	<b>19</b>	<b>5</b>	<b>30</b>	<b>5</b>	<b>59</b>

patients were excluded due to a lack of follow-up data. As a result, 62 patients were included in the final sample. The mean age of these patients was 43 years old. A total of 28 patients were male (45%). The majority of referrals were from medical oncologists referring lymphoma patients (n = 24; 39%) and infectious diseases specialists referring patients (n = 9; 15%), primarily for the localisation of infection sites. Seven patients (11%) were paediatric haematology cases; the remaining patients were chest medicine, paediatric, rheumatology, nephrology, neurology or acute medicine cases.

A total of 90 <sup>67</sup>Ga scans were performed during the study period. Assessment of lymphomas constituted the bulk of the referrals, with a total of 59 scans (66%). Of the remaining scans, 29 (32%) were performed for infection assessment and two (2%) were performed

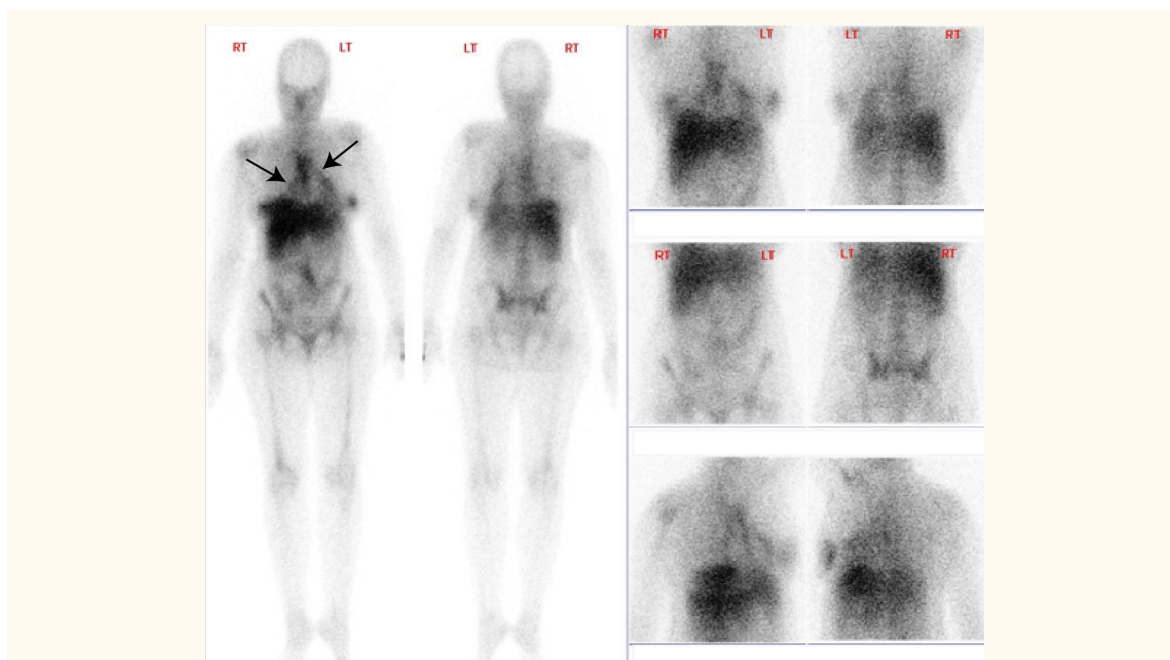
**Table 2:** Comparison of the findings of gallium-67 scintigraphy infection assessment scans to subsequent clinical and radiological follow-up data (N = 29)

Scan type	Result				Total
	True-positive	True-negative	False-positive	False-negative	
PUO	12	7	0	3	22
Follow-up of known infection	5	2	0	0	7
<b>Total</b>	<b>17</b>	<b>9</b>	<b>0</b>	<b>3</b>	<b>29</b>

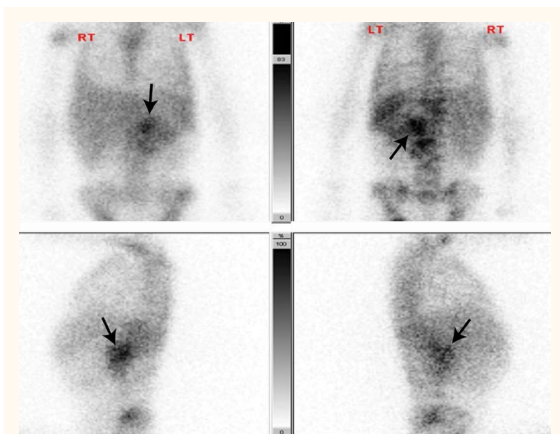
PUO = pyrexia of unknown origin.

for sarcoidosis. Of the <sup>67</sup>Ga scans carried out for lymphoma patients, 32 were for Hodgkin's lymphomas (HL), 23 were for non-Hodgkin's lymphomas (NHL), three were for mucosa-associated lymphoid tissue lymphomas and one was for T cell lymphoma.

Lymphoma scans were divided into six baseline scans, 10 mid-therapy response assessment scans and 43 post-therapy scans for the assessment of relapse [Table 1]. Of the six baseline studies, five scans yielded true-positive results and one showed a false-negative result. Of the 10 mid-therapy studies performed to assess response to therapy, six were true-negative, three were true-positive and one yielded a false-negative result. The majority of the <sup>67</sup>Ga lymphoma scans were performed to assess relapse: 24 scans yielded true-negative results (i.e. no evidence of gallium-avid lesions); 11 scans produced true-positive



**Figure 1:** Gallium-67 scintigraphy images revealing pericardial uptake (arrows) in a patient with pyrexia of unknown origin. Echocardiography and aspiration revealed tuberculosis (TB) pericarditis. The patient was subsequently treated with anti-TB medication.  
RT = right; LT = left.



**Figure 2:** Gallium-67 scintigraphy images showing left suprarenal uptake (arrows) in a child with pyrexia of unknown origin. Computed tomography and a subsequent biopsy revealed a neuroblastoma.  
RT = right; LT = left.

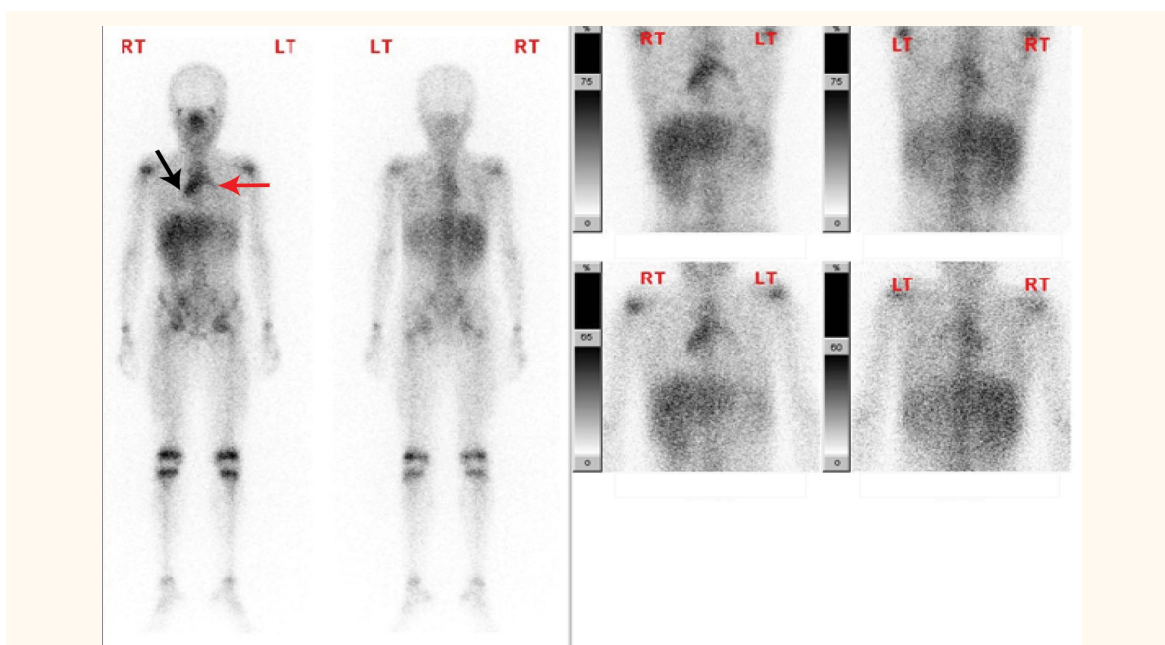
results (either recurrence in the same sites or relapses in new sites); and five scans gave false-positive results (infection sites which were mistaken for lymphoma lesions). The remaining three scans yielded false-negative results as the lesions were not avid on <sup>67</sup>Ga scans but were positive on a subsequent <sup>18</sup>F-FDG-PET/CT scan or via biopsy. These results indicated a sensitivity and specificity of 80% and 88%, respectively, for assessing lymphomas using <sup>67</sup>Ga scintigraphy.

Infection assessments were carried out either for patients with PUO in order to localise the source of infection (n = 22) or for follow-up of a known infection (n = 7) [Table 2]. For known infection follow-

up scans, five yielded true-positive results while two yielded true-negative results. Of the 22 patients who were scanned for PUO, nine indicated positive uptake at different sites and these areas were subsequently targeted during treatment. One of these patients had a positive 24-hour whole body <sup>67</sup>Ga scan with pericardial uptake indicating active pericarditis, which turned out to be secondary to tuberculosis [Figure 1]. A further three patients were found to have <sup>67</sup>Ga-avid lesions. Of the three, one patient showed suprarenal uptake, with a biopsy revealing neuroblastoma [Figure 2]. The second patient had supraclavicular lymph node uptake revealing HL [Figure 3], while the third patient showed lung uptake which was found to be Wegener's granulomatosis.

There were no <sup>67</sup>Ga-avid lesions found in the remaining 10 PUO assessment scans. In three patients, no source of infection was found and the patients were treated empirically with antibiotics. In another three patients, the negative scans were attributed to prolonged antibiotic therapy (n = 2) and fungal infection (n = 1). In the final four negative <sup>67</sup>Ga scans, no source of infection was found and the fevers were attributed to different disease processes, including systemic lupus erythematosus, adult-onset Still's disease, a connective tissue disease and myelodysplastic syndrome. These results showed sensitivity and specificity rates of 80% and 100%, respectively, in the assessment of infection using <sup>67</sup>Ga scintigraphy.

Two patients were known to have sarcoidosis and were referred for an assessment of disease activity. One was negative with no <sup>67</sup>Ga-avid uptake related to



**Figure 3:** Gallium-67 scintigraphy images showing mediastinal (red arrow) and thymic uptake (blue arrow) in a patient referred for lymphoma assessment. A biopsy revealed Hodgkin's lymphoma.  
RT = right; LT = left.

sarcoidosis, while the other showed bilateral breast uptake which, upon clinical examination, was found to be caused by bilateral mastitis.

## Discussion

PET/CT has almost replaced  $^{67}\text{Ga}$  scintigraphy in the assessment of both oncology and infection; this imaging modality plays a well-documented and clinically proven role not only in tumour staging, but also in evaluating treatment response and predicting treatment outcomes.<sup>1,8,9</sup> In addition, the use of PET/CT in the imaging of inflammation and in the evaluation of patients with PUO is well-known.<sup>10,11</sup> In spite of the efficacy of this modality, some nuclear medicine departments may nevertheless lack PET/CT facilities or resources. Hence,  $^{67}\text{Ga}$  scintigraphy is still used for tumour and infection imaging.  $^{67}\text{Ga}$  uptake is highest in diffuse large cell and high- and intermediate-grade lymphomas due to their high cell division rates.<sup>4,5</sup>

$^{67}\text{Ga}$  citrate was used extensively in the past for several pathological conditions, particularly when the presence of tumours, infection or inflammation was in question.<sup>3</sup> In past decades, the role of  $^{67}\text{Ga}$  scintigraphy in nuclear oncology mainly focused on assessing the response of lymphoma to therapy. However, it was also used as a baseline for staging and to assess gallium avidity, patient response to treatment and residual disease activity post-therapy.<sup>5</sup>

In a study evaluating 50 lymphoma patients,  $^{67}\text{Ga}$  was used in routine staging and was found to provide information that was missed or equivocal by other diagnostic modalities in 20–25% of patients.<sup>12</sup> Another study compared the positive and negative predictive values and disease-free survival rates in 43 patients with HL and 56 patients with NHL.<sup>13</sup> A significant difference in disease-free survival was found between patients with positive and negative  $^{67}\text{Ga}$  scans. It was concluded that  $^{67}\text{Ga}$  was a reliable predictor of clinical outcomes in these cases.<sup>13</sup>

Regarding the use of  $^{67}\text{Ga}$  scintigraphy in evaluating infection and inflammation, high sensitivity has been demonstrated for both infectious as well as non-infectious inflammation processes.<sup>14</sup> The most common clinical scenarios where  $^{67}\text{Ga}$  is still utilised include PUO, sarcoidosis and in cases of malignant *otitis externa*. In addition,  $^{67}\text{Ga}$  has been successfully utilised in the evaluation of spinal discitis and vertebral osteomyelitis, mainly to assess disease activity.<sup>3</sup>

Technetium-99m ( $^{99\text{m}}\text{Tc}$ ) sulesomab is another modality for evaluating infection and can be used instead of  $^{67}\text{Ga}$  in most indications.<sup>15</sup> This anti-granulocyte antigen-binding fragment has been

used for more than a decade to image soft tissue infections and osteomyelitis.<sup>15</sup> At the Royal Hospital,  $^{99\text{m}}\text{Tc}$  sulesomab has been used since 2013 to evaluate patients with total knee replacements for septic loosening. It is also valuable in detecting osteomyelitis in patients with sickle cell disease, particularly when a three-phase bone scan might yield a false-positive result in sites with regenerating bone marrow following vaso-occlusive crises.<sup>15</sup>

$^{18}\text{F}$ -FDG-PET/CT imaging is not yet available in Oman.<sup>16</sup> Almost all oncology patients from the Royal Hospital are sent abroad for  $^{18}\text{F}$ -FDG-PET/CT imaging for initial staging and the evaluation of residual disease and treatment response. Currently,  $^{67}\text{Ga}$  citrate is used for the imaging of patients with PUO and the evaluation of patients with malignant *otitis externa*. In addition to a three-phase bone scan,  $^{67}\text{Ga}$  is also used to evaluate patients with total knee replacements for septic loosening.

## Conclusion

Although the utilisation of  $^{67}\text{Ga}$  citrate has become less common with the introduction of new imaging modalities such as PET/CT and new radiotracers such as  $^{99\text{m}}\text{Tc}$ , the findings of this study confirm that there is a continuing role for this radiotracer in infection and tumour imaging, particularly when PET/CT facilities are not available. Furthermore, the results from this study were consistent with other reported rates of  $^{67}\text{Ga}$  scan sensitivity and specificity in the evaluation of lymphomas and infections.

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