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Gallium citrate-67 single-photon emission computed tomography/computed tomography for localizing the foci of classic fever and inflammation of unknown origin: A retrospective study of diagnostic yield

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ABSTRACT

Objective(s): Only few studies have assessed the use of gallium citrate-67 single-photon emission computed tomography/computed tomography (^{67}Ga-SPECT/CT) for localizing the foci of classic fever of unknown origin (FUO) and inflammation of unknown origin (IUO). Hence, the current study aimed to assess the diagnostic contribution of ^{67}Ga-SPECT/CT in a tertiary referral setting where nuclear imaging tests are performed after an unsuccessful comprehensive primary diagnostic workup.

Methods: We retrospectively assessed the medical records of 27 adult patients with FUO/IUO who had an unsuccessful diagnostic workup and who underwent ^{67}Ga-SPECT/CT for the localization of FUO/IUO foci in our university hospital between 2013 and 2019. The primary outcome was diagnostic yield. The secondary outcomes were overall clinical efficacy and spontaneous remission of FUO/IUO symptoms in patients with a negative ^{67}Ga-SPECT/CT finding.

Results: Almost all patients completed the recommended diagnostic workup, except for urine culture and abdominal ultrasonography. Moreover, prior to ^{67}Ga-SPECT/CT, all patients underwent thoraco-abdominopelvic CT scan, which was a non-diagnostic procedure. After a median follow-up of 843 days, the cause was identified in 16 (59%) patients. ^{67}Ga-SPECT/CT successfully localized the FUO/IUO foci in eight patients (diagnostic yield = 30%; 95% confidence interval [CI]: 14%–50%). However, the causes remained unknown during follow-up in 11 (41%) patients. Among them, five experienced spontaneous regression of symptoms. ^{67}Ga-SPECT/CT was negative in four of the five patients with spontaneous regression in symptoms without a definite cause. Considering this an important event, the overall clinical efficacy of ^{67}Ga-SPECT/CT increased to 44% (95% CI: 25%–65%).

Conclusion: ^{67}Ga-SPECT/CT had an acceptable diagnostic yield for the localization of FUO/IUO foci, which are challenging to diagnose, in a contemporary tertiary referral care setting. In patients who experienced spontaneous regression in symptoms with an unexplained cause, the absence of abnormal uptake might indicate prospective spontaneous remission. Thus, ^{67}Ga-SPECT/CT could be an active first-line nuclear imaging modality in settings where fluorine-18-fluorodeoxy glucose positron emission tomography and computed tomography is not available for the assessment of FUO/IUO causes.

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Introduction

Classic fever of unknown origin (FUO) (1) and inflammation of unknown origin (IUO) (2) are two diagnostically challenging medical conditions observed in generally healthy, immunocompetent patients. These two conditions have different characteristics. That is, patients with IUO typically do not present with high fever, and the primary manifestation of patients with FUO is fever at > 100.9˚F (38.3°C) (1). Nevertheless, their diagnostic approach overlaps, and the underlying etiologies are significantly common (2).

Nuclear imaging tests using a tracer that highly accumulates in inflamed, infected, or neoplastic cells are advanced diagnostic technologies that can help localize foci that may represent the cause of FUO or IUO. The use of fluorine-18-fluorodeoxy glucose positron emission tomography and computed tomography (^{18}F-FDG PET/CT) can accurately identify the foci of the cause in approximately 60% of patients with FUO who have no diagnostic clue after a routine diagnostic workup (3, 4). However, despite the recent recommendations of experts, the health insurance coverage does not include ^{18}F-FDG PET/CT for this clinical indication in several countries including Japan (5, 6).

Gallium citrate-67 (^{67}Ga) scintigraphy is another widely available nuclear imaging test that can assess the anatomical location of a tumor or inflammation foci (7, 8). In Japan, planer imaging with or without single photon emission computed tomography (SPECT) using ^{67}Ga is the standard test for assessing such lesions in patients with FUO or IUO. However, the diagnostic yield of ^{67}Ga scintigraphy in patients with FUO ranged from 21% to 54%, with an average of 35% (3, 9-14). However, this was evaluated from the 1980s to 2000s when diagnostic technologies were limited.

Recently, low-dose CT scan has been integrated with SPECT (SPECT/CT) to complement anatomical information and to facilitate attenuation correction for better image reconstruction similar to positron emission tomography/computed tomography (PET/CT) (15, 16). Theoretically, hybrid ^{67}Ga SPECT/CT (^{67}Ga-SPECT/CT) can improve the limited ability of conventional SPECT and planer images in localizing FUO or IUO foci (3). The first study on the clinical application of ^{67}Ga-SPECT/CT in patients with FUO and in those with confirmed bone or soft tissue infections was performed in 2006 (17). However, it failed to provide detailed data on FUO. Subsequently, only two recent studies have used ^{67}Ga-SPECT/CT on patients with FUO. Results showed that this imaging modality can accurately localize the FUO foci in up to 51% of patients (18, 19).

SPECT/CT has been increasingly used in Japan in this decade (20). Hence, the diagnostic contributions of ^{67}Ga-SPECT/CT in patients with classic FUO or IUO in contemporary settings should be evaluated. The current study aimed to report a 7-year experience in the use of ^{67}Ga-SPECT/CT in identifying the cause of unexplained FUO or IUO.

Methods

Study design

This was a retrospective study conducted at the General Internal Medicine Department of Fujita Health University Hospital, a 1,435-bed tertiary care teaching hospital in Japan, between 2013 and 2019. The Institutional Review Board of Fujita Health University approved this study, and the need for informed consent was waived (approval no.: HM17-460). This research was conducted in accordance with the updated Standards for Reporting Diagnostic Accuracy statement (STARD 2015) (21) and STARD for Abstracts (22).

Eligibility criteria on FUO and IUO

We included all patients with classic FUO or IUO who underwent ^{67}Ga-SPECT/CT as the first-line nuclear imaging test because of unexplained etiologies despite an aggressive diagnostic workup between April 1, 2013, and December 31, 2019. FUO was defined as 1) body temperature of ≥38.3°C (101°F) on at least two occasions, 2) illness duration of ≥3 weeks, and 3) failure in identifying FUO etiology after three visits in the outpatient clinic or a 3-day inpatient investigation (23). In case the first febrile criterion was not met, as proposed in previous reports, the patient must meet at least either of the following to be diagnosed as IUO: C-reactive protein (CRP) level of > 7 mg/L or erythrocyte sedimentation rate (ESR) calculated as > age/2 in men or (age + 10)/2 in women (2, 24). Patients who were immunocompromised and neutropenic or those who were hospitalized due to other preexisting causes were excluded.

Pre-^{67}Ga-SPECT/CT diagnostic workup

According to the recent opinion of experts, the routine primary diagnostic workup comprised history taking and physical examination; laboratory testing including ESR, platelet count, leukocyte count with differentiation, or CRP, hemoglobin, electrolyte, creatinine, total protein, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine phosphokinase, antinuclear antibody, and rheumatoid factor levels; protein electrophoresis test; urinalysis; blood culture; urine culture; chest radiography; abdominal ultrasonography;

and interferon-γ release assay (1). Rather than abdominal ultrasonography, non-contrast-enhanced thoraco-abdominopelvic CT scan was performed. Other specific but noninvasive tests were conducted individually if indicated. The median completion rate for each mandatory examination, except for urine culture and abdominal ultrasonography, was 100% (range: 89%–100%). All patients underwent thoraco-abdominopelvic CT scan. The compliance rates for our primary diagnostic workup are presented in Table 1.

Table 1. Compliance rates for the mandatory examinations for FUO or IUO

Characteristics of the patients, n (%)	All patients (n=27)	Patients with FUO (n=17)	Patients with IUO(n=10)
Erythrocyte sedimentation rate	27 (100)	17 (100)	10 (100)
C-reactive protein level	27 (100)	17 (100)	10 (100)
Leukocyte and differential blood count	27 (100)	17 (100)	10 (100)
Hemoglobin and red blood cell count	27 (100)	17 (100)	10 (100)
Total protein level	27 (100)	17 (100)	10 (100)
Alkaline phosphatase level	27 (100)	17 (100)	10 (100)
Alanine/aspartate aminotransferase level	27 (100)	17 (100)	10 (100)
Lactate dehydrogenase level	27 (100)	17 (100)	10 (100)
Creatinine kinase level	27 (100)	17 (100)	10 (100)
Ferritin level	27 (100)	17 (100)	10 (100)
Soluble interleukin-2 receptor* level	24 (89)	17 (100)	7 (70)
Antinuclear antibody level	26 (96)	16 (94)	10 (100)
Rheumatoid factor level	26 (96)	16 (94)	10 (100)
Antineutrophil cytoplasmic antibody level*	26 (96)	16 (94)	10 (100)
Urinalysis results	25 (93)	17 (100)	8 (80)
Blood culture results	25 (93)	16 (94)	9 (90)
Urine culture results	12 (56)	9 (53)	3 (30)
Chest radiography results	27 (100)	17 (100)	10 (100)
Abdominal ultrasonography results	13 (48)	8 (47)	5 (50)
Interferon-γ release assay results	24 (89)	16 (94)	8 (80)
Chest and abdominopelvic CT scan results*	27 (100)	17 (100)	10 (100)
Contrast-enhanced chest and abdomino-pelvic CT scan results*	17 (63)	13 (76)	6 (60)

*These tests are not mandatory in the Bleeker-Rovers criteria on FUO.
CT = computed tomography; FUO = fever of unknown origin; IUO = inflammation of unknown origin

^{67}Ga-SPECT/CT

Whole-body SPECT/CT images were obtained using Symbia T6 (Siemens, Munich, Germany) 48 h after intravenous injection of 74–185 MBq of ^{67}Ga (1.85 MBq/kg in body weight). SPECT images were acquired from the head to the toes, and low-dose CT images of the corresponding body parts were subsequently obtained. We did not obtain planar images. All patients routinely received oral laxatives for bowel preparation. We performed image reconstruction and generated SPECT/CT fusion images using the Syngo MI Applications (Siemens, Munich, Germany). SPECT images were reconstructed using Flash 3D in a reconstruction algorithm, and processing was done without scatter correction and with attenuation correction using low-dose CT images .

Interpretation of imaging results

The SPECT/CT images were visually interpreted using other medical data by either a pair of junior staff nuclear medicine physician and a board-certified experienced senior nuclear medicine specialist, or a single board-certified nuclear medicine specialist. The interpreters were not aware of the final diagnosis. Positive findings were defined as increased accumulation of ^{67}Ga that cannot be explained by background physiological distributions .

Diagnosis of FUO etiology

All diagnostic and therapeutic managements were determined based on the results of ^{67}Ga-SPECT/CT. Biopsy was commonly performed if the ^{67}Ga-SPECT/CT results were positive. If malignancy was suspected, additional biopsy was conducted. However, a diagnosis was established clinically if noninfectious inflammatory diseases (NIIDs) were suspected. Local pathologists made a diagnosis using all clinical information including nuclear imaging results. An investigator (ST) who was blinded to the findings of ^{67}Ga-SPECT/CT validated the final diagnosis based on the medical records including microbiology and pathology reports. The same investigator then extracted all data on nuclear imaging findings unless the clinical diagnosis was explicitly based on the imaging results.

Data extraction

One investigator (ST) collected data from the medical records, which included the demographic characteristics of the participants; medical history; symptoms; vital signs; physical examination results; findings of mandatory tests, whole-body CT scan, and other imaging studies; results of ^{67}Ga-SPECT/CT; and the final diagnosis with its supporting rationales.

Outcomes

There was no single perfect reference standard, and clinical follow-up was considered an integral part of the clinical reference standard for classic FUO or IUO. In addition, in theory, a status of "disease negative" (vs. "disease positive") in the standard framework of diagnostic accuracy studies does not apply to classic FUO or IUO because any one disease should exist. However, this clinically challenging status is considered a condition of unexplained FUO or IUO. Therefore, the standard framework for assessing sensitivity and specificity, which uses a cross-classification system comprising true-positive [TP], false-positive [FP], false-negative [FN], and true-negative [TN] results based on whether the ^{67}Ga-SPECT/CT finding was positive or negative crossed with whether the specific etiology of FUO/IUO was identified, could not appropriately represent test performance (25). To address this limitation, when the etiology of FUO or IUO was identified in a patient with positive imaging results, we explicitly differentiated whether the lesion was within or outside the ^{67}Ga-SPECT/CT positive site(s) (i.e., TP vs FP1) (Figure 1). In case of positive SPECT/CT findings with unexplained FUO or IUO cause, the patient was categorized as FP2. Further, patients with unexplained FUO or IUO cause were subclassified into sustained FUO or IUO and spontaneous remission based on post-^{67}Ga-SPECT/CT clinical follow-up.

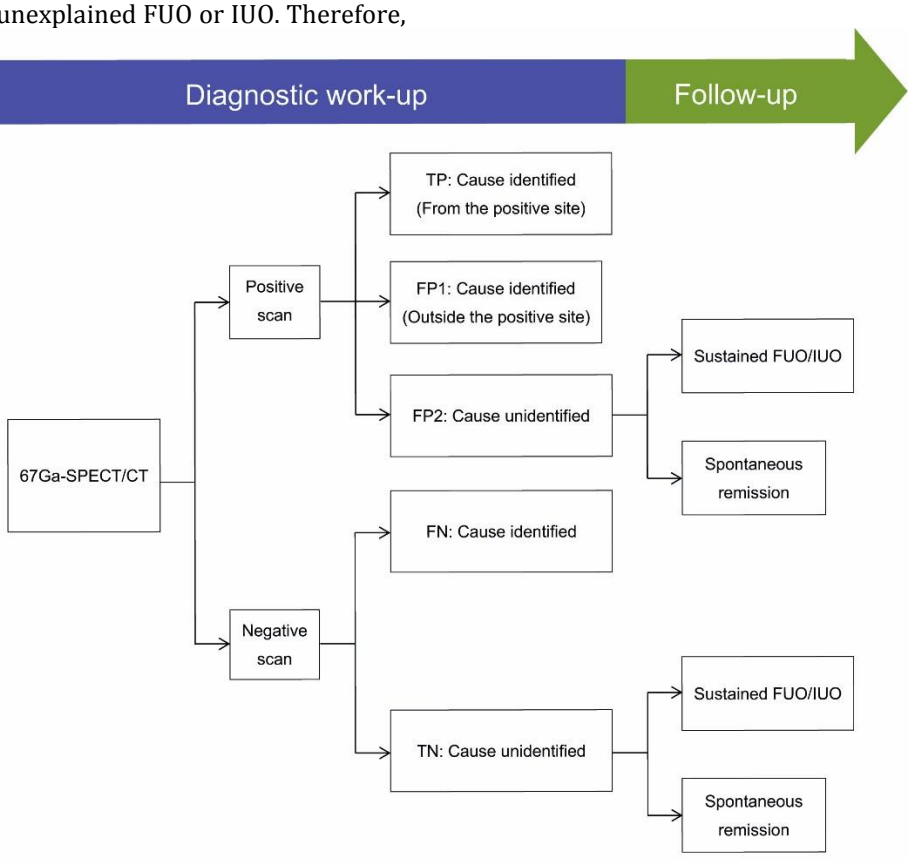

Figure 1. Study design
CT=computed tomography; FN=false negative; FP=false positive; FUO=fever of unknown origin; ^{67}Ga=gallium citrate-67; IUO=inflammation of unknown origin; SPECT=single photon emission computed tomography; TP=true positive; TN=true negative

The primary outcome of interest was diagnostic yield, which is conventionally defined as the proportion of patients categorized as TP in relation to the total number of tests performed (3, 25):

Diagnostic yield = TP / (TP + FP1 + FP2 + FN + TN).

To identify a single cause from multiple target conditions in different screening tests, the diagnostic yield is an effective measure for understanding the overall diagnostic impact of the test (26). However, due to the difference in the proportion of patients with unexplained cause of FUO or IUO who experience spontaneous regression in symptoms without

therapeutic interventions (27), a negative result could be beneficial in preventing subsequent (particularly invasive) diagnostic procedures. With consideration of this benefit and to simultaneously prevent the potential underestimation of the overall efficacy of a diagnostic test by focusing on diagnostic yield (4), the overall clinical efficacy, which was considered a secondary outcome, was evaluated. It was defined as the proportion of patients categorized as TP and those as TN who subsequently experienced remission in symptoms during follow-up in relation to the total number of tests:

Overall clinical efficacy = (TP + spontaneous remission in TN) / (TP + FP1 + FP2 + FN + FN).

Finally, we assessed the predictability of spontaneous remission based on a negative imaging result, which was another secondary outcome. It was operationally defined as the cumulative incidence of SR in patients with a negative imaging result (28).

Statistical analyses

All analyses were performed using Stata SE version 16.1 (StataCorp, College Station, TX, the USA). In all analyses, two-tailed p-values < 0.05 were considered statistically significant. All variables were presented as means and standard deviations or medians and ranges or interquartile ranges (IQRs), or as numbers and percentages as appropriate. We assessed the 95% confidence intervals (CIs) of proportions using the standard exact method. We only qualitatively compared the clinical characteristics between patients who satisfied the diagnostic criteria on FUO and those who satisfied the criteria on IUO due to the small sample size.

Results

Participants

There were 27 consecutive patients (17 with FUO and 10 with IUO) who underwent ^{67}Ga-SPECT/CT as the first-line nuclear imaging test for identifying the cause that was not detected on pre-^{67}Ga-SPECT/CT diagnostic workup.

Characteristics of the participants

The median age of the patients was 71 (range: 40–87) years, and 22 (84%) of 27 patients underwent ^{67}Ga-SPECT/CT within 3 months from symptom onset (Table 2). Although the small sample size across-category comparisons were limited, patients with FUO and those with IUO had similar laboratory results.

Table 2. Characteristics of the patients

Characteristics of the patients	All patients (n=27)	Patients with FUO (n=17)	Patients with IUO (n=10)
Median age (range), years	70 (40–87)	67 (52–87)	76 (40–87)
Male sex, n (%)	13 (48)	8 (47)	5 (50)
Use of medications, n (%)			
Steroids*	1 (4)	1 (6)	0 (0)
Antimicrobials	0 (0)	0 (0)	0 (0)
Comorbidities, n (%)			
Diabetes	7 (26)	4 (24)	3 (30)
Autoimmune disorders†	1 (4)	0 (0)	1 (10)
Previous malignancy	4 (14)	3 (18)	1 (10)
Median laboratory values (range)			
CRP level, mg/dL	8.6 (0.3–27.4)	9.3 (0.3–27.4)	5.4 (0.6–9.0)
ESR, mm	96 (24–140)	101 (51–140)	74 (24–125)
Hb level, g/dL	11.1 (8.0–13.5)	11.1 (8.0–12.6)	10.9 (8.4–13.5)
LDH level, IU/L	206 (108–715)	206 (108–715)	202 (150–329)
Leukocyte level, /μL	9,800 (1,800–22,700)	12,200 (3,500–22,700)	8,700 (1,800–13,100)
sIL-2R level, U/mL§	1,281 (422–35,716)	1,472 (514–35,716)	1,044 (422–2,704)
Time between symptom onset and ^{67}Ga-SPECT/CT			
<1 month, n (%)	7 (26)	7 (41)	0 (0)
1–3 months, n (%)	15 (56)	9 (53)	6 (60)
3–6 months, n (%)	2 (7)	1 (6)	1 (10)
6–12 months, n (%)	1 (4)	0 (0)	1 (10)
>12 months, n (%)	2 (7)	0 (0)	2 (20)
Median (IQR), days	51 (27–77)	41 (22–53)	82 (52–194)

*One patient with FUO who had Tolosa-Hunt syndrome treated with prednisolone at a maintenance dose of < 5 mg daily.

†One patient with IUO who had rheumatoid arthritis.

§Based on a total of 24 patients (17 with FUO and 7 with IUO)

CRP=C-reactive protein; CT=computed tomography; ESR=erythrocyte sedimentation rate; FUO=fever of unknown origin; ^{67}Ga=gallium citrate-67; Hb=hemoglobin; IQR=interquartile range; IUO=inflammation of unknown origin; LDH=lactate dehydrogenase; NIID=noninfectious inflammatory disease; sIL-2R=soluble interleukin-2 receptor

Reference standards and cause of FUO or IUO

The cause of FUO or IUO was successfully identified in 16 (59%) patients (3 [11%] with malignancy, 11 [41%] with noninfectious inflammatory diseases, and 2 [7%] with miscellaneous causes) (Table 3). Biopsy, which was performed based on positive ^{67}Ga-SPECT/CT findings, confirmed the diagnosis in six patients. In other patients, because only the ^{67}Ga-SPECT/CT result was equivocally positive, bone marrow aspiration and biopsy were conducted based on other clinical findings, which confirmed the diagnosis of myelodysplastic syndrome. In nine patients in whom the cause of FUO or IUO was diagnosed clinically without histological confirmation, positive ^{67}Ga-SPECT/CT findings supported the clinical diagnosis in four patients (polymyalgia rheumatica [n=1], pseudogout [n=1], ulcerative colitis-related polyarthritis [n=1], and giant cell arthritis [n=1]). The selected images are presented in Figures 2 and 3. In other patients, the clinical diagnosis was based on the ^{18}F-FDG PET/CT results in one (giant cell arteritis), conventional clinical diagnostic criteria in three (adult-onset Still's disease [n=2] and polymyalgia rheumatica [n=1]), and clinical course in one (drug fever) patient.

The cause was not identified in 11 (41%) patients (Table 3). Only one patient had a histological diagnosis (lymph node biopsy based on the results of ^{18}F-FDG PET/CT performed after obtaining equivocally positive ^{67}Ga-SPECT/CT findings), which was undiagnostic. In these patients, the cause remained unexplained, and it was clinically followed-up for a median of 396 days.

Table 3. Cross-classification of the ^{67}Ga-SPECT/CT results, reference standards, and causes of FUO or IUO

^{67}Ga-SPECT/CT results	**Type of reference standard**	**Number of identified FUO or IUO causes, n (median follow-up duration, days)**					**Total, n**
		Malignancy [TP/FP1/FN]	NIIDs [TP/FP1/FN]	Miscellaneous [TP/FP1/FN]	Total number of diagnosed cases [TP/FP1/FN]	No. of diagnosis [FP2/TN]	
All patients				**(n = 843; IQR: 58–1859)**			
Positive	Histological	2 [2/0/0]	2 [2/0/0]	0[0/0/0]	4 [4/0/0]	1 [1/0]	5
	Clinical	0 [0/0/0]	4† [4/0/0]	1§ [1/0/0]	5 [5/0/0]	5 [5/0]	10
Negative	Histological	1 [0/0/1]	1 [0/0/1]	0 [0/0/0]	2 [0/0/2]	0 [0/0]	2
	Clinical	0 [0/0/0]	4 [0/0/4]	1 [0/0/1]	5 [0/0/5]	5 [0/5]	10
Total		3 [2/0/1]	11 [6/0/5]	2 [1/0/1]	16 [9/0/7]	11 [6/5]	27
FUO				**(n = 958; IQR: 58–1685)**			
Positive	Histological	2 [2/0/0]	1 [1/0/0]	0[0/0/0]	3 [3/0/0]	0 [0/0]	3
	Clinical	0 [0/0/0]	2† [2/0/0]	1§ [1/0/0]	3 [3/0/0]	4 [4/0]	7
Negative	Histological	0 [0/0/0]	1 [0/0/1]	0 [0/0/0]	1 [0/0/1]	0 [0/0]	1
	Clinical	0 [0/0/0]	4 [0/0/4]	1 [0/0/1]	5 [0/0/5]	1 [0/1]	6
Subtotal		2 [2/0/0]	8 [3/0/5]	2 [1/0/1]	12 [6/0/6]	5 [4/1]	17
IUO				**(n = 682; IQR: 396–993)**			
Positive	Histological	1 [1/0/0]	1 [1/0/0]	0[0/0/0]	1 [1/0/0]	1 [1/0]	2
	Clinical	0 [0/0/0]	2 [2/0/0]	0 [0/0/0]	2 [2/0/0]	1 [1/0]	3
Negative	Histological	1 [0/0/1]	0 [0/0/0]	0 [0/0/0]	1 [0/0/1]	0 [0/0]	1
	Clinical	0 [0/0/0]	0 [0/0/0]	0 [0/0/0]	0 [0/0/0]	4 [0/4]	4
Subtotal		2 [1/0/1]	3 [3/0/0]	0 [0/0/0]	4 [3/0/1]	6 [2/4]	10

*Metastatic uterine cancer was diagnosed clinically based on PET/CT findings (n=1). Peripheral T-cell lymphoma, unspecified, was clinically diagnosed independent from the PET/CT findings (n=1). The pathology observed in the biopsy specimens obtained from the PET/CT negative skin was inconclusive

†^{67}Ga-SPECT/CT results were used as the rationale for the diagnosis of polymyalgia rheumatica (n=1)

§^{67}Ga-SPECT/CT results were used as the rationale for the diagnosis of pseudogout (n=1)

CT=computed tomography; FN=false negative; FP=false positive; FUO=fever of unknown origin; ^{67}Ga=gallium citrate-67; IQR=interquartile range; IUO=inflammation of unknown origin; TN=true negative; TP=true positive

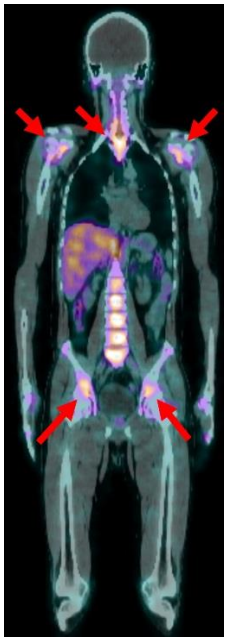

Figure 2. Inflammatory bowel disease associated spondyloarthritis localized on [67]Ga-SPECT/CT
A 43-year-old man with Crohn's disease that was in remission who was referred to our hospital for the assessment of IUO. A [67]Ga-SPECT/CT showed increased uptakes in multiple joints including the bilateral shoulder, sternoclavicular, and hip joints (red arrows). The patient was then clinically diagnosed with inflammatory bowel disease associated spondyloarthritis
CT=computed tomography; [67]Ga=gallium-67citrate; IUO=inflammation of unknown origin; SPECT=single photon emission computed tomography

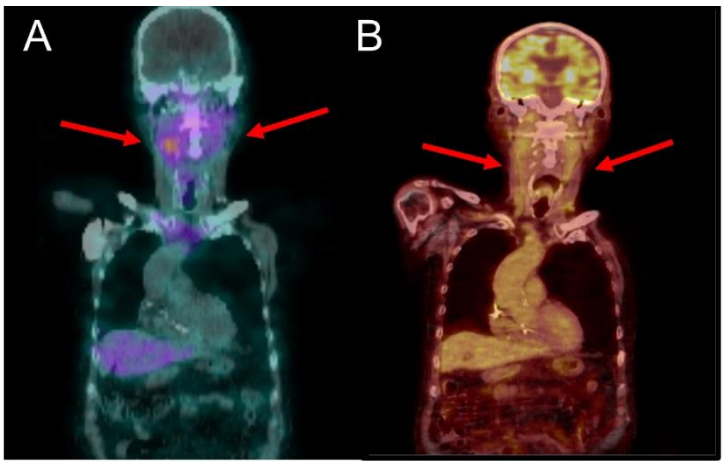

Figure 3. Giant cell arteritis localized on [67]Ga-SPECT/CT
[67]Ga-SPECT/CT was performed in a 77-year-old man with IUO who was experiencing anorexia. Results showed right-side dominant, bilateral uptakes in the common carotid artery (red arrows) (A). This result was indicative of giant cell arteritis, and it was confirmed on [18]F-FDG PET/CT (red arrows) (B)
[18]F-FDG = 2-deoxy-2-[[18]F]fluoro-D-glucose; FUO = fever of unknown origin; PET=positron emission tomography

Diagnostic yield and overall efficacy

[67]Ga-SPECT/CT contributed in diagnosing the cause of FUO or IUO in 8 of 27 patients (diagnostic yield=30%; 95% CI: 14%–50%) (Table 4). Positive [67]Ga-SPECT/CT results helped identify malignancy in 2 (67%) of 3 and NIIDs in 5 (45%) of 11 patients. The foci of FUO or IUO were not successfully localized in patients with myelodysplastic syndrome (n=1) for malignancy and adult-onset Still's disease (n=3), giant cell arthritis (n=1), polymyalgia rheumatica (n=1), and intestinal Behçet's disease (n=1) for NIIDs (Table 5). When spontaneous symptom remission in patients with a negative imaging result and sustained unexplained etiology was additionally considered as a clinically useful event, [67]Ga-SPECT/CT was found to be effective in 12 of 27 patients (overall clinical efficacy=44%; 95% CI: 25%–65%) (Table 4). The limited sample size precluded formal statistical analyses on the differences in diagnostic yield and overall clinical efficacy between patients with FUO and those with IUO.

Contrast-enhanced thoraco-abdominopelvic CT was performed on 17 (63%) patients, and it identified diagnostic clues that could have led to a direct diagnosis without [67]Ga-SPECT/CT in three additional patients. When these three patients were excluded post-hoc, the efficacy decreased. Hence, positive [67]Ga-SPECT/CT findings contributed to the diagnosis of the cause of FUO or IUO in 6 of 24 patients (diagnostic yield=25%; 95% CI: 10%–47%), and negative [67]Ga-SPECT/CT results accurately identified four additional patients who experienced spontaneous remission in symptoms (overall clinical efficacy=42% [10/24]; 95% CI: 22%–63%).

Table 4. Diagnostic yield, spontaneous remission, and overall clinical efficacy of ^{67}Ga-SPECT/CT in patients with FUO or IUO

Outcomes	All patients (n=27)	Patients with FUO (n=17)	Patients with IUO (n=10)
Diagnostic yield			
All patients, n (% [95% CI])	8/27 (30 [14–50])	5/17 (29 [10–56])	3/10 (30 [7–65])
Stringent indication only*, n (% [95% CI])	6/24 (25 [10–47])	4/15 (27 [8–55])	2/9 (22 [3–60])
Proportion of patients with SR who had a negative imaging result			
All patients, n (% [95% CI])	4/11 (36 [11–69])	0/7 (0 [0–41])	4/4 (100 [40–100])
Stringent indication only*, n (% [95% CI])	4/10 (40 [12–74])	0/6 (0 [0–46])	4/4 (100 [40–100])
Overall clinical efficacy			
All patients, n (% [95% CI])	12/27 (44 [25–65])	5/17 (29 [10–56])	7/10 (70 [35–93])
Stringent indication only*, n (% [95% CI])	10/24 (42 [22–63])	4/15 (27 [8–55])	6/9 (67 [30–93])

*Three patients with inconclusive, equivocal diagnostic clues identified who further underwent contrast-enhanced thoraco-abdominopelvic CT were excluded
CI=confidence interval; SR=spontaneous remission

Table 5. Final diagnosis and respective diagnostic yield of ^{67}Ga-SPECT/CT in patients with FUO or IUO

FUO/IUO cause	All patients (n=27)	Patients with FUO (n=17)	Patients with IUO (n=10)
Malignancy	**2/3 (67)**	**2/2 (100)**	**0/1 (0)**
Diffuse large B-cell lymphoma	1/1 (100)	1/1 (100)	–
Chronic lymphocytic leukemia	1/1 (100)	1/1 (100)	–
Myelodysplastic syndrome	0/1 (0)	–	0/1 (0)
NIID, n (%)	**5/11 (45)**	**2/8 (25)**	**3/3 (100)**
Adult-onset Still's disease	1/4 (25)	1/4 (25)	–
Giant cell arteritis	1/2 (50)	0/1 (0)	1/1 (100)
Polymyalgia rheumatica	1/2 (50)	1/2 (50)	–
Intestinal Behçet's disease	0/1 (0)	0/1 (0)	–
Sarcoidosis	1/1 (100)	–	1/1 (100)
UC-related arthritis	1/1 (100)	–	1/1 (100)
Miscellaneous	**1/2 (50)**	**1/2 (50)**	**–**
Pseudogout	1/1 (100)	1/1 (100)	–
Drug fever	0/1 (0)	0/1 (0)	–
No diagnosis	**0/11 (0)**	**0/5 (0)**	**0/6 (0)**

FUO=fever of unknown origin; IBD=inflammatory bowel disease; IUO=inflammation of unknown origin

Survival and spontaneous remission

Four patients, of whom three presented with FUO (1 with intestinal Behçet's disease [FN ^{67}Ga-SPECT/CT], 1 with chronic lymphocytic leukemia [TP ^{67}Ga-SPECT/CT], and 1 with unexplained FUO [FP ^{67}Ga-SPECT/CT]) and one with IUO (giant cell arthritis [TP ^{67}Ga-SPECT/CT]), died at a median follow-up of 843 (IQR: 58–1859) days (Figure 4). Patients with sustained unexplained FUO or IUO who presented with a negative ^{67}Ga-SPECT/CT scan had a higher risk of spontaneous remission than those with a positive imaging finding (four [80%] of five in patients with a negative result vs. one [17%] of six with a positive result). However, the result was not significant (log-rank test, P=0.11).

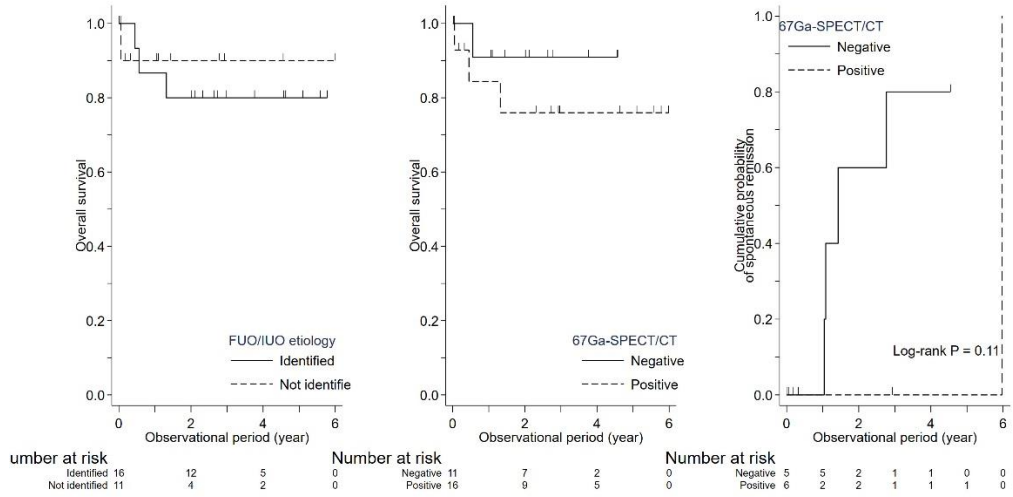

Figure 4. Survival and spontaneous remission of patients with classic FUO or IUO
Overall survival according to successful versus unsuccessful diagnosis of FUO/IUO etiologies (A) and positive versus negative ^{67}Ga-SPECT/CT results (B). Spontaneous remission in patients who remained undiagnosed (sustained FUO/IUO) based on positive versus negative ^{67}Ga-SPECT/CT results (C)

Discussion

Key results

This single-center retrospective study validated the efficacy of ^{67}Ga-SPECT/CT in diagnosing the cause of FUO or IUO in a tertiary care setting. After an unsuccessful routine clinical workup, ^{67}Ga-SPECT/CT was performed, and it had a diagnostic yield of 30%. This value decreased to 25% when three patients with additional diagnostic clues identified on contrast-enhanced CT scan were excluded. Patients with sustained unexplained cause of FUO or IUO who had a negative ^{67}Ga-SPECT/CT result had a higher risk of spontaneous remission of symptoms than those with a positive imaging finding. However, the results were inconclusive due to the small sample size.

The results of the current study (a diagnostic yield of 30%) might be similar to those of a recent study conducted in Taiwan by Hung et al. The latter study reported that the diagnostic yield (based on our definition) of ^{67}Ga-SPECT/CT was 33% (18). However, this finding must be cautiously validated via a between-study indirect comparison because the spectrum of differential diagnoses varies based on the level of care (e.g., primary vs. tertiary) and intensiveness of pre-^{67}Ga-SPECT/CT diagnostic workup. Our study was based on the clinical practice in a tertiary referral hospital with an aggressive and extensive diagnostic workup, as proposed by Bleeker-Rovers et al. (1). This workup included a series of assessment on autoantibodies and inflammation markers and interferon-γ release assay. Further, it was routinely supplemented by plain torso CT scan in all patients and contrast-enhanced CT scan in > 50% of patients. This method can identify and exclude substantial proportions of malignancy, infection, and NIID, which are the three classic causes of FUO (29). In contrast, the diagnostic workup implemented in the study of Hung was based on rather basic laboratory and imaging tests only, thereby indicating that ^{67}Ga-SPECT/CT was likely to be performed early in the series of diagnostic workup (Table 6). Indeed, our university hospital-based cohort did not include patients with infectious causes. This was in contrast to the study of Hung et al. as 23 (40%) of 58 patients presented with infections, including 10 documented tuberculosis cases (18). Our cohort was also different from that of the previous study because the malignant causes were exclusively hematologic neoplasms, and patients with systematic lupus erythematosus were not included. In another recent study by Vincente et al. (19) in Spain, a diagnostic yield of 51% was reported, which is higher than the other two studies, although they did not report on the exact workup strategy or clinical setting. However, a different clinical context, such as an earlier level of care setting and/or a less intensive pre-^{67}Ga-SPECT/CT workup, was inferred based on the high prevalence (27 [47%] of 57 patients) of infectious causes (Table 6). Therefore, between-study indirect comparisons of the diagnostic yields may not be justified.

Table 6. Cohort studies of ^{67}Ga-SPECT/CT in patients with FUO or IUO*

Study ID	Sample size, n	Target condition (criteria)	Setting	Pre-^{67}Ga-SPECT/CT workup (compliance rate, %)	Prevalence of malignancy, % (diagnostic yield, n [%])	Prevalence of infections, % (diagnostic yield, n [%])	Prevalence of NIIDs, % (diagnostic yield, n [%])	Overall diagnostic yield, n (%)
Hung 2017 (18)	58	FUO (Petersdorf 1961 or Durack 1991)	Primary and tertiary care	CBC (100), CRP (100), ESR (100), UA (100), BCx (100), UCx (100), CXR (100) CCT (13), AUS (100)	17 (8/10 [80])†	40 (8/23 [35])	19 (3/11 [27])‡	19/68 (33)
Vicente 2018 (19)	57	"FSUO" (ND)§	ND	ND	2 (ND)	47 (ND)	26 (ND)	29/57 (51)
Current study	27	FUO(Durack 1991)/IUO (Vander schueren)	Tertiary care	CBC (100), CRP (100), ESR (100), TP (100), ALP (100), LDH (100), CK (100), Ferritin (100), sIL-2R (89), ANA (96), RF (96), ANCA (96), IGRA (89), UA (93), BCx (93), UCx (56), CXR (100), CCT (100), AUS (48), APCT (100), CECT (63)	11 (2/3 [67])‖	0 (NE [NE])	41 (5/11 [45])**	8/27 (30)

*The diagnostic yield was recalculated based on the definition adopted in the current study. See text.

†^{67}Ga-SPECT/CT was not effective in identifying malignant lymphoma (n=1) and neuroendocrine tumor (n=1).
‡^{67}Ga-SPECT/CT was not effective in identifying systemic lupus erythematosus (n=4), adult-onset Still's disease (n=2), anti-phospholipid antibody syndrome (n=1), and hemophagocytic lymphohistiocytosis (n=1).
§The inclusion criteria were not explicitly reported.
||^{67}Ga-SPECT/CT was not effective in identifying myelodysplastic syndrome (n=1).
**^{67}Ga-SPECT/CT was not effective in identifying adult-onset Still's disease (n=3), giant cell arteritis (n=1), polymyalgia rheumatica (n=1), and intestinal Behçet's disease (n=1).
ALP = alkaline phosphatase; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; APCT = abdominopelvic computed tomography; AUS = abdominal ultrasound; BCx = blood culture; CBC = complete blood count; CCT = chest computed tomography; CECT = contrast-enhanced computed tomography of the chest, abdomen, and pelvis; CK = creatine phosphokinase; CRP = C-reactive protein; CT = computed tomography; CXP = chest x-ray; ESR = erythrocyte sedimentation rate; FUO = fever of unknown origin; FSUO = febrile syndromes of unknown origin; ^{67}Ga = gallium citrate-67; IGRA = interferon gamma release assay; IUO = inflammation of unknown origin; LDH = lactate dehydrogenase; ND = no data; NE = not estimable; NIID = noninfectious inflammatory disease; RF = rheumatoid factor; sIL-2R = soluble interleukin receptor 2; SPECT = single photon computed tomography; TP = total protein; UA = urinalysis; UCx = urine culture

Limitations

First, this was a retrospective observational study of routine medical records, and it was based on clinical practice. Moreover, the sample size was small. Then, pre- and post-^{67}Ga-SPECT/CT diagnostic workups were individually performed and were not completely standardized, despite the high completion rates for the recommended mandatory tests (1). Second, direct comparison of diagnostic yield of ^{67}Ga-SPECT/CT with that of ^{67}Ga-SPECT alone is a useful information for demonstrating the additional benefit of fusion images over stand-alone SPECT images. Our retrospective observation failed to provide this information because all the three images (i.e., SPECT alone, CT alone, and fusion images) were simultaneously and comprehensively interpreted in clinical practice. Therefore, this research cannot answer whether ^{67}Ga-SPECT/CT outperforms stand-alone ^{67}Ga-SPECT.

Implications for clinical practice

^{67}Ga is a widely available and approved standard nuclear imaging tracer for assessing the foci of FUO or IUO. In addition, SPECT/CT devices have been increasingly used. They are now more accessible in Asia in this decade (30), and this finding is well-documented in South Korea (31) and Japan (20). The generalizability of our results is based on each individual setting. However, with consideration of the availability of this modality and the lack of formal health insurance coverage for the use of ^{18}F-FDG PET/CT, a 30% diagnostic yield indicate that ^{67}Ga-SPECT/CT is an active first-line nuclear imaging modality for identifying FUO/IUO foci in settings where SPECT/CT scanner is available. In particular, this is applicable in the context of clinically challenging cases of FUO or IUO after an unsuccessful diagnostic workup including chest and abdominopelvic CT.

Conclusions

^{67}Ga-SPECT/CT had an acceptable diagnostic yield for localizing FUO or IUO foci in challenging cases in a contemporary tertiary referral care setting in Japan. Hence, this modality is an active first-line nuclear imaging test in settings where ^{18}F-FDG PET/CT is not available for assessing the cause of FUO or IUO.

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Conflicts of interest

All authors declare no conflicts of interest associated with this study. For complete transparency, MI has received honoraria from Otsuka Pharmaceutical Co., Ltd., Astellas Pharma Inc., Eisai Co., Ltd., and Daiichi Sankyo Co., Ltd. However, it is not associated with the current study.

Ethical considerations

This study was conducted in compliance with the Declaration of Helsinki and was approved by the Institutional Review Board of Fujita Health University (approval no. HM17-460). Informed consent was waived because of the retrospective nature of the study and the use of anonymized clinical data in the analysis.

Availability of data and material

The datasets supporting the conclusions of this article were included in the manuscript.

Authors' contributions

ST and TT established the study design. TT drafted the initial version of the research protocol. All authors suggested amendments and approved the final version of the protocol. ST, AW, and TT acquired data. ST and TT performed statistical analyses. All authors interpreted the results. ST and TT drafted the initial version of

the manuscript. All authors reviewed the manuscript and suggested amendments. All authors read and approved the final version of the manuscript. ST and TT are the guarantors of the research.

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