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ORIGINAL ARTICLE

Visual and Quantitative Analysis by Gallium-67 Single-photon Emission Computed Tomography/Computed Tomography in the Management of Malignant Otitis Externa

SSM Wong, K Wang, EHY Yuen, JKT Wong, A King, AT Ahuja

Department of Imaging and Interventional Radiology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

ABSTRACT

Objective: *To evaluate the value of Gallium-67 single-photon emission computed tomography/computed tomography in the diagnosis and monitoring treatment response of malignant otitis externa.*

Methods: *Eight patients underwent 12 Gallium-67 single-photon emission computed tomography/computed tomography scintigraphy for eight suspected malignant otitis externa and were subsequently subjected to visual and quantitative analysis. Relevant patient clinical data and other investigation results were also retrieved for correlation.*

Results: *Gallium-67 single-photon emission computed tomography/computed tomography improved anatomical localisation of lesion uptake. All patients (7/7) with active malignant otitis externa achieved a statistically significant higher Gallium-67 uptake on the side of the lesion than the contralateral side ($p < 0.05$). All patients (5 out of 5) without active malignant otitis externa had no significant difference in Gallium-67 uptake between the two sides. Serum inflammatory markers (white cell count, erythrocyte sedimentation rate, and C-reactive protein) did not correlate with disease activity.*

Conclusion: *Gallium-67 single-photon emission computed tomography, when combined with computed tomography, improves anatomical localisation of lesional uptake. It is also accurate in reflecting active infection and hence can confirm or exclude active malignant otitis externa.*

Key Words: *Gallium radioisotopes; Otitis externa; Tomography, emission-computed, single-photon; Tomography, X-ray computed*

中文摘要

鎵67（Gallium-67）單光子發射電腦斷層攝影／電腦斷層攝影（SPECT/CT）融合作惡性外耳道炎的目測及定量分析

王先民、王琪、袁學遠、黃嘉德、金雅桃、AT Ahuja

目的：評估對於惡性外耳道炎，以鎵67 SPECT/CT融合作診斷和觀察治療結果的效果。

方法：擬有惡性外耳道炎的八名病人接受12次以鎵67 SPECT/CT融合診斷，並進行目測及定量分析。病人臨床資料及其他檢查結果用作相關研究。

結果：鎵67 SPECT/CT融合技術可改善病灶攝取的解剖定位。全部七名確診為惡性外耳道炎的患者中，有病灶的一邊的鎵67攝取值比無病灶的一邊明顯為高（$p < 0.05$）。而全部五位未有活躍性惡性

Correspondence: *Dr K Wang, Department of Imaging and Interventional Radiology, Prince of Wales Hospital, Shatin, New Territories, Hong Kong.*
Tel: (852) 2632 4006 ; Fax: (852) 2632 1323 ; Email: kiwang@hkcr.org

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外耳道炎的患者中，有灶和無灶的一邊對於鎵67攝取值並無顯著分別。血清炎症標誌物（白細胞數目、血沉速度和C反應蛋白）與病症的活躍程度並無相關。

結論：鎵67 SPECT並結合CT技術可改善病灶攝取的解剖定位。除此以外，也可以準確反映炎症的活躍程度，遂能確診或排除活躍性惡性外耳道炎的可能性。

INTRODUCTION

Malignant otitis externa (MOE) is a serious infection of the bone and soft tissue of the external ear and skull base, which confers significant morbidity and even mortality. Clinical assessment alone is often inadequate in diagnosis and monitoring the condition. Conventional imaging modalities such as computed tomography, magnetic resonance imaging (MRI), and bone scintigraphy often show changes that persist even after the infection subsides, and therefore monitoring the treatment response becomes problematic. Gallium-67 (Ga-67) scintigraphy has been reported useful in reflecting disease activity in MOE[1-3] and can help confirm or exclude residual or recurrent MOE. Hence it is a valuable means of guiding clinical management and the need for further antibiotics or surgery. Due to the rarity of this condition however, there is little local data in this subject. It was therefore of interest to evaluate the value of Gallium scintigraphy in the diagnosis and monitoring of MOE and ascertain whether quantitative analysis could improve its sensitivity. Thus, the aim of this study was to evaluate Ga-67 single-photon emission computed tomography/computed tomography (SPECT/CT) for the diagnosis and treatment monitoring of patients with MOE.

METHODS

Patients with suspected MOE referred for Ga-67 scintigraphy in the period between August 2010 and August 2011 were included in this study. A dose of 4 mCi Ga-67 citrate was administered intravenously. Scintigraphy was performed 48 hours later using a dual-head gamma camera coupled with low-dose CT (Infinia Hawkeye 4, General Electric, Israel) for anatomical localisation and soft tissue attenuation correction for SPECT analysis. SPECT studies were preformed using a 64 x 64 matrix, collecting images every 6 degrees (for 360 degrees) in the head and neck region. The acquisition time was 40 seconds per image. The data were auto-processed by a Xeleris 2 Functional Imaging Workstation (Volumetrix for Hawkeye) to give SPECT/CT fusion images. The images were interpreted by visual assessment, count rate analysis of the planar and SPECT/CT images of the lesional and non-lesional side in order to confirm or exclude presence of MOE. A region of interest (ROI) comprising the entire lesion was drawn on the planar and transaxial slice of the SPECT/CT images. This ROI was copied to the non-affected side and the total counts were used to calculate the uptake value. For planar images, the geometric mean of the counts from the lesional or non-lesional side were calculated using the following formula:

$$\text{Geometric mean of counts} = \sqrt{(\text{ROI counts from anterior view}) \times (\text{ROI counts from posterior view})}$$

For SPECT/CT images, the ROI counts of the lesional and non-lesional sides were taken as the uptake value. Clinical data including patient demographics, disease course, treatment received (including mastoidectomy), results of laboratory tests (leukocyte count, erythrocyte sedimentation rate, C-reactive protein, alkaline phosphatase, urea, and creatinine) and culture results of causative agents were retrieved for analysis.

Statistical Analysis

The count rate of the lesional and non-lesional sides from the planar and SPECT/CT images were tabulated. Data were tested for normality using Lilliefors test. A two-tailed paired Student's *T* test was used to evaluate differences in count rates between the lesional and non-lesional side. A p value of less than 0.05 was considered statistically significant.

RESULTS

Eight patients having 12 Ga-67 scans performed were included in this study. Six patients were suspected to suffer from MOE based on clinical features and confirmation by positive culture. Among the latter, patient numbers 1 to 4 were diagnosed to have MOE by conventional imaging (Lightspeed VCT, General Electric, Milwaukee, USA and TX 3T Philips MRI Achieva, Netherland), which further supported the diagnosis. They subsequently underwent mastoidectomy and treatment with intravenous antibiotics. Ga-67 SPECT/CT scans were done 21 to 47 days after the mastoidectomy and showed evidence of residual MOE. Intravenous antibiotics were therefore continued.

Subsequently, these patients showed clinical resolution of their active MOE, together with a negative microbiological workup. Moreover, three of these four patients then underwent a follow-up Ga-67 SPECT/CT within 59 to 82 days of the mastoidectomy, in which the scan showed no more residual infection. Accordingly, intravenous antibiotics were therefore terminated accordingly based on clinical perspectives and negative microbiological result.

Patients 5 and 7 had Ga-67 SPECT/CT before they were diagnosed to have MOE by pre-mastoidectomy Ga-67 SPECT/CT instead of conventional imaging. Patient 6 had a history of recurrent MOE and presented with further recurrent symptoms. However, the microbiological workup was negative, and the patient then underwent a Ga-67 SPECT/CT; recurrent MOE was excluded by a negative Gallium scan and subsequent clinical progress.

Patient 8 presented with clinical features of MOE and had a CT scan which supported the diagnosis. He then underwent a Ga-67 SPECT/CT one week before mastoidectomy. After mastoidectomy, he showed significant clinical improvement and no more cultures were positive. A follow-up Ga-67 SPECT/CT was then performed five weeks after the mastoidectomy (Table 1).

All data utilised for statistical analysis were tested to be normally distributed.

Table 2 lists the scintigraphic data of the seven Ga-67 scans in which the patients were clinically symptomatic and had positive cultures from ear swabs, or the tissue was highly suggestive of MOE. Based on visual analysis of the planar images, only five out of the seven scans showed increased uptake on the lesional side, and could be considered positive for MOE. However, the count rate analysis of the planar images showed that there was

Table 1. Clinical and demographic data of patients having Gallium-67 scintigraphy for suspected malignant otitis externa.

Patient No.	Age (years)	Sex	Site	Interval of Gallium scan after mastoidectomy (weeks)	DM (years)	WBC ($x10^9$/L)	ESR (mm/h)	ALP (IU/l)	CRP (mg/l)	Mastoid-ectomy	Organism
1	60	M	R	4	10	11.5	94	129	6.8	+	*Pseudomonas aeruginosa*
2	75	F	R	7	2	5.8	27	86	0.6	+	*Staphylococcus capitis*
3	94	F	L	4	Nil	3.9	40	81	1.9	+	*P. aeruginosa*
4	63	M	R	3	Nil	5.1	2	52	5.4	+	*Streptococcus agalactiae*
5	61	M	R	2 (before mastoidectomy)	Nil	2.5	76	87	50.4	+	*Enterococcus*
6	59	M	N/A	N/A	Nil	12.5	50	83	11.7	-	N/A
7	88	M	L	3 (before mastoidectomy)	10	4.5	39	49	3	+	*P. aeruginosa*
8	80	M	R	1 (before mastoidectomy) and 5 (after mastoidectomy)	20	9.5	26	56	1.6	+	*P. aeruginosa*

Abbreviations: R = right; L = left; DM = diabetes mellitus; WBC = white cell count; ESR = erythrocyte sedimentation rate; ALP = alkaline phosphatase; CRP = C-reactive protein; N/A = not applicable.

Table 2. Quantitative analysis of findings from Gallium-67 scintigraphy performed on seven patients suspected to have malignant otitis externa suggested by clinical features and confirmed by microbiological workup.

Patient No.	Planar				SPECT/CT			
	Counts (L)	Counts (NL)	L/N	Visual analysis	Counts (L)	Counts (NL)	L/N	Visual analysis
1	20 237	11 753	1.72	↑	942 706	444 521	2.11	↑
2	5 734	5 184	1.11	N	196 043	136 971	1.43	↑
3	12 322	10 314	1.19	N	421 991	234 536	1.8	↑
4	18 637	14 017	1.33	↑	598 163	173 432	3.45	↑
5	19 979	15 695	1.27	↑	89 784	30 536	2.94	↑
7	15 084	10 515	1.44	↑	229 682	94 507	2.43	↑
8	13 963	12 443	1.12	↑	144 765	95 808	1.51	↑
Mean	15 137	11 417	1.31		374 733	172 902	2.24	
	p Value	0.01			p Value	0.03		

Abbreviations: SPECT/CT = single-photon emission computed tomography/computed tomography; L = lesional side; NL = non-lesional side; L/N = lesional–to–non-lesional ratio; ↑ = increased uptake; N = normal uptake.

a statistically significant difference ($p < 0.05$) in count rates between the lesional and non-lesional sides, with a mean lesional/non-lesional ratio (L/N ratio) of 1.31. This difference was further magnified by using SPECT/CT where the count rates of the lesional side was even more significant. The mean L/N ratio also increased to 2.24, meaning that the subtle increase in tracer uptake of the lesional side in planar images could be unmasked by SPECT/CT images. An example is given in Figure 1.

Table 3 lists the scintigraphic data of the five Ga-67 scans in which the patients were clinically asymptomatic and did not yield a positive culture. Patients 1 to 3 had two Gallium scans after mastoidectomy. Result of the first (shown in Table 2) confirmed the presence of residual MOE and therefore antibiotics were continued. After a course of antibiotics, the symptoms of these three patients resolved and a follow-up Gallium scan confirmed clearance of the MOE (Table 3). Patient 6 had a history of recurrent MOE and presented with headache without other symptoms or any positive culture. A Ga-67 scan was performed as part of the work-up to exclude recurrent MOE. Patient 8 presented with clinical features of MOE and had a pre-

Table 3. Quantitative analysis of the five negative Gallium-67 scintigraphy performed for patients with no active malignant otitis externa clinically and negative microbiological workup.

Patient	Planar				SPECT/CT			
	Counts (L)	Counts (NL)	L/N	Visual analysis	Counts (L)	Counts (NL)	L/N	Visual analysis
1	15 962	14 651	1.09	N	442 894	301 178	1.47	↑
2	7 232	6 302	1.15	N	123 813	99 579	1.24	N
3	11 223	11 122	1.01	N	360 451	234 052	1.54	↑
6	6 344	7 115	0.89	N	44 032	46 877	0.94	N
8	9 738	9 744	1.00	N	29 483	30 499	0.97	N
Mean	10 100	9 787	1.03		200 135	142 437	1.23	
	p Value	0.44			p Value	0.14		

Abbreviations: SPECT/CT = single-photon emission computed tomography/computed tomography; L = lesional side; NL = non-lesional side; L/N = lesional–to–non-lesional ratio; ↑ = increased uptake; N = normal uptake.

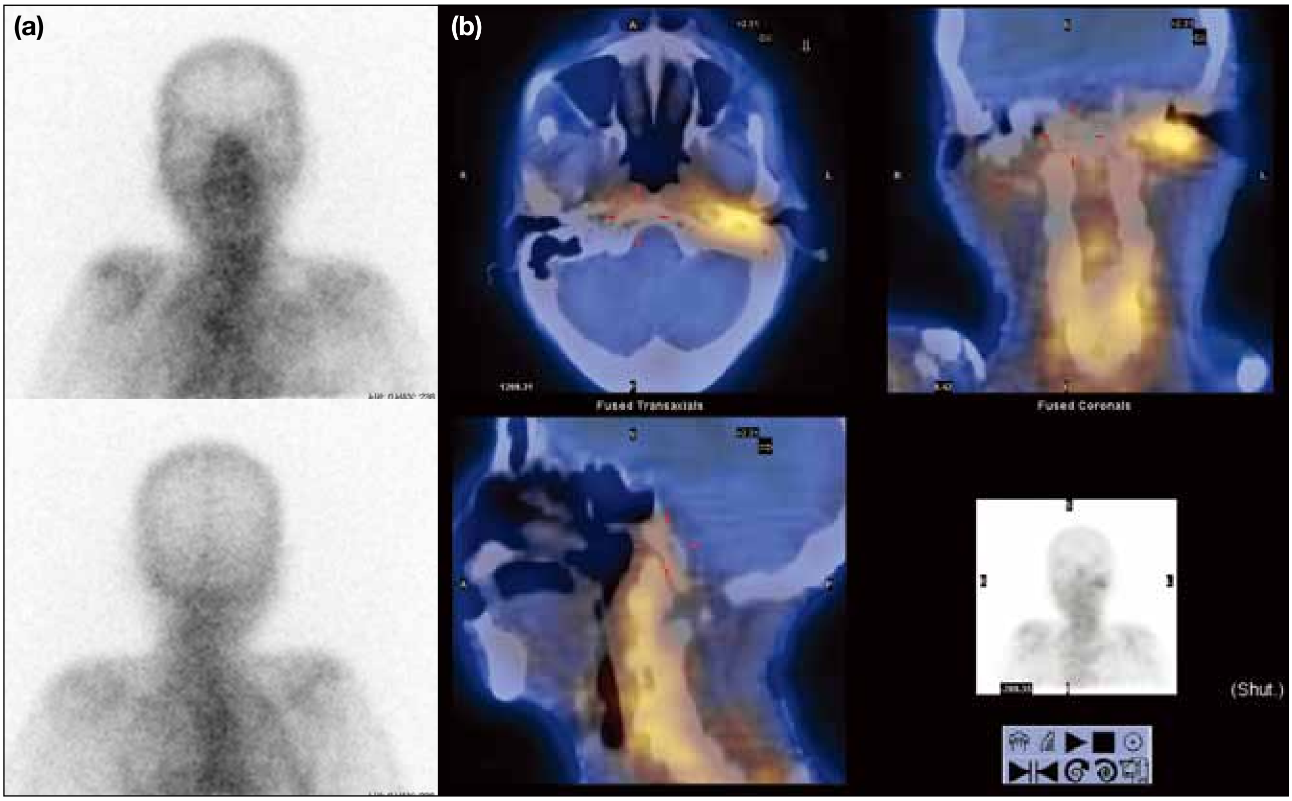

Figure 1. First Gallium scintigraphy of patient 3: (a) planar images show no significant difference in uptake on both sides; (b) SPECT/CT, however, revealed the subtle increase in uptake on the left side and therefore confirmed the presence of residual malignant otitis externa.

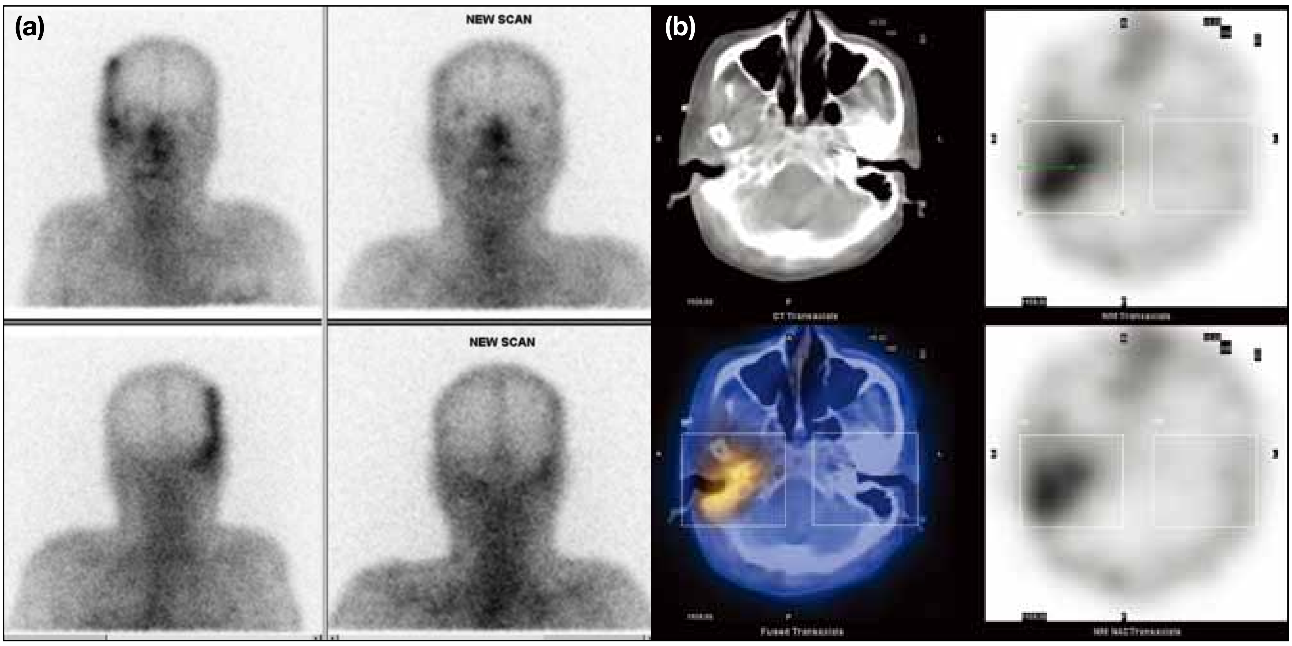

Figure 2. Patient 1: (a) The images show early post-mastoidectomy planar Gallium scan and follow-up scan with residual mild inflammation only. (b) The images show Ga-67 SPECT/CT of an early post-mastoidectomy scan, lesional–to–non-lesional (L/N ratio) = 2.11. SPECT/CT on follow-up scan showed L/N ratio = 1.3 (not shown).

mastoidectomy Ga-67 scan, with findings as shown in Table 2. After mastoidectomy, he had significant clinical improvement without a positive culture. He then underwent a follow-up Ga-67 scan with findings as shown in Table 3. Notably, though visual analysis of the SPECT/CT images suggested some increase of uptake in two of the four patients, there was no statistically significant difference of count rates between the two sides on both the planar and SPECT/CT images. This provided objective measurement indicating no significant increase in tracer uptake on the lesional side. This therefore helped to exclude residual / recurrent MOE. Accordingly, antibiotic therapy was stopped for these patients. An example is given in Figure 2.

Inflammatory parameters (white cell count, erythrocyte sedimentation rate, and C-reactive protein) were also analysed during the Ga-67 SPECT/CT scanning, which showed that these inflammatory parameters did not correlate with significant Gallium scan findings.

DISCUSSION

MOE is an uncommon infection of the external ear that commonly occurs in elderly, diabetic or immunocompromised persons. Extensive bone and soft tissue involvement of the external ear and skull base are its hallmark, which makes the infection difficult to clear. It has a propensity to involve the exiting cranial nerves and spread intracranially and therefore confers significant morbidity and sometimes mortality. Clinical features and microbiological work-up may suggest the diagnosis, but radiological examination is often necessary to confirm the diagnosis and map the extent of disease. CT and MRI are useful in making the initial diagnosis. However, the radiological changes often persist after the infection subsides and therefore these modalities have limited value in monitoring treatment response and recurrence. Bone scintigraphy is sensitive but not specific, and cannot differentiate infection from other causes of increased uptake such as tumour or trauma.

Ga-67 scintigraphy has gained popularity for assessing MOE, particularly if combined with SPECT/CT. There are a number of case series documenting its ability to reflect the activity of an infection and is therefore useful in monitoring treatment response and disease recurrence.[4] This has significant clinical implications as it can determine whether further management such as antibiotics or surgery are necessary. Nevertheless, there is little data concerning the role of quantitative analysis of Ga-67 SPECT/CT in MOE. Stokkel et al[5] studied eight patients with a clinical diagnosis of MOE who underwent Ga-67 SPECT. In addition to visual analysis of the images, they also measured the count rate on the lesional and non-lesional side to calculate the L/N ratio. They found that L/N ratio is accurate in assessing disease activity, and that a L/N ratio of 1.0 ± 0.1 during a follow-up scan is highly indicative of complete recovery.

In our study, visual analysis of the planar images showed that five out of seven patients with active MOE had increased Ga-67 uptake. Further quantitative analysis of both the planar and SPECT/CT images showed that there was a statistically significant increase ($p < 0.05$) in count rates on the lesional compared to non-lesional side. This improved the detection of a subtle increase in uptake, which was not apparent on visual analysis. Although there was mild increase in Ga-67 uptake on visual analysis in patients without active MOE in two patients, quantitative SPECT/CT analysis showed no statistically significant difference in count rates between the two sides. Thus, quantitative analysis by Ga-67 SPECT/CT can help in determining whether there is significant increase in uptake by the lesion concerned. Overall, Ga SPECT/CT findings correlate with disease activity of MOE.

The timing of post-mastoidectomy Ga-67 scans is also important as the uptake soon after mastoidectomy may be due to postoperative inflammatory processes, which makes distinction from residual MOE difficult. Currently there is no established guideline concerning the proper timing of a post-mastoidectomy Ga-67 scan in MOE. In our study, five patients (patients 1 to 4, and 8) had post-mastoidectomy Ga-67 scans 3 to 7 weeks (mean, 5 weeks) after the operation. Among them, patients 1 to 4 had clinical and microbiological evidence of active MOE even after mastoidectomy; their Ga-67 scans have shown significantly increased uptake on the lesional side. Patient 8 showed significant clinical and microbiological improvement after mastoidectomy and his Ga-67 scan showed no increased uptake on the lesional side. It therefore seems that Ga-67 scans 4 to 5 weeks after mastoidectomy correlate well with presence or absence of residual MOE and are not confounded by postoperative inflammatory changes.

We also found that combining CT and SPECT images rather than using SPECT alone may greatly improve anatomical localisation. Osteolytic changes of MOE are also readily appreciable on CT. These advantages increase the confidence for diagnosing MOE.

We found no direct correlation between serum inflammatory markers and disease activity, which may be due to the fact that MOE is an indolent infection and patients are often partially treated. Hence, as in other acute bacterial infections, inflammatory markers are not always raised and therefore do not serve as useful monitoring tools.

Limitations of this study included the small sample size of patients (as MOE is an uncommon condition), its retrospective nature, and the absence of a standardised protocol to assess MOE. Moreover, patients with active infection were not adequately matched with controls, not all patients had follow-up Ga SPECT/CT, which makes assessment of follow-up Ga scans difficult. We recommend that future studies should be prospective, have a larger sample size to further evaluate the accuracy of quantitative analysis of Ga-67 SPECT/CT, and possibly generate a cutoff L/N ratio for diagnosing active MOE.

CONCLUSION

Ga-67 SPECT/CT improves anatomical localisation for detection of infective changes in MOE. The Ga-67 SPECT/CT findings correlated with MOE disease activity and constituted a useful adjunct to conventional imaging, which allowed precise measurement of residual activity on follow-up scans. In addition, Ga-67 SPECT/CT can replace conventional imaging by CT or MRI as a means of diagnosing or excluding MOE, and can influence clinical management of malignant otitis externa. Thus, by reflecting whether there is active MOE, Ga-67 SPECT/CT can help clinicians to decide whether antibiotic treatment is still necessary. In our study, follow-up Ga-67 SPECT/CT early after mastoidectomy could determine the time of discontinuing intravenous antibiotics.

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