FDG-PET/CT for Diagnosis and Follow-up of Necrotizing (Malignant) External Otitis

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INTRODUCTION

Necrotizing (malignant) external otitis (NEO) is an aggressive infection with 14% disease-specific mortality despite appropriate antibiotic treatment.1 The infection originates in the external ear canal and spreads to adjacent structures. By definition, NEO consists of osteomyelitis of the temporal bone.

Due to the rarity of this disease, it poses a clinical challenge. Evidence-based knowledge is derived from small case series or historical cohorts in which diagnosis is based mostly on physical examination and response to treatment.2,3 In 1987, Cohen and Friedman described diagnostic criteria for NEO, including: 1) typical signs and symptoms such as otalgia, otorrhea, edema, and granulation tissue; 2) patient characteristics of old age and diabetes mellitus, and 3) imaging findings that include positive bone scan with methylene diphosphonate (MDP)-technetium-99m (Tc99m) as a major criterion and positive radiography as minor.4

Nevertheless, consensus is lacking regarding the best imaging modality for initial diagnosis and follow-up. Whereas positive findings on computed tomography (CT) scan have been proven a useful tool for diagnosis and prognosis prediction,1 its role in routine follow-up is debatable. Suggestive features in CT scans such as bone resorption may take months to develop and are irreversible.4

Until recently, MDP-Tc99m and gallium-67 (Ga67) scans were commonly used in our medical center for NEO diagnosis and follow-up. Tc99m scan is highly sensitive for NEO diagnosis, but less specific5 because it is also positive for malignancies and trauma. The scan remains positive until cessation of osteoblastic activity; thus, its role in follow-up is limited.4,6–7 Ga67 scan was the imaging modality of choice for follow-up because the uptake resolves once inflammation subsides. However, both methods do not provide adequate anatomical references. Magnetic resonance imaging (MRI) is useful for soft tissue involvement,4,6–10 but it is less adequate for bone involvement, expensive, and not available at all centers. MRI scans also mandate the patient to lay still for...
FDG accumulates in inflammatory processes such as osteomyelitis and was found to be superior to Tc99m, Ga67, leukocyte scintigraphy, and MRI for diagnosing chronic osteomyelitis. In a meta-analysis conducted to determine the best imaging modality for diagnosing chronic osteomyelitis, 18F-FDG-PET/CT was found to have a sensitivity of 96% and a specificity of 91%, with the highest accuracy for confirming or excluding osteomyelitis compared to all other modalities.

The aim of this study was to describe our experience using 18F-FDG-PET/CT for diagnosing and assessing response to treatment in NEO.

**MATERIALS AND METHODS**

The electronic database of the department of otolaryngology–head and neck surgery of a university-affiliated medical center was retrospectively reviewed for all adult patients admitted for NEO from January 2013 through December 2017. The medical center is a major referral site for NEO. Patients were diagnosed with NEO and included in the study if presenting with all the following criteria: 1) external otitis with compatible physical examination of severe otalgia, external ear canal edema, exudate, and granulations; 2) failure to respond to systemic and local antibiotic treatment for at least 1 week; 3) positive finding on 18F-FDG-PET/CT; and 4) histological findings compatible with inflammation (histology was used to rule out malignancy in all the patients).

According to nuclear department protocol, 18F-FDG-PET/CT was performed using an integrated PET/CT scanner (Discovery STE, GE Medical Systems, Milwaukee, WI). 18F-FDG dose varied from 74 to 185 megabecquerel (MBq) (2–5 millicurie [mCi]) according to patient’s weight. Computed tomography was performed from vertex to upper neck, with hands down. The tube voltage was 120 peak kilovoltage, spiral CT at 0.8 second per rotation with modulated 40 to 300 milliamperes, section thickness of 3.75 mm, and 3.75 mm interval with image reconstruction every 2.5 mm. PET emission images were obtained using a weight-based protocol, with 2 to 3 minutes of acquisition time per bed position (two bed positions) resulting in an acquisition time of about 10 minutes. All PET images were reconstructed using an iterative algorithm, with CT-based attenuation correction applied.

After NEO was diagnosed, antibiotics were prescribed for a minimum of 6 weeks. Treatment was discontinued based on normal appearance of the external ear canal; pain resolution; normal C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values; and negative 18F-FDG-PET/CT, which was performed 2 weeks after antibiotic cessation to avoid a false negative result.

Information collected from medical records included age, sex, comorbidities, findings from physical examination, type and duration of treatment, values of inflammatory markers, culture results, histopathological findings, imaging findings, follow-up data, and patient status at the last follow-up. The study protocol was approved by the institutional review board (0019-17-RMC) with waiver of informed consent.

**RESULTS**

A total of 12 patients were diagnosed with NEO from 2013 through 2017. Mean age was 74 ± 11.5; 10 patients (83%) were male; 10 (83%) had type 2 diabetes; five (42%) had renal failure; one was under immunosuppressive treatment (after lung transplantation); and only one patient had no known comorbidities. Mean duration of otalgia prior to hospitalization was 36 ± 23 days. All patients failed to improve after topical and oral antibiotics for at least 1 week prior to admission. All patients presented with edema and sensitivity of the external ear canal; eight patients (67%) had otorrhea; five (42%) had inflammatory granulation tissue at the external canal; and one (8%) had facial nerve palsy. Bacterial culture was taken from all patients, and 10 (83%) had positive isolation. The most common bacteria were *Pseudomonas aeruginosa* (25%), *Staphylococcus aureus* (8%), *Klebsiela pneumonia* (8%), and *Streptococcus anginosus* (8%). Candida was isolated in five patients (42%), and two (16%) had negative cultures. Mean CRP level was 4.1 ± 3.74 mg/dL (normal range 0–0.5).

All 12 patients underwent PET-CT. Abnormal, high FDG uptake was in good correlation with CT findings, suggestive of bone erosion. The posterior wall of the external canal was most commonly involved (Fig. 1A–C), with lower rates of involvement for the mastoid, nasopharynx (Fig. 2A–C) anterior external ear canal, and temporomandibular joint (Fig. 3A–C). Involved anatomical locations of individual patients are detailed in Table I.
All patients received antibiotic treatment, 92% intravenously, mostly with ceftazidime. One patient (8%) was treated with high-dose oral quinolones. Three patients were treated with voriconazole in addition to antibiotic therapy. Mean duration of treatment was 61 days ± 44. The maximum was 192 days.

One patient underwent surgery and hyperbaric oxygen therapy due to exacerbation of facial nerve palsy during treatment (patient 3).

Follow-up and Prognosis
Mean follow-up was 16 ± 15 months.
Eight patients (67%) underwent a second PET/CT scan after completing 6 weeks of antibiotic treatment. The second scan demonstrated no FDG uptake in four patients and substantially reduced FDG uptake in three patients. Hence, treatment was stopped for all seven patients (Figs. 2G–I, 3D–F). CT scan, however, demonstrated resolution of findings in only one patient; three had some improvement in soft tissue enhancement and slight bone mineralization; and the rest demonstrated no change in bone erosions and soft tissue involvement despite negative FDG uptake (Figs. 2G–I, 3D–F).

One patient had significant FDG uptake in the skull base (Fig. 2D–F) after 6 weeks of antibiotic treatment, despite normal otoscopy. The patient completed a second 6-week course of antibiotic treatment until a third scan demonstrated no FDG uptake (Fig. 2G–I), whereas the CT scan demonstrated positive bony findings. At the completion of antibiotic treatment, CRP was within normal range in five patients and elevated in five; mean level was 0.92 ± 0.88 (excluding 2 patients who did not survive completion of treatment).
After an average follow-up of 16 months, the remaining eight patients were free of NEO symptoms. Two patients died before the second PET/CT while still treated with antibiotics for active osteomyelitis (patients 9 and 11) (Table I); their death was attributed to general deterioration due to sepsis. Two patients were lost to follow-up and did not complete the second scan (patients 3 and 5) (Table I). No recurrence was diagnosed in any of the patients.

**Radiation Dose**

Effective radiation exposure dose for the different imaging modalities as published by medical internal radiation dose (MIRD) are elaborated in Table II. NEO diagnosis by PET/CT results in patient exposure of 4.5 millisieverts (mSv), whereas the combination of Tc99m, Ga67, and temporal bone CT scans results in exposure of 19.2 mSv.

**TABLE I.** 18F-FDG-PET Uptake Correlated to CT Findings for Patients’ Diagnosis.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age</th>
<th>Com</th>
<th>CRP</th>
<th>Anterior EAC</th>
<th>Posterior EAC</th>
<th>Mastoid</th>
<th>TMJ</th>
<th>Nasopharynx</th>
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<td>F</td>
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<td>− −</td>
<td>− −</td>
<td>−</td>
<td>− − − −</td>
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</tbody>
</table>

+ positive finding; − negative finding; 18F-FDG-PET/CT = 2-deoxy-2-[fluorine-18] fluoro-D-glucose-positron emission tomography/computed tomography; Com = comorbidities; CRP = C-reactive protein at presentation (normal range 0–0.5 mg/dl); DM = diabetes mellitus; EAC = external ear canal; F = female; IS = immunosuppressive treatment; M = male; Pt = patient; TMJ = temporomandibular joint.
NEO follow-up by PET/CT causes exposure of 4.5 mSv compared to 13 mSv for the Ga67 scan.

**Cost Comparison**

In accordance with the fees of our health maintenance organization, the cost of 18F-FDG-PET/CT is $1,390 US. The alternative diagnostic paradigm consisting of Tc99m scan ($677), Ga67 scan ($1676), and temporal bone CT ($197) costs a total of $2550 US. Follow-up imaging with 18F-FDG-PET/CT ($1390) is less expensive than with Ga67 scan ($1676).

**DISCUSSION**

Imaging studies play a significant role in the diagnosis and follow-up of patients with NEO. Early diagnosis of this potentially lethal disease often poses a dilemma because the clinical findings on physical examination are no different than in external otitis and may improve quickly after treatment is initiated. However, bone involvement is difficult to detect and assess by otoscopy. Hence, imaging findings are crucial and are part of the diagnostic criteria. For decades, the protocol for NEO diagnosis included a Tc99m scan, which is highly sensitive, followed by a Ga67 scan, which is more specific for infection (Fig. 4A, 4B). As long as 30 years ago, the combination of these two tests was shown to be more sensitive and specific for diagnosing NEO than was any other available test. Since then, it has become the most common protocol used by many physicians worldwide. However, in several meta-analyses both tests, separately or combined, were shown to have lower sensitivity and specificity than did 18F-FDG-PET/CT in diagnosing axial osteomyelitis. Another substantial disadvantage is that these tests do not provide adequate anatomical reference for disease spread; hence, an additional CT scan was routinely added (Fig. 4C).

Computed tomography scan is a useful diagnostic tool, and different grading systems were developed over the years in an effort to predict correlation with disease severity. A previous publication from our institution reported that any positive findings in a CT scan increase the risk for mortality by 4.5-fold. Positive correlation was found by others as well. Neither Tc99m nor Ga67 scan findings were found to correlate with disease prognosis.

Magnetic resonance imaging is also a sensitive tool for diagnosing osteomyelitis and NEO, with 84% sensitivity. It is especially useful for the assessment of soft tissue and intracranial involvement. However, specificity is significantly lower than of 18F-FDG-PET/CT (60% vs. 91%); thus, it should not be used as a single diagnostic modality. The test is often difficult to perform in an elderly, uncooperative patient and susceptible for false positive changes in comparison to the quick PET/CT scan. All this and the expensive cost ($720 US) highlight PET/CT as a superior diagnostic modality.

In the 12 patients included in the current case series, all had typical history and clinical features compatible with NEO; CT findings suggestive of NEO; and a positive, matching FDG uptake in the PET/CT (Table I). The PET/CT has other potential advantages as well: results are available within 30 to 60 minutes; it has a distinctly higher spatial resolution than do Tc99m and Ga67 scans (Figs. 1–3 in comparison with Fig. 4); imaging is not affected by metallic implant artifacts; and it provides combined anatomical and physiological information. Moreover, it is less expensive ($1390 vs. $2550 US) and results in less radiation exposure than the combination of Tc99m, Ga67, and CT scans (4.5 mSv vs. 19.2 mSv).

Although the advantage of PET/CT in diagnosing osteomyelitis is clear, its role in therapy assessment and

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**TABLE II. Radiation Dosage of Different Modalities According to MIRD**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Injected Effectiveness (mCi)</th>
<th>Radiation Exposure (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG/PET</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>CT, head</td>
<td>25</td>
<td>4.2</td>
</tr>
<tr>
<td>Tc99m</td>
<td>25</td>
<td>4.2</td>
</tr>
<tr>
<td>Ga67</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

CT = computed tomography; FDG = fluoro-D-glucose; Ga67 = gallium-67; mCi = millicurie; mSv = millisieverts; PET = positron emission tomography; Tc99m = technetium-99m.

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**Fig. 4.** Patient diagnosed with necrotizing external otitis in 2012 by previous protocol. (A) Technetium (Tc99m)–methylene diphosphonate bone scan demonstrating uptake in the right ear. (B) Gallium-citrate (Ga67) scan demonstrating uptake in the right ear. (C) Computed tomography scan demonstrating soft tissue infiltration in the right ear canal with petrous bone destruction.
disease follow-up is less well studied.7 Specifically for NEO patients, to the best of our knowledge, no study regarding the role of PET/CT has been published. In a systematic review of the literature regarding osteomyelitis, no biologic markers such as CRP or ESR were found to correlate with successful treatment24; thus, imaging has a vital role in guiding termination of treatment. In our cohort, abnormally elevated CRP was found in 50% of cases that completed antibiotic treatment and had normalized FDG uptake. Considering the good prognosis in this group of patients, the role of CRP in decision making is probably limited.

Computed tomography scan and MRI have a significant role in NEO diagnosis. However, bone erosion and soft tissue involvement may persist long after infection resolves, and both modalities have limited usefulness in determining response to treatment. Among the eight patients who underwent a second PET/CT in our study, only one demonstrated reversal of the bony damage in the CT scan, whereas all the other patients showed bony erosion despite recovery from NEO (Figs. 2B, 2E–H). Al-Noury and Lofty reviewed CT and MRI scans 6 and 12 months after treatment initiation for 18 NEO patients and found that 100% had persistent bone involvement on CT; 60% had soft tissue involvement; and 33% had bone marrow abnormalities on MRI after 1 year.10

Bone scan (Tc99m) has no role in follow-up because it cannot differentiate bone remodeling from active infection. Therefore, repeated Ga67 scans were used in our previous protocol and by others to monitor treatment response. Gallium-67 scan has a high radiation exposure, requires delayed imaging longer than 48 hours, is more expensive, and has limited spatial resolution (Fig. 4B). 18F-FDG-PET/CT seems to avoid all these disadvantages.

A small number of studies evaluated the utility of PET/CT as a tool for assessing treatment response. Ito et al. demonstrated a strong impact of PET/CT results on the clinical management of over 52% of patients with infectious spondylitis.22 PET/CT was found to be more useful than were MRI findings for decision making regarding termination antibiotics in children with osteomyelitis.23 PET/CT is also useful for assessing response in sarcoidosis, vasculitis, autoimmune diseases,1 and Q fever.24

In our series, PET/CT-guided decision making regarding the duration of treatment led to good outcomes. By the end of 16 months of follow-up, none of the patients with a negative PET/CT scan had disease recurrence. This study was limited by the small number of patients due to the rarity of this disease, its retrospective nature, and the lack of comparison with a non-NEO control group and other imaging modalities.

CONCLUSION

18F-FDG-PET/CT is a reliable imaging modality for diagnosis, disease localization, and decision making regarding treatment cessation of NEO. 18F-FDG-PET/CT should be considered as the imaging modality of choice for initial diagnosis and follow-up in NEO patients due to its advantages in sensitivity, specificity, cost, and radiation exposure. PET/CT might not differentiate NEO from temporal bone malignancies; therefore, results should be considered in the setting of the clinical and histological picture. Larger, controlled studies are warranted to confirm the true value of PET/CT for patients with NEO.

BIBLIOGRAPHY