68Ga-DOTATATE for Tumor Localization in Tumor-Induced Osteomalacia

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Abstract
Phosphaturic mesenchymal tumors (PMTs) are small, typically difficult to localize, and express somatostatin receptors. Recent work suggests imaging studies using 68Gallium (68Ga)-conjugated somatostatin peptide analogues, such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)TATE, which enables somatostatin receptor imaging with positron emission tomography (PET), may be useful at identifying these tumors.

Reference

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**68**Ga-DOTATATE for Tumor Localization in Tumor-Induced Osteomalacia


**Context:** Phosphaturic mesenchymal tumors (PMTs) are small, typically difficult to localize, and express somatostatin receptors. Recent work suggests imaging studies using 68Gallium (68Ga)-conjugated somatostatin peptide analogues, such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)TATE, which enables somatostatin receptor imaging with positron emission tomography (PET), may be useful at identifying these tumors.

**Objective:** Our objective was to evaluate the use of 68Ga-DOTATATE PET/computed tomography (CT) for tumor localization in tumor-induced osteomalacia (TIO).

**Design:** This was a single-center prospective study of patients with TIO.

**Setting:** The study was conducted at the National Institutes of Health Clinical Center between February 2014 and February 2015.

**Subjects:** Eleven subjects (six females, five males) with TIO were included.

**Intervention:** Subjects underwent 68Ga-DOTATATE PET/CT in addition to 111In-pentetreotide single-photon emission CT (Octreoscan-SPECT/CT) and fluorodeoxyglucose-PET/CT (18F FDG-PET/CT) scan.

**Main Outcome Measures:** Localization of PMTs on the previously described imaging modalities were determined.

**Results:** The tumor was successfully localized in 6/11 (54.5%) subjects (one was metastatic). The tumor was identified by 68Ga-DOTATATE in all six cases. Both Octreoscan-SPECT/CT and 18F FDG-PET each identified the tumor in 4/6. In no cases was 68Ga-DOTATATE the only imaging study to identify the tumor.

**Conclusions:** In this first prospective study comparing 68Ga-DOTATATE PET/CT to Octreoscan-SPECT/CT and 18F FDG-PET in TIO localization, 68Ga-DOTATATE PET/CT demonstrated the greatest sensitivity and specificity, suggesting that it may be the best single study for localization of PMTs in TIO. (J Clin Endocrinol Metab 101: 3575–3581, 2016)

Tumor-induced osteomalacia (TIO) is a paraneoplastic disorder caused by small mesenchymal tumors that produce high levels of the hormone fibroblast-growth-factor 23 (FGF23). Complete surgical resection leads to cure; however, these tumors are notoriously difficult to locate due to their small size.

In our recent series of subjects with TIO, we found that successful localization was achieved in only 61% of subjects, even with a combination of localization studies that included two functional imaging modalities, 111In-pentetreotide single-photon emission computed tomography (SPECT) (Octreoscan-SPECT/CT) and fluorodeoxyglucose-positron emission tomography (18F FDG-PET/CT), anatomical localization studies (magnetic tomography imaging [MRI] and CT), and as needed, selective venous sampling (1). Recent reports suggest 68Gallium (68Ga)-

Abbreviations: DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; 18F FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; FGF23, fibroblast-growth-factor 23; 68Ga, 68Gallium; NIH, National Institutes of Health; Octreoscan-SPECT/CT, 111In-pentetreotide single-photon emission/computed tomography; PMT, phosphaturic mesenchymal tumors; SSTR, somatostatin receptors; SUV, standardized uptake value; TIO, tumor-induced osteomalacia.
conjugated somatostatin peptide analogues, such as DOTATATE PET/CT may be useful at identifying phos-
phatic mesenchymal tumors (PMTs), but in none of
these reports was there a direct comparison to conven-
tional studies, including both Octreoscan-SPECT/CT and
18F FDG-PET together (2–4). The possible superiority of
68Ga-DOTATATE lies in its higher affinity than Oct-
reoscan for somatostatin receptors 2 and 5, which PMTs
express (3, 5). Furthermore, the optimal physical charac-
teristics of 68Ga (PET emitter) enables faster acquisition
of images and lower radiation dose, in addition to the
vastly superior performance of PET imaging over scintig-
raphy in the case of Octreoscan-SPECT/CT. In this pro-
spective study, we compared 68Ga-DOTATATE PET/CT
vs Octreoscan SPECT/CT and 18F FDG-PET/CT scan in
subjects with TIO referred to a tertiary referral center
for tumor localization over a 12-month period.

Subjects and Methods

The diagnosis of TIO was based upon an acquired condition of
hypophosphatemia from renal phosphate wasting and an ele-
vated blood FGF23. The onset of symptoms (weakness, multiple
fractures) occurred within 2–24 years of presentation, with a
median of 7 years (Table 1). All patients had a biochemical pro-
tile consistent with TIO, including low serum phosphorus and
1,25-dihydroxyvitamin D, low tubular reabsorption of phos-
phorus, and an elevated blood FGF23, as measured by an intact
FGF23 ELISA assay (Kainos or Immutopics) or C-terminus
ELISA assay (Immutopics) for patient 1. All subjects had failed
tumor localization at least once before referral. Four subjects had
had prior surgical attempts. Subject 4, who was ultimately
shown to have metastatic disease, had undergone four failed
surgical attempts previously (all in the right mandible, where the
primary tumor originated). Subject 5 had had an unsuccessful
resection to prove cure (Table 1).

The cohort consisted of 11 subjects (six females, five
males), with mean age of age of 38 (range, 19–60) (Table 1).

Results

The cohort consisted of 11 subjects (six females, five
males), with mean age of age of 38 (range, 19–60) (Table 1).
Seven of 11 subjects had findings on 68Ga-DOTATATE sug-

gestive of PMT. After anatomical confirmation by CT and
MRI, four underwent surgical resection and were cured
Discussion

The culprit tumor was successfully localized and treated in 54.5% (6/11) of subjects, including one patient with metastatic disease; and not localized in 45.5% (5/11).

<table>
<thead>
<tr>
<th>Sex, Age of Onset (y)</th>
<th>Symptoms, Duration (mo)</th>
<th>Initial FGF23 PET/CT</th>
<th>68Ga-DOTATATE</th>
<th>OctreoScan SPECT/CT</th>
<th>18F FDG-PET/CT</th>
<th>Outcome on Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Male (60)</td>
<td>60</td>
<td>247</td>
<td>Negative</td>
<td>Right acetabulum</td>
<td>Negative</td>
<td>Tumor not found</td>
</tr>
<tr>
<td>2. Male (19)</td>
<td>19</td>
<td>1787</td>
<td>Negative</td>
<td>Right femur</td>
<td>Right acetabulum</td>
<td>Cured</td>
</tr>
<tr>
<td>3. Male (43)</td>
<td>43</td>
<td>1063</td>
<td>Negative</td>
<td>Left femur</td>
<td>Negative</td>
<td>Cured</td>
</tr>
<tr>
<td>4. Male (38)</td>
<td>38</td>
<td>5939</td>
<td>Negative</td>
<td>Metastatic</td>
<td>Right femur</td>
<td>Widespread disease</td>
</tr>
<tr>
<td>5. Female (21)</td>
<td>21</td>
<td>860</td>
<td>Negative</td>
<td>Metastatic</td>
<td>Left femur</td>
<td>Tumor not found</td>
</tr>
<tr>
<td>6. Female (52)</td>
<td>52</td>
<td>1156</td>
<td>Negative</td>
<td>Metastatic</td>
<td>Left femur</td>
<td>Tumor not found</td>
</tr>
<tr>
<td>7. Female (44)</td>
<td>44</td>
<td>218</td>
<td>Negative</td>
<td>Right inferior pelvis</td>
<td>Right inferior pelvis</td>
<td>Tumor not found</td>
</tr>
<tr>
<td>8. Male (47)</td>
<td>47</td>
<td>1515</td>
<td>Negative</td>
<td>Left maxilla</td>
<td>Negative</td>
<td>Cured</td>
</tr>
<tr>
<td>9. Female (27)</td>
<td>27</td>
<td>105</td>
<td>Negative</td>
<td>Right maxilla</td>
<td>Negative</td>
<td>Cured</td>
</tr>
<tr>
<td>10. Female (17)</td>
<td>17</td>
<td>353</td>
<td>Negative</td>
<td>Right clavicle and pelvis</td>
<td>Right clavicle and pelvis</td>
<td>Cured</td>
</tr>
<tr>
<td>11. Female (48)</td>
<td>48</td>
<td>286</td>
<td>Negative</td>
<td>Right clavicle and pelvis</td>
<td>Right clavicle and pelvis</td>
<td>Cured</td>
</tr>
</tbody>
</table>

Bold data represent discrepancy between 68Ga-DOTATATE PET/CT and Octreoscan SPECT/CT.

* With the exception of subject 1 who underwent measurement of C-terminus FGF23 (normal range <180 RU/ml), all patients underwent measurement of intact FGF23 (normal range 8–78 pg/ml).

* Subject had one or more surgical procedures to resect tumor before the study.

* Ultimately considered to be false positive as determined by biopsy and/or venous sampling, and/or surgical resection.

68Ga-DOTATATE imaging correlated with Octreoscan-SPECT/CT in 9/11 cases, and detected lesions in 2/11 cases not seen on Octreoscan-SPECT/CT but seen on 18F FDG-PET/CT, both of which were confirmed to represent the culprit tumor (Table 1). Interestingly, four of five subjects with localized tumors had intact FGF23 levels higher than 1000 pg/ml (subjects 2, 3, 6, 8), suggesting that markedly elevated levels of FGF23 may be associated with larger and/or tumors that have stronger somatostatin receptor (SSTR) uptake on imaging. Findings on 68Ga-DOTATATE imaging were accurate in localizing tumor in six of seven cases, and proved to be false positive in one; Octreoscan-SPECT/CT was accurate in four of the five positive imaging studies and false positive in one of five; 18F FDG-PET/CT was accurate in four of six positive studies and false negative in two of six. Based on these findings, the sensitivity and specificity of 68Ga-DOTATATE was 54.5% and 85.7%; Octreoscan-SPECT/CT 36.3% and 80%; and 18F FDG-PET/CT 36.3% and 86%, respectively.

PMTs are reported to express a variety of somatostatin receptors (SSTR1, 2A, 2B, 3, 4, 5). 68Ga-DOTATATE, like octreotide, is an antagonist of the SSTR, which upon receptor binding is internalized resulting in accumulation of radioactivity in tumor cells (8). However, 68Ga-DOTATATE is a positron emitter, a type of beta decay, which affords greater resolution than the gamma ray emitting 111Indium isotope. In vitro, somatostatin analogues have been shown to have variable affinity for different receptors: SSTR2 > SSTR5 for 68Ga-DOTATATE, SSTR5 > SSTR2 for DOTATOC, and SSTR2,3,5 for DOTANOC (9, 10). Octreoscan-SPECT/CT imaging on the other hand has high affinity for SSTR 2,5 (11). Breer et al reported immunohistochemical staining on 15 PMTs
from 14 patients with TIO, and found diffuse and strongly positive SSTR2A staining in all tumors (3). Thus, the proposed superiority of $^{68}$Ga-DOTATATE imaging over Octreoscan-SPECT/CT imaging may be based on the higher affinity of $^{68}$Ga-DOTA-conjugated peptides for SSTR2 receptors as compared to Octreoscan-SPECT/CT (5). In addition to the higher affinity of $^{68}$Ga-DOTATATE for SSTR2, Octreoscan-SPECT/CT is limited by relatively poor spatial resolution compared to PET, thus accounting for why SSTR-imaging using $^{68}$Ga-DOTATATE enables better visualization of organs with higher octreotide-physiologic uptake (eg, liver). Additionally, $^{68}$Ga-DOTATATE imaging provides advantages in shorter acquisition time and lower radiation exposure.

Figure 1. Example of a subject in whom $^{111}$In-pentetreotide SPECT/CT (Octreoscan) was negative and $^{18}$F FDG-PET/CT and $^{68}$Ga-DOTATATE PET/CT (DOTATATE) were positive (subject 2). (A1) Axial SPECT, (A2) axial SPECT/CT, (A3) coronal SPECT/CT, and (A4) sagittal SPECT/CT images of whole-body $^{111}$In Pentetreotide-Octreotide SPECT/CT scan that did not show abnormal uptake by the right acetabulum region. (B1) Axial PET, (B2) axial PET/CT, (B3) coronal PET/CT, (B4) sagittal PET/CT images of whole-body $^{18}$F-FDG PET/CT scan showing increased activity (SUVmax, 4.05) in the right posterior inferior acetabulum associated with bony changes. (C1) axial PET, (C2) axial PET/CT, (C3) coronal PET/CT, and (C4) sagittal PET/CT images of whole-body $^{68}$Ga-DOTATATE PET/CT scan showing increased uptake (SUVmax, 23.8) by the right acetabulum.

Figure 2. Example of a study in which all three imaging studies, $^{111}$In-pentetreotide SPECT/CT (Octreoscan), $^{18}$F FDG-PET/CT, and $^{68}$Ga-DOTATATE PET/CT (DOTATATE) were positive (subject 3). (A1) Axial SPECT, (A2) axial SPECT/CT, (A3) coronal SPECT/CT, and (A4) sagittal SPECT/CT images of whole-body $^{111}$In Pentetreotide-Octreotide SPECT/CT scan that showed focus of abnormally increased uptake by the right femoral head. (B1) Axial PET, (B2) axial PET/CT, (B3) coronal PET/CT, and (B4) sagittal PET/CT images of whole-body $^{18}$F FDG-PET/CT scan showing increased activity (SUVmax, 13.8) in the right femoral head. (C1) Axial PET, (C2) axial PET/CT, (C3) coronal PET/CT, and (C4) sagittal PET/CT images of whole-body $^{68}$Ga-DOTATATE PET/CT scan showing increased uptake (SUVmax, 54.1) by the right femoral head.
because of its short half-life of 68 minutes, compared with 2.8 days for $^{111}$In, the isotope used in Octreoscan-SPECT/CT imaging (5). The presumed greater sensitivity of $^{68}$Ga-DOTATATE as compared to Octreoscan is accounted for both the radiotracer ($^{68}$Ga), which is a positron emitter that enables STTR imaging with PET and the use of higher affinity to somatostatin receptors compounds like DOTATATE.

In the largest retrospective study published to date evaluating $^{68}$Ga-DOTATATE imaging in TIO, Zhang and colleagues found that $^{68}$Ga-DOTATATE imaging was positive in 32 of 32 subjects who had TIO confirmed pathologically; however, patients with negative $^{68}$Ga-DOTATATE imaging were excluded from the analysis as not having TIO, whereas the cause of the hypophosphatemia in at least half of the patients was unclear (12). No comparison to other imaging modalities was performed.

Clifton-Bligh et al were the first to study the localization of TIO tumors using $^{68}$Ga-DOTATATE imaging and successfully localized TIO tumors in six of six cases (10). However, Octreoscan-SPECT/CT was performed in only one case, along with other imaging modalities such as $^{18}$F FDG-PET (performed in two of six patients) or Tc-Sestamibi scan (performed in one of six) (only $^{68}$Ga-DOTATATE imaging localized the tumors) (10). Although the study found 100% sensitivity and specificity for $^{68}$Ga-DOTATATE, the study was retrospective and included only a subset of patients with presumed TIO. It is unclear if the other subjects with suspected TIO and in whom the tumor was not localized had $^{68}$Ga-DOTATATE imaging. In a study similar to ours, Breer et al compared the efficacy of $^{68}$Ga-DOTATATE to Octreoscan-SPECT/CT for tumor localization in five patients with TIO (three females, two males) (3). Whereas only one of five cases showed focal uptake by Octreoscan-SPECT/CT, all five cases showed focal activity on $^{68}$Ga-DOTATATE imaging. All subjects were cured after surgical resection. However, the low sensitivity of Octreoscan-SPECT/CT in this study is likely due to the fact that SPECT was not performed from head to feet as in our study, but confined to suspicious regions identified on planar images. Two
studies from India, one with six subjects (Agrawal et al) and one with nine subjects (Jadhav et al) used 68Ga-DOTATATE and 18F FDG-PET; in both studies, the sensitivity and specificity of 18F FDG-PET was 50%, sensitivity of 68Ga-DOTATATE was 83.3–100%, and specificity of 68Ga-DOTATATE was 100% (2–4). Jadhav et al also used 99mTc-HYNIC-Octreoscan, with 100% sensitivity and specificity in all six patients undergoing this imaging (4). A recent case series also described the successful use of 68Ga-DOTA peptide PET/CT imaging in localizing PMT tumors in all three of three patients presenting with TIO (13). 68Ga-DOTANOC has been evaluated in one study of 10 TIO patients showing a sensitivity and specificity of 90% (9). Several case reports also report successful localization using this radiopharmaceutical (14–16). 68Ga-DOTATOC has also been described in the successful localization of PMT in an adolescent boy (17). Other imaging modalities studied include 99mTc-HYNIC-Octreoscan, with a sensitivity and specificity of 86.3% and 99.1%, respectively (18), and 99Tc-octretide in which 49% had positive imaging and 41% were found to have TIO (19).

In this cohort, we found that 68Ga-DOTATATE as a single study provided the highest sensitivity/specificity. However it was not superior to our previously reported sensitivity and specificity of combined Octreoscan-SPECT/CT and 18F FDG-PET in localization of PMTs (1). Although our study showed high specificity for all three imaging modalities used, it showed low sensitivity for all three. In the case of 68Ga-DOTATATE, the sensitivity of 54.5% for 68Ga-DOTATATE is the lowest reported among other published studies, which have reported sensitivities of 83–100% (2–4, 10, 12). This difference is probably best explained by the fact this cohort consisted of subjects who had previously failed extensive, sometimes multiple, localization attempts before being seen at our center, and in some cases had failed localization at our center before the availability of 68Ga-DOTATATE imaging. Therefore, this likely represents a group of tumors that are extremely small and difficult to localize. Although comprehensive testing was performed to rule out other acquired forms of hypophosphatemia, such as Fanconi syndrome, heavy metal exposure, etc., other as-yet unknown causes of this disorder may exist. An important feature of this study is the fact that it was prospective. Previously published studies were retrospective and, as such, may have excluded subjects with negative imaging and/or reclassified them as having alternative causes of hypophosphatemia. This would significantly reduce the sensitivities of the reported imaging modalities.

An important feature of this study and previous work in this area from our institution is the manner in which the Octreoscan-SPECT/CT is performed. SPECT imaging is typically performed from head to toe, an approach that can require 5–6 hours of scanning time over 2 days; an approach that is undertaken at few other centers, but necessary to maximize the sensitivity of Octreoscan-SPECT/CT in localizing PMTs. Because 68Ga-DOTATATE was only recently approved by the US Food and Drug Administration for clinical use in the detection of rare neuroendocrine tumors (6), and a cost structure has not been established; therefore, a cost-benefit analysis at this time is not possible. Finally, an important limitation in this study is the small number of subjects. Potential studies characterizing SSTR pattern and its correlation to imaging response may prove useful. Future studies with similar comparison imaging modalities will be needed to definitively define the ideal single imaging study for identifying PMTs.

Conclusion

In this first prospective study of SSTR imaging using 68Ga-DOTATATE in TIO, 68Ga-DOTATATE PET/CT had greater sensitivity and specificity than either Octreoscan-SPECT/CT or 18F FDG-PET/CT but was not more sensitive than Octreoscan-SPECT/CT and 18F FDG-PET/CT combined. Future prospective studies, including a larger sample size, and possibly the use of radiolabeled somatostatin analogues with different SSTR affinities, such as DOTATOC and DOTANOC, may show added benefits over functional imaging modalities such as combined Octreoscan-SPECT/CT and 18F FDG-PET/CT.

Acknowledgments

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