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# The Utility of Ga-68 DOTA-TATE PET/CT on Clinical Management of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)

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## Abstract

**Objective:** Gallium (Ga)-68 DOTA-TATE positron emission tomography/computed tomography (PET/CT) is successfully used for imaging gastroenteropancreatic-neuroendocrine tumors (GEP-NET) and guiding treatment management especially in cases with heterogeneous morphology. This study investigates the effect of DOTA-TATE PET/CT on therapy management in GEP-NET.

**Methods:** Sixty-nine patients (29 women, 40 men) with well-differentiated GEP-NET were referred to our department for Ga-68-DOTA-TATE PET/CT scan analyzed retrospectively. Patients were scanned for staging (n=18), re-staging (n=36) and evaluation for treatment response (n=15). Treatment decisions were blindly correlated before and after PET/CT scan.

**Results:** The mean age was 56.63±13.03 (27-79) years. Patients had grade 1 (n=38) grade 2 (n=24) and grade 3 (n=7) tumors. More than half of the patients (53%) had positive findings for primary tumor and/or metastases. Thirteen patients with grade 2; 18 patients with grade 1; 6 patients with grade 3 tumors had positive findings with PET/CT scan. Primary tumors were in the pancreas, stomach, small bowel, appendix and colon. Additionally, metastases in liver, bone, lung, regional and distant lymph nodes were detected. Nineteen of 69 patients (27.5%) had a change in their treatment protocol. The highest change rate was detected at the group with grade 3 tumors.

**Conclusion:** Ga-68-DOTA-TATE PET/CT was shown as a successful method for imaging and guiding management of GEP-NET. The highest benefit in the treatment plan has been shown in patients with grade 3 tumors and group in the follow-up. Patients with a positive scan were also evaluated for peptide receptor radionuclide therapy as an alternative treatment.

**Keywords:** Positron emission tomography, DOTA-TATE, gastroenteropancreatic neuroendocrine tumor NET

## INTRODUCTION

Neuroendocrine tumors can progress without any clinical symptoms, which makes it difficult to detect the primary tumor before reaching later stages. Prognosis is related to the grade and the metastatic disease. Especially, extrahepatic metastases have been related to lower survival rates (1). Survival is relatively longer that makes patients quality of life as an important factor to be considered during follow-up and management of the clinical disease. Conventional imaging techniques like computerized tomography or magnetic resonance imaging are used to determine the disease involvement. However, the somatostatin labeled hybrid imaging techniques are defined as the gold standard as being also a functional imaging technique. Somatostatin receptor labeled imaging techniques have been shown to be helpful in evaluating neuroendocrine tumors in staging, re-staging and assessment of treatment response. Due to the availability of positron emission tomography/computed tomography (PET/CT), somatostatin analogs labeled with gallium (Ga)-68 become more frequently used with the higher resolution images correlated with the scintigraphy images (2).

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) have been mostly diagnosed with the clinical symptoms of the

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patients. Clinical management of the neuroendocrine tumors is mostly related to stage, grade and the symptoms of the patients. Tumors can release hormone and somatostatin analogs are used for controlling symptoms and disease growth (3). When surgery is not an option or cannot control the disease spread, other treatment options like systemic or locoregional therapies are need to be discussed. Chemotherapy, mTOR inhibitors, local treatments like radioembolisation or the combination are the options to control the disease. Low-grade tumors mostly show increased uptake in somatostatin labeled radionuclide imaging. Patients with uptake have a chance to receive peptide receptor radionuclide therapy (PRRT) which has shown benefits for the patients especially with the metastatic disease (4).

Ga-68-DOTA-TATE PET/CT has been shown to be useful for detecting GEP-NET with higher sensitivity and specificity (5). A study emphasized the impact of Ga-68 DOTA-TATE PET/CT on management in the patient group with gastrointestinal NET. Almost half of the patients have changed their treatment protocol after PET/CT scan (6). Liver metastases are mostly detected during the initial diagnosis of the patient. Heterogeneous spread of the disease with a different kind of grade in metastases of the same primary makes it difficult to distinguish by conventional imaging techniques. Fludeoxyglucose (FDG) PET/CT is shown to be useful in the heterogeneous morphology of NET as a complementary to DOTA-TATE PET/CT scan (7). When a treatment protocol could affect a lesion, it might not be useful to the other metastatic lesions with different grades. Combined treatment models have been shown to have benefit, whereas FDG positivity is also detected in PET/CT images of GEP-NET tumors (8).

This complex structure of GEP-NET makes it difficult in clinical management. Higher the grade, more aggressively the tumor can grow, which needs different or combined patient-specific treatment protocols. Follow-up or diagnosis with Ga-68 DOTA-TATE PET/CT can shed light on conducting the clinical patient management. The aim of the study was to understand the effect of somatostatin labeled PET/CT images the in follow-up and the management of the treatment in GEP-NET.

## METHODS

Sixty-nine patients with biopsy proven well-differentiated GEP-NET who were referred to our department for evaluation with Ga-68 DOTA-TATE PET/CT between 2015 and 2020 were retrospectively evaluated. Staging, re-staging and evaluating the treatment response were the indications included in our study. Patients younger than 18 years old with clinically suspected neuroendocrine tumors without biopsy proof were excluded. All the patients were biopsy proven and underwent conventional imaging modalities other than Ga-68 PET/CT scan during the diagnosis of the disease.

Patients were not asked to make any specific preparations before the day of the scan. After on-site synthesis of Ga-68 from the germanium generator and labeling with peptide (30 µg), a quality control with HPLC (high-performance liquid chromatography) technique has been done before injecting the radiopharmaceutical. The whole body images were obtained after 50-60 minutes from receiving 11-370 Mbq (3-10 mci) Ga-68 DOTA-TATE (130kV, 50-80 mAs, slice thickness of 3mm) (GE Healthcare, Wisconsin, USA). Oral contrast was used in all patients, meantime intravenous contrast could not be performed in all patients.

All the patients were grouped due to their stages (AJCC) and grades obtained from ki-67 levels of the biopsy results. Additionally, the referral indications to PET/CT scan of the patients were gathered in 3 groups. PET/CT images of the patients were evaluated retrospectively by an experienced nuclear medicine physician. Physiological distribution for DOTA-TATE was considered before the decision for pathological uptake. Uptake higher than background in the PET images was accepted as positive. CT images were checked and confirmed that the pathological lesion was in the same cross-section. Furthermore, oncologist evaluated the patient information initially without and later with the results of PET/CT scan. A form of treatment choice before and after seeing the PET/CT result of the patient was filled.

Informed consent form was received from all the patients. Local Ethics Committee approval was gained due to our hospital regulations (University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital; date: 02.02.2021, number: 3113).

### Statistical Analysis

All the data were analyzed with SPSS (Statistical Package for the Social Sciences) software for Windows (v17.0; IBM, Armonk, NY, USA). Individual and aggregate data were summarized using descriptive statistics including mean, standard deviations, medians (minimum-maximum), frequency distributions and percentages.

## RESULTS

Sixty-nine patients with a mean age of 56.63±13.03 (minimum-maximum=27-79) year, 40 males and 29 females, with biopsy proven well differentiated GEP-NET were included to our study group (Table 1). Patients were grouped as the primary tumor

origin consisting of the small intestine (n=13), pancreas (n=26), colorectal (n=4), stomach (n=21) and appendix (n=5). Ki-67 levels from the biopsy or surgery histopathology reports were between <1% and 45%. Patients' grade classification was also grouped as grade 1 (n=38), grade 2 (n=24) and grade 3 (n=7) tumors. Patients were referred to PET/CT for staging (n=18), re-staging (n=36) and evaluating the treatment response (n=15) (Figure 1, 2).

PET/CT images revealed either negative or positive for the findings of pathological lesions with increased DOTA-TATE uptake. Thirty-seven of 69 patients had positive findings for either primary tumor or metastases. From positive scans, 18 patients were with grade 1 tumors and 13 patients had grade 2 tumors. Furthermore, 6 patients with grade 3 tumors demonstrated positive lesions on PET/CT scan. Positive lesions were grouped as primary tumors (n=19) and metastases to local lymph nodes (n=12), liver metastases (n=16), bone metastases (n=5), lung metastases (n=1) and in other regions (n=8).

A clinical management plan was also observed before and after evaluation of patients' DOTA-TATE PET/CT images. From the available clinical data, 6 patients had increased chromogranin A level, 13 patients had gastrointestinal symptoms like abdomen pain and nausea. Nineteen patients (27.5%) have had a change in their treatment protocol (Table 2). That change was grouped as either stopping somatostatine analog (n=6); leaving follow-up protocol (n=7), receiving or change to chemotherapy (n=3); including mTOR inhibitor agent (n=3); locoregional therapy (n=1) or PRRT (n=5). Ten of 69 patients (14.49%) were upstaged after DOTA PET/CT scan. Seven out of this group of 10 patients (70%) had change in the treatment protocol. From this group, 4 patients with grade 2 tumors and 2 patients with grade 1 tumors given or changed somatostatine analogs, and a patient with grade 3 tumor was considered for chemotherapy after scan.

**Table 1. Demographics of the patients enrolled to study**

| Patient characteristics | Numbers |
|---|---|
| **Sex (n)** | |
| Male | 40 (57.9%) |
| Female | 29 (42.1%) |
| Age mean ± SD (minimum-maximum) | 56.2±12.6 (27-79) |
| **Primary tumor region (n)** | |
| Small intestine | 13 (18.8%) |
| Pancreas | 26 (37.7%) |
| Colorectal | 4 (5.8%) |
| Stomach | 21 (30.4%) |
| Appendix | 5 (7.3%) |
| **PET/CT findings (n)** | |
| Positive | 37 (53.6%) |
| Negative | 32 (46.4%) |
| **PET/CT positive lesions (n)** | |
| Primary tumor | 19 |
| Lymph nodes | 12 |
| Liver | 16 |
| Lung | 1 |
| Bone | 5 |
| Other | 8 |
| **Grade (n)** | |
| 1 (ki-67% 1-3) | 38 (55.1%) |
| 2 (ki-67 <3-20) | 24 (34.8%) |
| 3 (ki-67% >20) | 7 (10.1%) |

SD: Standard deviation, PET/CT: Positron emission tomography/computed tomography

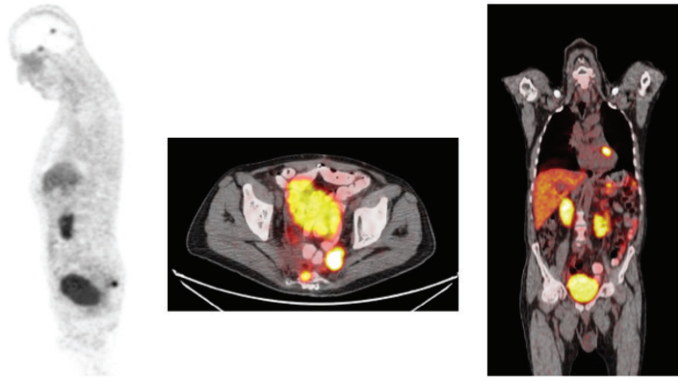

**Figure 1.** Fifty-six year-old male patient, referred for re-staging. He had rectum NET, ki-67 6% grade 2 tumor, was under sandostatine treatment before DOTA-TATE PET/CT scan. PRRT decision was given after PET/CT images revealed relapse in pelvic region, metastatic lesions in heart and cranium

PET/CT: Positron emission tomography/computed tomography, PRRT: Peptide receptor radionuclide

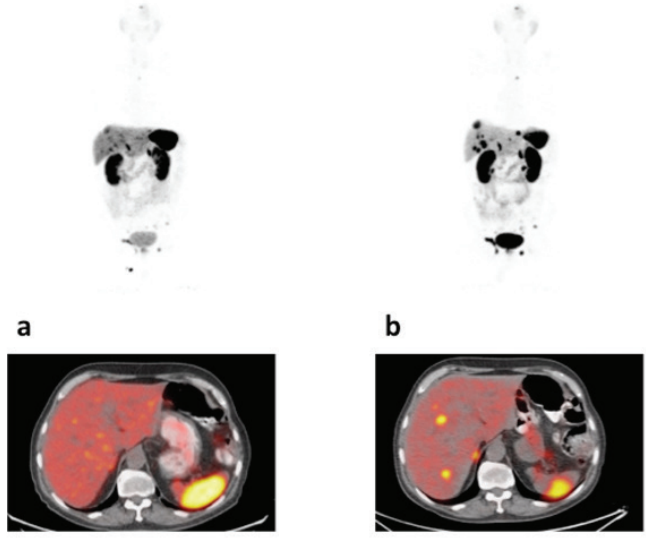


**Figure 2.** Seventy-six year-old male patient with grade 2 metastatic colon NET, Ki-67 3-4%, was referred for therapy assessment. (a); images before treatment. DOTA-TATE PET/CT images revealed progression in liver after treatment, (b); images after treatment

PET/CT: Positron emission tomography/computed tomography

**Table 2. The treatment plan before and after DOTA-TATE PET/CT with change rates**

| Impact on therapy | Before PET/CT (n) | After PET/CT (n) | Change % |
|---|---|---|---|
| Follow-up | 66.6% (46) | 56.5% (39) | 10.1% |
| **Somatostatin analogue**<br>Octreotide<br>Lantreotide | <br>30.4% (21)<br>1.4% (1) | <br>21.7% (15)<br>1.4% (1) | <br>8.7%<br>- |
| Chemotherapy<br>mTOR inhibitor | 2.89% (2)<br>- | 7.2% (5)<br>4.34% (3) | 4.34%<br>4.34% |
| Locoregional therapy | - | 1.4% (1) | 1.4% |
| PRRT | - | 7.2% (5) | 7.2% |

PET/CT: Positron emission tomography/computed tomography, PRRT: Peptide receptor radionuclide

Nineteen patients from the study group were also scanned with FDG PET/CT after the DOTA PET/CT scan. From this group; 5 of 19 patients were positive with both scans. Two out of 5 were patients with grade 2 tumors and the rest were the patients with grade 3 tumors. Four out of 5 positive patients with both scans had a change in treatment protocol. Three of them were considered receiving chemotherapy and being candidates for combination therapies with PRRT, following after the response. One patient from this group was considered for PRRT in the beginning, due to clinical evaluation of both PET/CT scans.

According to the tumor grade classification, the treatment changing rates after DOTA-TATE PET/CT scan were 13.15% in patients with grade 1 tumor; 33.3% in grade 2 tumor and 85.7% in grade 3 tumor patients. The lowest rate of treatment change was in group of patients with grade 1 tumor, whereas lesion detection rate was also lower than the other groups. The reason could be related to the distribution of the PET-negative patients in the grade 1 group, who were mostly scanned for re-staging and had a history of surgery. Also, for the indications of PET/CT scan; 8 of 15 patients referred for therapy evaluation (%53.3), 3 out of 18 from the staging group (16.6%) and 8 of 36 patients (22.2%) from the re-staging group had a treatment protocol change after PET/CT scan. Some of the clinical data were not available for every patient cause of referral from other hospitals.

## DISCUSSION

Modification of therapy management is not only affected by the tumor burden or the spread of the metastases, but also from the receptor function as demonstrated in DOTA PET/CT scan. GEP-NET treatment plan consists of surgery, symptomatic therapy and/or anti-proliferative therapy. It can be changed due to symptoms or progressive disease in case of non-respondent to treatment. In the literature, treatment changes have been reported to be between 19-60% in the studies demonstrating the impact of Ga-68 DOTA PET/CT scan in GEP-NET patients (9-13). Tan et al. (6) also emphasized the DOTA-TATE PET/CT scan can support clinician with providing at least 52,4% change in decision in gastrointestinal neuroendocrine tumors. Moreover, Anderson et al. (14) has showed 23.4% change in management in a patient group with mixt type of neuroendocrine tumor. Our patient numbers are lower than most of the similar studies in the literature, with a change rate of 27.5% in therapy management.

Chan et al. (15) has observed that having both FDG and Ga-68 DOTA-TATE PET/CT scan in NET patients could be significantly related to the survival rates of the patients whereas 19% of the patients with grade 3 NET. Moreover, another group reported 59% change in treatment protocol after evaluation of the both scans in GEP-NET (7). We also had 5 patients, with grade 2 and 3 tumors, who also had positive FDG PET/CT scans. This also proved the heterogeneity of the NET to evaluate the other treatment methods in the case of progression under somatostatin analogs. Increased glucose metabolism in tumor behavior can change the treatment protocol in NET patients as mentioned in previous studies. More aggressive therapies, including chemotherapy and targeted anti-cancer therapy can be a combination if there is FDG-positive component in the tumor (16,17) Nicolini et al. (8) has also recently demonstrated the benefit of combined PRRT and capecitabine treatment method for the GEP-NET tumors, including grade 3 tumors in their study group. This novel approach for grade 3 tumors with PRRT is promising for the patients resistant to other treatment modalities and the effects are remarkable. Nevertheless, more clinical trials with effects on survival should be discussed.

Nevertheless, each treatment can have drawbacks and side effects, might not be possible for every patient. The highest rate (85.7%) in therapy management was detected in the grade 3 tumor group in our patients. Grade 3 tumors group and the patients who were referred for therapy response were the patients who had the major effect in management after PET/CT scan. Tan et al. (6) has defined a group of patients (25%) who had down staged after PET/CT scan. However, our patients mostly had no change in stage (36.8%; n=7) or up-staged after PET/CT scan (6).

Somatostatin labeled imaging techniques change the era of the neuroendocrine tumor management and the outcomes with PRRT due to favorable results (18). NETTER phase III trial showed supportive results for the PRRT given midgut tumors with 79% lower rates for progression or death compared to somatostatine analogs (19). A retrospective study with a patient

group of GEP-NET patients who were treated with lutetium-177 (Lu-177) therapy also mentioned 84% disease control rate and 54% regression (20). In our study group; 3 patients with grade 1 tumors and 2 patients with grade 2 tumors were decided to be given PRRT after PET/CT scan. The reason was either progression or the progression under other treatments.

In conclusion, the management of GEP-NET tumors requires a complex plan of treatment and follow-up. DOTA-TATE PET/CT imaging was useful and has shown major benefit for the patients in our study group. Even the grades and symptoms of the patients are the most important factors of the treatment decision; management needs to be supported by functional imaging for patient-specific therapy plan.

### Study Limitations

This study is not without limitations. Since the design was retrospective, it was impossible to gain all histological information for every positively evaluated lesion in PET/CT. Follow-up data were used for these purposes. Moreover, prospective clinical trials are needed to evaluate the effect on cost-effectiveness or survival after treatment change.

## CONCLUSION

Based on our findings, Ga68-DOTA-TATE PET/CT was shown as a successful method for imaging primary GEP-NET and clinical management in our study. Furthermore, grade 3 tumors and follow-up patients have the highest rate of treatment change in our study group. Consideration of a therapy plan including PRRT is expected to improve the quality of life.

### Ethics

**Ethics Committee Approval:** Local Ethics Committee approval was gained due to our hospital regulations (University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital; date: 02.02.2021, nunber: 3113).

**Informed Consent:** Informed consent form was received from all the patients.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Ö.E., N.B.K., Concept: Ö.E., Design: Ö.E., Data Collection or Processing: Ö.E., N.B.K., Analysis or Interpretation: Ö.E., N.B.K., Literature Search: Ö.E., Writing: Ö.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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