

# The quantification for the treatment response evaluation of Metastatic Gastroenteropancreatic Neuroendocrine Tumors in Ga-68 DOTATATE PET/CT

✉ Zehra Pinar Koç<sup>1</sup> ✉ Pinar Pelin Özcan<sup>2</sup> ✉ Emel Sezer<sup>3</sup> ✉ Tuba Kara<sup>4</sup> ✉ Esra Erdem<sup>5</sup>

\*Corresponding Author

<sup>1,2</sup>Mersin University, Faculty of Medicine, Department of Nuclear Medicine, Mersin, Turkey

<sup>3,5</sup>Mersin University, Faculty of Medicine, Department of Oncology, Mersin, Turkey

<sup>4</sup>Mersin University, Faculty of Medicine, Department of Pathology, Mersin, Turkey

## Abstract

**Aim:** The treatment response evaluation by means of Ga-68 DOTATATE PET/CT in Metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEPNET's) needs careful attention due to the subtle changes that might affect decision. The aim of this study is to analyze a new modified method in quantification of the Ga-68 DOTATATE PET/CT in treatment response evaluation of GEP-NET's.

**Materials and Methods:** Thirty Seven patients with diagnosed of metastatic GEP-NET were included in the study. Comparative evaluation of Ga-68 DOTATATE PET/CT images before and after treatment was performed. Quantitative analysis as well as visual interpretation results were compared with oncology follow up. The patients were divided according to oncology follow up results as responders and nonresponders.

**Results:** The comparative analysis results showed that the difference between mean SUVmax and index values after and before the treatment were not significant for primary lesions. However both the index values were significantly different between groups in metastatic lesions.

**Conclusion:** The SUVmax levels of the metastatic lesions could be considered for determination of treatment response and quantification for the treatment response might be indicated in special cases.

**Keywords:** Ga-68 DOTATATE, malignancy, positron emission tomography, fluorodeoxyglucose.

## Introduction

Two third of the NET's arise from gastroenteropancreatic channel which are called GEPNET's (1). Most of the patients with GEPNET's have metastasis at first presentation (2, 3). Previous observations with imaging characteristics of these tumors showed that the most efficient way to follow up these tumors is tumor specific

**Address for Correspondence:** Zehra Pinar Koç, Mersin University Training and Research Hospital, Clinic of Nuclear Medicine, Mersin, Turkey

**Phone:** + 90-324-2410000/22524 **E-mail:** zehrapinarkoc@gmail.com **ORCID ID:** <https://orcid.org/0000-0002-3274-5790> **Received:**

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imaging by means of Peptide receptor imaging. The Indium labelled somatostatin imaging by means of gamma cameras are recently replaced by Ga-68 labeled receptor imaging by PET/CT devices.

The treatment options are determined by the well known prognostic pathologic indicis (Grade and Ki-67 index) however the pathology of the tumors might be complicated and might change during the disease course (4-7). Combination of two Nuclear Medicine imaging modalities (Ga-68 DOTA-SR and F-18 FDG PET/CT) are considered the best diagnostic imaging method in recent studies (8).

Ga-68 DOTATATE PET/CT is the method of choice in the treatment response evaluation of metastatic GEPNET's. Additionally, the patients eliable for the treatment modality Lu-177 DOTATATE could be decided by the Ga-68 DOTATATE uptake. Quantification studies in Ga-68 DOTATATE showed that the whole body 'Volume of interest' and cut off levels for SUVmax provided promising results for prognostic decisions (9). One of the most important treatment evaluation study 'NETTER-1' trial included 'Krenning Score' which is a quantitative analysis (10).

The aim of this study was to provide a robust reflection of treatment response in follow up Ga-68 DOTATATE PET/CT imaging.

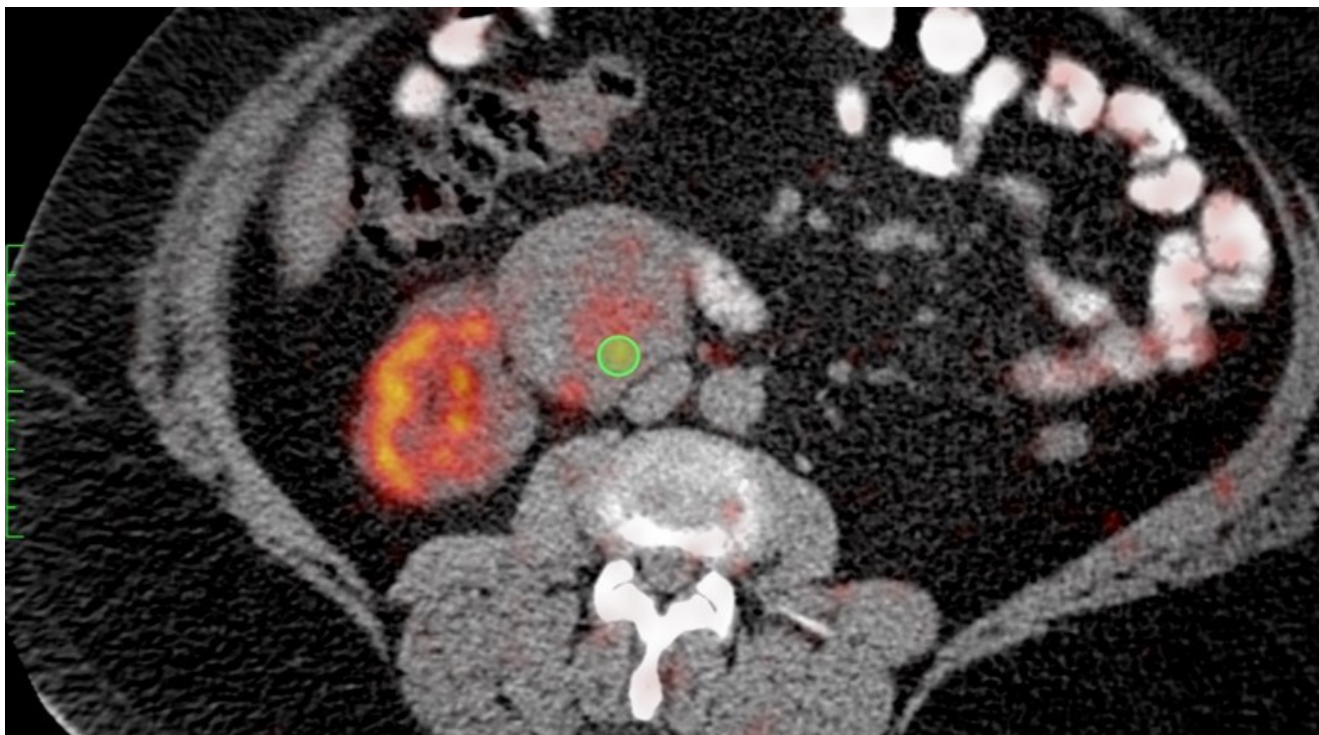
#### **Materials and Methods:**

Thirty seven patients (20 F, 17 M; 35-82;  $59,3 \pm 12,38$  years) were included in the study. The inclusion criteria were having a metastatic neuroendocrine tumor and the patients with additional secondary malignancies were excluded from the group. Additionally, the patients with pregnancy or lactation were not included in the study group. The informed consents of the patients for imaging procedures were obtained prior to the study. The study was approved by University Ethics Committee.

The interpretation of the images was performed by experienced Nuclear Medicine physician and additional quantification of the results were performed by one of them. The quantification method was based on the SUVmax levels obtained from the region of interest (ROI) derived from the primary tumor, metastatic lesion (index lesion with most significant uptake), as well as physiologic uptake recorded (Figure 1). The ratio of the ROI's obtained from the lesion and nonlesion background (liver/spleen) were calculated as index values for all images of the patients prior to and after the chemotherapy.

The quantitative values were analyzed by parametric tests (Student T test; one way ANOVA) and  $p < 0.05$  considered statistical significance.

The oncologic follow up of the patients for the duration of 1-12; mean  $5,18 \pm 2,77$  months was recorded and considered as gold standard. The patients were divided into two groups as responders and nonresponders.



**Figure 1.** The transaxial fusion Ga-68 DOTATATE PET/CT image of a patient in this series and the ROI indicating the index lesion for quantification

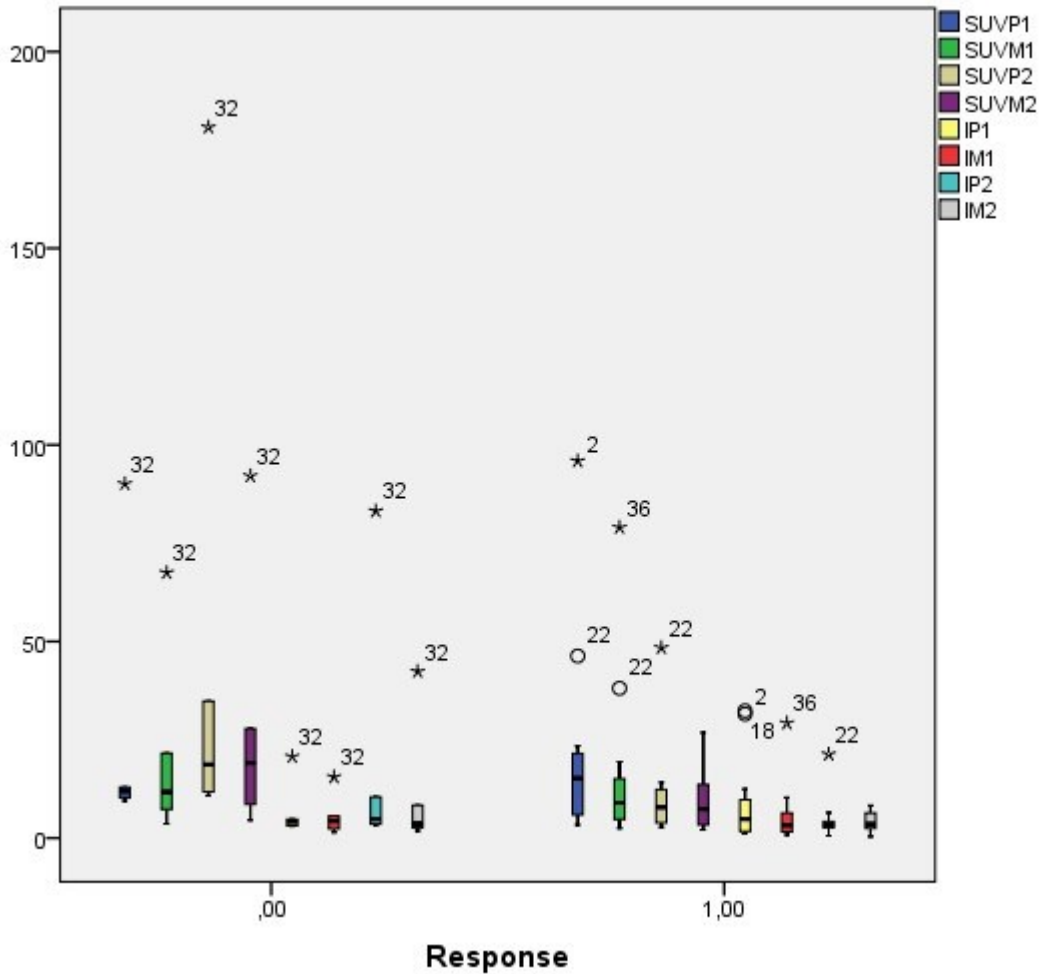
## Results

The patients' primary tumors were in the enteric system (colon or small intestine) (n=12), stomach (n=12), pancreas (n=4) and unknown sites (n=9) according to the frequency. The patients metastatic sites were lymph nodes (n=22), bone (n=13), liver (n=11), lung (n=2) respectively.

Progressive disease was accepted as non-responders and other groups (partial responders, stable disease, responders) were considered as responders. Four patients were removed from the statistical analysis because of extremely high values. The mean SUVmax levels of the patients were  $23.25 \pm 28.1$  and  $22.91 \pm 42.37$  respectively before and after treatment in primary tumors and  $17.1 \pm 19.22$  and  $17.06 \pm 23.05$  for metastatic lesions.

The mean index values of the primary and metastatic lesions before and after treatment were  $8.36 \pm 9.75$  and  $9.26 \pm 19$  and  $6.78 \pm 9.09$  and  $6.98 \pm 11.92$  respectively.

The difference between Index values and SUVmax levels of the primary lesions before and after treatment was not significant however the SUVmax level and index of the metastatic lesions were significantly different according to the statistical analysis (Graph).



**Graph:** The SUVmax and Index values of the primary (SUVP, IP) and metastatic lesions (SUVM, IM) before (1) and after (2) treatment (column) distributed according to the responders and non-responders (row).

### Discussion

The Somatostatin receptor imaging by means of PET/CT depends on the Somatostatin receptor composition of the tumors. Thus, the most reliable indicator of the treatment response is the difference in uptake values in Ga-68 DOTA SR PET/CT. However, it is not easy to compare the results due to conflicting imaging factors. Comparison with liver uptake which is one of the important parts of response evaluation in FDG PET/CT imaging might not be enough due to the fact that liver is the target organ for metastatic involvement in GEPNET's. That is why this study included liver and spleen ratio for quantitative analysis. The results of this study showed that comparison of the uptake of primary tumor might not reflect the response but metastatic lesions should be preferred. SUVmax levels of the metastatic lesions sufficiently reflected the treatment response according to the statistical analysis. In case of discrepancy quantification method might be implicated.

Previous studies including large series for response evaluation showed that Ga-68 DOTATATE imaging significantly changed patients management in nearly half of the patients (44%) (11). Additionally, the metastatic involvement (90%) and multiple lesions (35%) were determined at first staging in most of the patients included in previous series (12). The diagnostic comparison of the morphologic imaging modalities and Ga-68 DOTATATE PET/CT revealed higher detection rates in previous series; PET/CT determined 22/33 patients who were metastasis negative for liver (13). The similar findings were presented for the peritoneal carcinomatosis (14) and recurrent tumor detection in another series (15).

F-18 FDG PET/CT in conjunction with Ga-68 DOTATATE imaging serves as a prognostic decision making modality which determines the cases with worse prognosis who needs aggressive treatment protocol (16). Another prognostic factor in Ga-68 DOTA SR imaging was the target/liver ratio according to a previous study (17). The best treatment group was determined to be the lesions with low and very low FDG accumulation and high Ga-68 DOTA SR uptake in a previous study and SUVmax cut off value was determined to be '15' for predicting the survi (18). Another study indicated the relationship between survi and the tumor/spleen ratio (19).

Recent studies with PET/MR devices showed slight improvement over Ga-68 DOTATATE PET/CT for liver metastasis (20).

Limitations of this study are retrospective nature of the study and limited number of the patients. However, the homogenous group of patients were included for a sufficient result.

### **Conclusion**

The most efficient treatment response reflection was the SUVmax levels of metastatic lesions of the GEPNET's in Ga-68 DOTATATE PET/CT according to the results and additional quantification might be performed in case of conflicting results.

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### **Authorship Contributions**

**Concept:** Z.P.K., P.P.O., E.S., T.K., E.S., **Design:** Z.P.K., P.P.O., E.S., T.K., E.S., **Supervision:** Z.P.K., P.P.O., E.S., T.K., E.S., **Data Collection and/or Processing:** Z.P.K., **Analysis and/or Interpretation:** Z.P.K., **Literature Review:** Z.P.K., **Writer:** Z.P.K.

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