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# Role of $^{68}$Ga-DOTA-NOC PET/CT in detection of primary site in patients with metastatic neuroendocrine tumor of unknown origin: Experience from Pakistan


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## INTRODUCTION

Neuroendocrine tumors (NETs), historically referred to as APUDomas are genetically diverse, predominantly slow-growing tumours with relatively good prognosis (1). They are rare tumors accounting for 0.5% of all cancers. Gastrointestinal tract is the most common location (4) and is responsible for two-thirds of cases, followed by lung accounting for one-third of the cases (2). The incidence has gradually increased during the last three decades, particularly for gastric and rectal NETs (3). NETs can be either functioning or non-functioning in nature.

The primary site of GI NET is often small and occult. Moreover, the possibility of multiple and variable primary sites makes the evaluation challenging (5). Patients with metastatic NETs and unknown primary site, referred to as CUP-NET, constitute less than 5% of overall carcinomas of unknown primary (CUP) population (6) and 10-13% of NET population (7).

NETs are characterized by over-expression of somatostatin receptors (SSTRs) and this has proven to be highly valuable for their detection using functional imaging techniques like Somatostatin-receptor-scintigraphy (SRS) and $^{68}$Ga-labeled-somatostatin analogues (DOTA-peptides) PET/CT (8). There are three major peptides available (TOC, NOC, TATE) which exhibit variable affinity to the 5 somatostatin receptor subtypes. $^{68}$Ga-DOTA PET/CT is not only superior to conventional anatomical imaging but also functional SRS in many ways (9) including better visualization through better spatial resolution of latest PET/CT scanners, low radiation dose to the patient, reduced imaging time and cost-effectiveness (10).

## MATERIALS & METHODS

In this prospective, single-arm, single-institutional study, 38 patients with histologically proven metastatic NETs and unknown primary site on conventional imaging were recruited for the study. All patients underwent diagnostic $^{68}$Ga-DOTA-NOC PET/CT. Histopathology whenever possible and/or visualization of lesion on follow-up imaging using $^{68}$Ga-DOTA-NOC PET/CT and other imaging modalities such as USG, CT scan and endoscopy were taken as reference standard. The mean follow-up period was 12.2±6.0 months (range, 4.2-16.6 months). Maximal standardized uptake value (SUV*max*) of possible primary and metastatic sites was calculated. Consent was taken from all patients. Following patient characteristics (Table 1) were noted for all 38 patients: age, sex, histopathologically proven metastatic sites, sites of possible primary lesions, SUVmax in metastatic as well as detected primary sites.

| Characteristics | n (%) |
|---|---|
| **Total patients** | 38 |
| **Males** | 25 (66%) |
| **Females** | 13 (34%) |
| **Age (in years)** | |
| **Mean** | 55.2±11.4 |
| **Median** | 55 |
| **Range** | 29-77 |
| **Histopathologically proven metastatic sites** | |
| **Liver** | 23 |
| **Lymph nodes** | 9 |
| **Mesentery** | 4 |
| **Skeleton** | 2 |
| **Possible Primary Sites** | |
| **Small intestine** | 12 |
| **Pancreas** | 6 |
| **Lung** | 1 |
| **Rectum** | 1 |

Table 1. Patient Characteristics: gender, age, metastatic sites & sites of possible primary.



## MATERIALS & METHODS

**Imaging protocol**

Patients were administered I/V injection of 3-4 mCi (111-148 MBq) of $^{68}$Ga-DOTA-NOC and were asked to void just prior to start of image acquisition. Images were acquired 60±10 minutes later from vertex to mid-thigh using Discovery STE PET/CT system (GE, healthcare, USA) with 16 slice CT scan. Regional/delayed views were taken as and when required. Daily QC procedures were done according to the manufacturer's recommendation. CT-based attenuation corrections were performed for the PET images, and reconstruction was carried out using an iterative reconstruction algorithm. The reconstructed data was available in maximal intensity projection (MIP), coronal, sagittal and axial slices.

**Image & Statistical analysis**

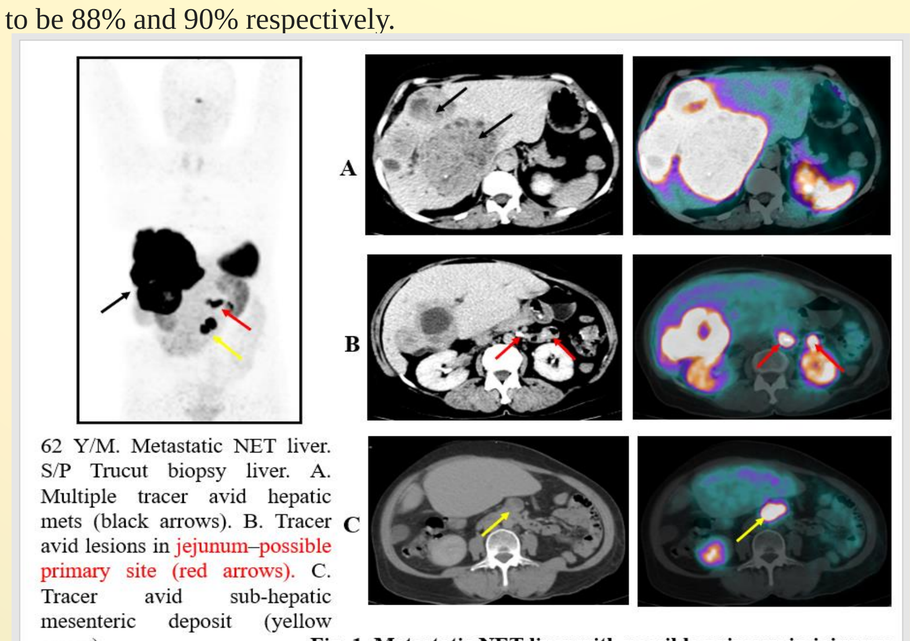
PET/CT images were reviewed visually and quantitatively by two experienced nuclear medicine physicians who were aware of the patient's history. Tracer accumulations in structures that do not take up the tracer physiologically, or accumulations higher than background activity, were considered as abnormal. For quantitative assessment, SUVmax values of lesions were used and were automatically calculated by the computer according to region of interest. Data was analysed using Statistical Package for the Social Sciences (SPSS Version 21.0).

## OBJECTIVE

Our study was aimed to prospectively evaluate the efficacy of 68Ga-DOTA-NOC PET/CT imaging in detecting the primary site in patients presenting with metastatic NETs of unknown origin.

## RESULTS

$^{68}$Ga-DOTA-NOC PET/CT scan was performed in 38 patients with histopathologically proven metastatic NETs and unknown primary site (CUP-NET). 25 were males (66%) and 13 females (34%). Their mean age was 55.2±11.4 years with a range of 29-77 years (Table 1). The highest number of patients presented with hepatic metastases, that is, 23 out of 38 patients (60%). Rest of the patients presented with lymph nodal (9) mesenteric (4) and skeletal (2) metastases. $^{68}$Ga-DOTA-NOC PET/CT was able to identify the possible primary site in 20 out of these 38 patients (52%). Most common possible primary sites were small intestine (12) and pancreas (6) followed by lung (1) and rectum (1) (Fig. 1 & 2*)*. Histopathology and follow-up imaging confirmed the primary site in 16 out of 20 patients (True positives 80%). Biopsy/follow-up imaging was not able to confirm the primary site in 2 patients (False positives 10%) and 2 patients were lost to follow-up (Table 2). Amongst the 18 patients in whom $^{68}$Ga-DOTA-NOC PET/CT was not able to identify the possible primary site, follow-up imaging reflected the same in 16 patients (True negatives 88%), whereas follow-up imaging revealed possible primary sites in 2 patients, that is ileum and pancreas (False negatives 11%). The sensitivity and specificity of $^{68}$Ga-DOTA-NOC PET/CT came out to be 88% and 90% respectively.

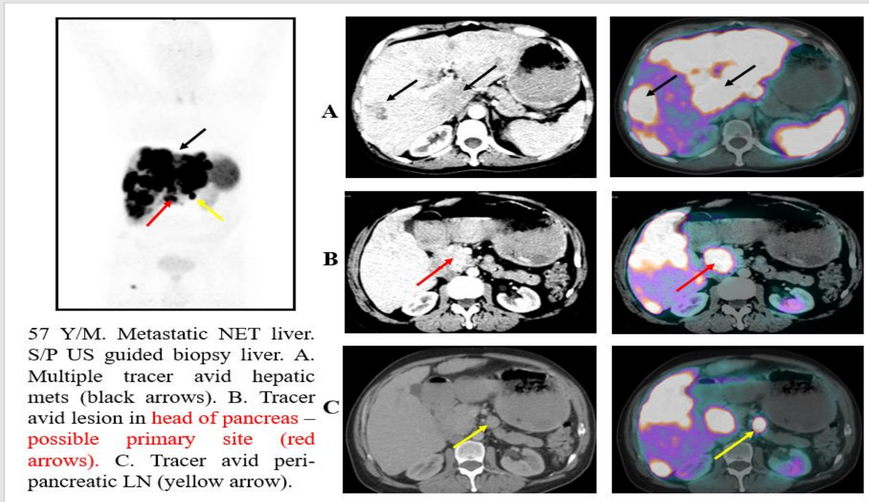



62 Y/M. Metastatic NET liver. S/P Trucut biopsy liver. A. Multiple tracer avid hepatic mets (black arrows). B. Tracer avid lesions in jejunum–possible primary site (red arrows). C. Tracer avid sub-hepatic mesenteric deposit (yellow arrow).

**Fig. 1. Metastatic NET liver with possible primary in jejunum.**

| Characteristics | Percentage |
|---|---|
| **True Positive** | 80 |
| **False Positive** | 10 |
| **True Negative** | 88 |
| **False Negative** | 11 |

Table 2. Performance Characteristics of $^{68}$Ga-DOTA-NOC PET/CT in detection of Unknown Primary NET (n=38).




57 Y/M. Metastatic NET liver. S/P US guided biopsy liver. A. Multiple tracer avid hepatic mets (black arrows). B. Tracer avid lesion in head of pancreas – possible primary site (red arrows). C. Tracer avid peri-pancreatic LN (yellow arrow).

**Fig. 2. Metastatic NET liver with possible primary in pancreas.**

## DISCUSSION

There is a growing trend in the use of of Ga-68 labeled somatostatin analogues PET/CT for clinical evaluation of NETs. Till date various indications have been studied including staging with a reported sensitivity of 78-92% and specificity of 92-98% for detection of NETs (11, 12).

CUP-NET patients generally have a poorer prognosis compared to other NET patients (13) with a reported 10-year survival rate of just above 20% (14). Identifying the primary tumor is crucial as surgical resection of primary tumor is considered curative and is recommended even in cases where metastasis is present (15, 16). In our study of a total of 38 patients with metastatic NET and an unknown primary, 60.5% presented with hepatic (23 out of 38 patients), 9 with lymph nodal, 4 with mesenteric and 2 with skeletal metastases.

Most commonly detected primary site was small intestine (12 patients) including duodenum, jejunum and ileum, followed by pancreas (6 patients). In all 4 patients who presented with mesenteric metastases, primary site was diagnosed in small intestine. Small bowel NETs are known to metastasize first to mesentery, followed by hepatic metastases.

In one of the largest studies published till date, Prasad *et al.* (17) found that $^{68}$Ga-DOTA-NOC PET/CT identified primary sites in 59% patients with most common site being the pancreas followed by small intestine. In a study by Screiter *et al.* (18) published in 2014, they found that $^{68}$Ga-DOTA-TOC PET/CT detected primaries in 45.5% patients with most common site being the small intestine. Another relatively recent study by Pruthi *et al.* (19) published in 2016 showed a similar percentage of 59%. The results of our study are concordant with the above-mentioned studies, and we were able to identify the possible primary site in 20 out of 38 patients, that is, approximately 52.6% patients.

In our study, $^{68}$Ga-DOTA-NOC PET/CT was able to identify the true positives in 80% of the cases, that is 16 out of 20 patients with possible primary sites through histopathology and follow-up imaging. Two patients or 10% had false-positive findings in the pancreatic head, leading to recommended endoscopic procedures that failed to identify a primary tumor. 2 patients were lost to follow-up. Amongst the 18 patients in whom $^{68}$Ga-DOTA-NOC PET/CT was not able to identify the possible primary site, follow-up imaging confirmed this in 16 patients (True negatives 88%), whereas follow-up imaging revealed possible primary sites in 2 patients, that is ileum and pancreas (False negatives 11%). The sensitivity and specificity of $^{68}$Ga-DOTA-NOC PET/CT came out to be 88% and 90% respectively.

There were certain limitations in our study. Not all possible primary tumor sites suggested by $^{68}$Ga-DOTA-NOC PET/CT could be verified by histology because some patients could not undergo surgery after the initial workup. This limitation underscores the practical challenges in confirming the identified sites. The workup before $^{68}$Ga-DOTA-NOC PET/CT was not uniform. Conventional imaging studies were conducted at different institutions, using different protocols, and were interpreted by different readers. This lack of standardization in the pre-imaging workup could introduce variability and impact the reliability of the results.

## CONCLUSION

The findings of our study highlight the fact that $^{68}$Ga-DOTA-NOC PET/CT is a very promising tool in detection of primary site in patients with metastatic neuroendocrine tumor of unknown origin.

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