ROLE OF ^{68} Ga DOTA NOC PET/CT IN INITIAL EVALUATION, IMPACT ON MANAGEMENT AND ITS INCREMENTAL VALUE IN EVALUATION OF NET; SINGLE INSTITUTIONAL STUDY

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Abstract:

Neuroendocrine tumours (NETs) are rare, heterogeneous group of tumours which usually originate from small, occult primary sites and are characterized by over-expression of somatostatin receptors (SSTRs). Positron emission tomography/computed tomography (PET/CT) using Ga-68-labeled-somatostatin-analogues have shown superiority over other modalities for imaging of NETs. The objective of the study was to retrospectively evaluate the efficacy of Ga-68 DOTANOC PET/CT imaging in detecting the primary site in patients with metastatic NETs of unknown origin and its impact on clinical decision making in such patients.

Introduction:

Neuroendocrine tumors (NETs) are rare variety of neoplasm characterized by over expression of somatostatin receptors (SSTRs). Functional imaging like ^{68} Ga DOTANOC PET/CT plays a vital role in initial evaluation and management of NETs. In this paper we evaluated the sensitivity, specificity and accuracy of detecting primary, loco regional lymph nodes, distant metastasis, and its role in deciding therapy. Neuroendocrine tumours (NETs) are rare, genetically diverse, predominantly slow-growing tumours with relatively good prognosis (1). NETs predominantly arise from local multipotent gastro-intestinal (GI) stem cells (2) and are either symptomatic (functional) or asymptomatic (non-functional) based on their property of secreting biogenic amines and hormones. NETs account for less than 1% of all malignancies, however, according to Surveillance, Epidemiology and End Results (SEER) program data, their age-adjusted incidence increased 2.7 folds between 1973 and 2004 (3), primarily on account of increased physician awareness and better diagnostic facilities (4). Recent WHO classification allows an optimal prognostic stratification of NETs, which is helpful in deciding the best possible management (5, 6). NETs are characterized by over-expression of somatostatin receptors (SSTRs). SSTRs are G-protein coupled trans-membrane receptors which are internalized after binding to specific ligands. This property of over-expression of SSTRs in NETs has been extremely useful for their detection by functional imaging modalities such as somatostatin-receptor-scintigraphy (SRS) and Ga-68-labeled-somatostatin analogues (DOTA-peptides) positron emission tomography/computed tomography (PET/CT) (7).

Methodology:

Between January 2016 to April 2018, a total of 42 patients underwent ^{68} Ga DOTANOC PET/CT whole body scan from (vertex to mid thigh) after injecting 1-2 mCi of radiotracer. The images were taken 45 minutes of tracer injection if necessary delayed images were taken. Out of 42 (19 males, 23 females; Range 19 to 75 years, mean age of 58.25yrs, with histopathologically proven metastatic NETs and unknown primary site on conventional. Histopathology (wherever available) or follow-up imaging taken as reference standard. Quantitative estimation of SSTR expression in the form of SUVmax of detected primary and metastatic sites calculated. Follow-up data was collected through careful survey of hospital medical records. All patients voluntarily consented for the scan after obtaining relevant information including potential-benefits, radiation-exposure and costs.

Results:

DOTANOC PET/CT scan identify primary sites in 29 patients (69.04%). Mean SUVmax of the detected primary sites was 27.1 with a range of (2.7-160.8). The wide range could be due to tumor heterogeneity (variability in receptor expression).Significant positive correlation was found between SUVmax of detected primary site and SUVmax of the histopathologically proven sites of metastasis (r=0.769 (n=19); P<0.0001). Based on the findings of the Ga-68 DOTANOC PET/CT scan, 9 out of 42 (21.4%) patients underwent surgery, 21 sandostatin (50%), 10 peptide receptor radionuclide therapy (23.8%) and 2 chemotherapy (5%).

Table 1: Showing sensitivity, specificity and accuracy Ga-68 DOTANOC PET/CT

	SENSITIVITY	SPECIFICITY	ACCURACY
PRIMARY (T)	86.84% (95% CI: 71.9-95.6%)	100% (95% CI: 39.8-100%)	88.1 % (95% CI: 75.1-94.8 %)
LOCOREGIONAL NODES (N)	94.73 % (95% CI: 73.9-99.8 %)	91.30 % (95% CI: 71.9-98.8 %)	95.45 (95% CI: 75.6-99.3)
DISTANT METASTASIS (M)	100 % (95% CI: 84.6-100 %)	100% (95% CI: 83.1-100 %)	100% (95% CI: 91.6-100 %)

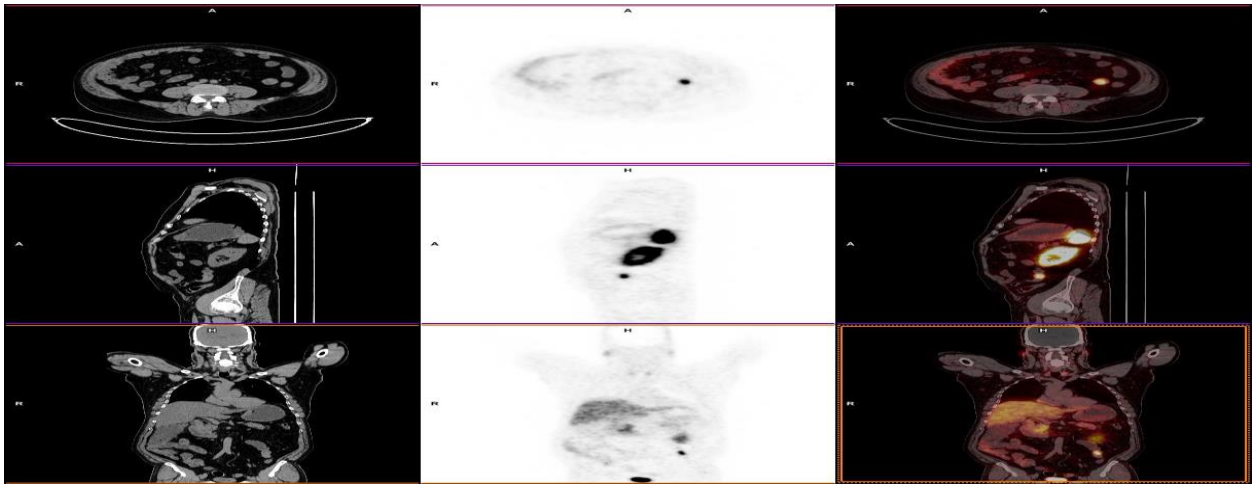

Figure1: CT image (A,D,G), MIP image (B,E,H) and corresponding axial fused image (C,F,I) of a case showing ileal NET; on biopsy. Intense DOTANOC avid ileal lesion in MIP and fused with no obvious morphological abnormality on corresponding CT scan.

Discussion:

The expanding use of Ga-68 labeled somatostatin analogues PET/CT imaging in clinical evaluation of NETs underlines the need to evaluate its appropriate role in the management of these tumours. Till date, various aspects of Ga-68 DOTANOC PET/CT imaging have been studied. The studies date back to last decade and most of the work has been done in European nations. Ambrosini *et al*. (9) and Naswa *et al*. (11) in their studies evaluating role of Ga-68 DOTANOC PET/CT in initial staging, found sensitivity in the range of 78–92% and specificity of 92.5–98% for detection of NETs.

Patients with metastatic NETs and unknown primary site (CUP-NET) constitute 10–13% of total NET study populations (9, 10) and have a relatively poorer prognosis than other NET patients (11). Catena *et al*. (10) reported that majority of CUP-NETs are well-differentiated. In our study, we found that majority of the patients (>50%) presented with well-differentiated (grade I) metastatic neuroendocrine lesions. Catena *et al*. (10) also found that patients with well-differentiated neuroendocrine tumor of unknown primary site usually have liver metastases. A total of 73.5% of our patients presented with hepatic metastasis (50 out of 68 patients). Rest of the patients presented with lymph nodal (10), mesenteric (6), skeletal (1), orbital soft tissue (1) metastasis.

Role of Ga-68-DOTA-peptides PET/CT in localizing the undiagnosed primary sites in patients with metastatic NETs has been studied earlier. In the largest bicentric study published till date, done on 59 patients, Prasad *et al*. (11) found that Ga-68 DOTANOC PET/CT identified primary sites in 35 out of 59 patients (59%) and concluded that Ga-68 DOTANOC PET/CT is superior to In-111-OctreoScan in this aspect. In their study, most commonly identified primary site was pancreas followed by small intestine. In a similar study by Naswa *et al*. (11), the group identified

primary site in 12 out of 20 patients (60%). In a recent study by Screiter *et al*. (13) published in 2014, the study group found that Ga-68 DOTATOC PET/CT detected primary mitotic site in 45.5% (15 out of 33 patients) with most common site being the small intestine. In our study, we were able to identify the primary mitotic site in 40 out of 68 patients i.e., in approximately 59% patients. The results of our study are concordant with the studies done by Prasad *et al*. (8) and Naswa *et al*. (11). In our study, rate of detection of primary sites was higher compared to study done by Screiter *et al*. (13). Possible reasons could be differences in study-population characteristics and tumour-heterogeneity. As histopathological grades were not available in all the patients, we are unable to comment upon the histopathological grade-wise identification rate in our study population. DOTANOC PET/CT scan identify primary sites in 29 patients (69.04%). Mean SUVmax of the detected primary sites was 27.1 with a range of (2.7-160.8).

Conclusion:

Our findings indicate that Ga-68 DOTANOC PET/CT is a promising sensitive, specific and accurate initial modality in patients with metastatic NETs for detection of the primary site, smaller lesion and in guiding therapeutic decisions for PRRT. Even in cases, where it is unable to detect the primary site, it provides useful information for guiding clinical management of such patients.

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