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Predictive value of FDG PET/CT in pediatric Neuroblastoma patients

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ABSTRACT:

Purpose: To explore the prognostic value of F-18 FDG PET/CT in neuroblastoma patients. **Materials and method:** comparative study with 63 pathologically proved NB patients with dominating high risk category (~65.1 %) who underwent F-18 FDG PET/CT using standard technique for purpose of initial, post-therapy or follow up assessment. Clinico-pathological, radiological and follow up data were also collected.**Results**:FDG uptake level was expressed in terms of maximum standardized uptake of the primary lesion against the maximum standardized uptake of the reference liver activity and maximum standardized uptake of the primary lesion stands alone where ROC curves marked cut off values of 1.95 & 2.05 respectively (both are almost double the reference hepatic activity). The marked cut-off values were tested in respect to the established clinico-pathological features and the disease outcome. we found significant relationship between the Shimada classification and FDG uptake level ,using 2.05 (cut-off value of the max SUV of the primary lesion), where 88.9% of those with favorable histology exhibit low FDG tumor uptake , while on the contrary 51.9 %

of those with unfavorable histology showed high FDG uptake level exceeding the cut-off value 2.05.The rest of correlation of both cut-off values with the other clinico-pathological features showed prevalence of increased primary tumor uptake of FDG (almost equal to or above double the reference hepatic activity) among those with less favorable clinico-pathological features yet was not statistically significant.As a trial to quantitatively evaluate the impact of variable patterns of tracer accumulation on overall survival using the suggested cut off values. Our results revealed higher risk for lower 2 years overall survival with increased tumor accumulation of FDG which was statistically significant when using max SUV of the primary/ max SUV of the hepatic activity cut-off value (1.95) (***p-value=0.05***) and a trend was seen with max SUV of the primary(***p-alue=0.07***).

CONCLUSION: PET-CT seems a valuable prognostic indicator where higher tracer accumulation of F-18 FDG seems to be linked to unfavorable histology and lower survival.

Keywords: FDG PET/CT, Neuroblastoma

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INTRODUCTION:

Neuroblastoma is an enigmatic disease with a variable outlook, broad spectrum of clinical presentation, biological features and prognosis.This wide range of clinical behavior reflects biologic and clinical heterogeneity of NB thus treatment of NB is tailored for the age of the patient, stage of the disease, and biology of the tumor ***(1).*** The published experience on neuroblastoma and PET is limited, yet PET scan findings appeared to correlate well with disease status as determined by MIBG scans, CT (or MRI),

bone marrow tests, urine catecholamine levels, and clinical history. Sequential PET scans accurately depict treatment effects and disease evolution ***(2).*** Because of the higher spatial resolution of the PET scanner and the tomographic nature of PET images, PET may be better than routine 123I- or 131I-MIBG scintigraphy for identifying small lesions and fordelineating the extent or localizing anatomic sites of disease ***(3).***PET may also yield useful clinical information in neuroblastoma patients beyond anatomic localization of disease. Through its depiction of the metabolic state of tumor cells, it might provide insights into the proliferative or malignant potential of disease. Whether the degree of uptake at diagnosis has prognostic significance has not been studied. The findings in patients with metastatic neuroblastoma can influence treatment decisions (***4).***

PATIENTS AND ETHODS:

This study was conducted on 63 patients were attending CCHE (Children's Cancer Hospital Egypt) for management, from Oct., 2009 till Jan. 2014. They were referred to Nuclear Medicine department in different clinical phases of disease (initial, post-therapy or follow up) and each patient underwent FDG PET-CT scan.

FDG PET/CT protocol: After fasting for 4-6 hours and ensuring blood glucose level below 150 mg/dl, injection of 3MBq /kg body weight 18F-FDG was done . Scanning started 60-90 min after tracer injection, 5–7 bed positions; acquisition time, 2-3 min/bed position using a dedicated PET-CT scanner (Biography, True-Point; Siemens). Patients were examined in the supine position with arms elevated, and CT scanning was started from the vault of skull with the following parameters: 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5. The CT scans reached caudally to feet or mid tibiae. PET over the same region was performed immediately after acquisition of the CT images (2-3min/bed position). The CT-data were used for attenuation correction, and images were reconstructed as 5-mm slices applying a standard iterative algorithm (ordered-subset expectation maximization). When necessary, sedation was used in accordance with guidelines before 18F-FDG PET/CT imaging to ensure patient immobilization and adequate image quality.

Image interpretation: Qualitative (Visual) assessment: All studies were reviewed by 2 nuclear medicine physicians in consensus. For each single study, the presence or absence of disease was recorded separately for the soft-tissue compartment (primary mass, nodal,and liver metastases) and bone–bone marrow compartment. Theinvolved regions detected by each modality were recorded. For 18F-FDG PET/CT

interpretation, any focal uptake, superior-to back ground in the primary mass, lymph nodes, liver, or skeleton was interpreted as positive or abnormal. Patchy inhomogeneous 18F-FDG uptake in the bone marrow, especially in the absence of recent chemotherapy or hematopoietic stimulating factors, was interpreted as positive for bone marrow infiltration. **Quantitative assessment:** The maximum standardized uptake values (max SUV) were recorded for primary NB lesions in each patient, after manual application of the volumetric regions of interest on the trans-axial attenuation-corrected PET slices, around the areas demonstrating the greatest accumulation of 18F-FDG and away from any nearby overlapping activity.Another sizable ROI was drawn over the liver where its max SUV was considered reference activity for further quantitative analysis to calculate max SUV Lesion/ max SUV liver ratio, ***Fig (1).***

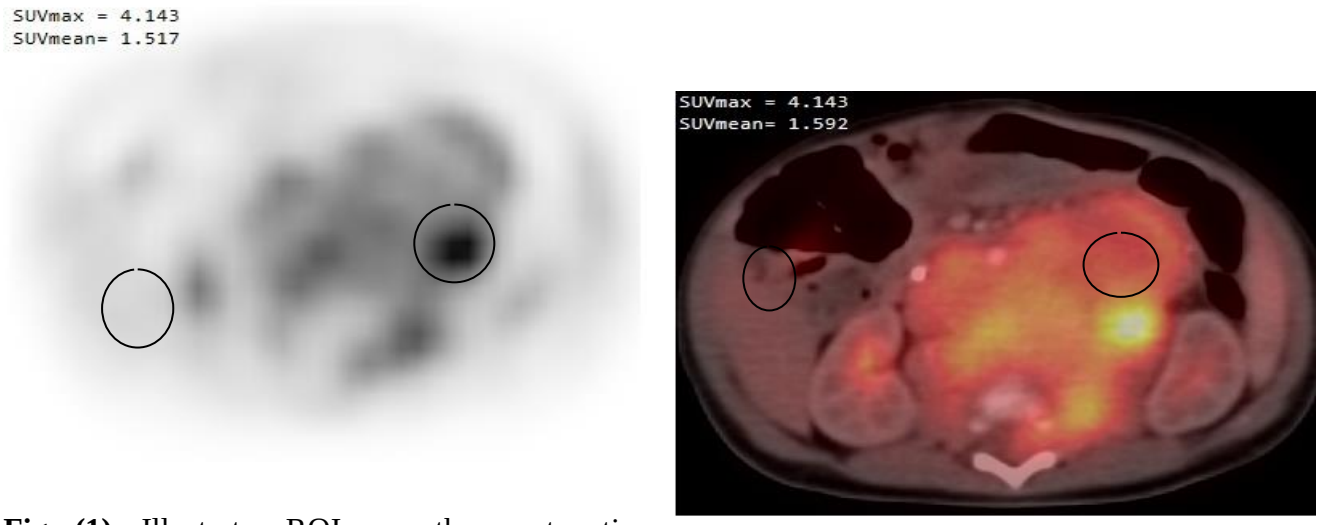

Fig. (1): Illustrates ROI over the most active region within the primary and over the liver in F-18 FDG PET/CT axial images.

Statistics: Data was analyzed using SPSS win statistical package version 20 (SPSS Inc., Chicago, IL). Receiver operator characteristic (ROC) curve analysis used to find the best cut off value to discriminate between progression & controlled status as a measure of prognosis with the highest sensitivity & specificity; this was done for SUV max of primary lesion/ SUV max of liver & SUV max of primary lesion alone. The cut off values for each of SUV max of primary lesion/ SUV max of liver & SUV max of primary lesion were correlated with all of the other factors using Chi-square test. A p-value < 0.05 was considered significant. Kaplan-Meier method calculated all survival estimates. Other predictor and prognostic variables were

related to survival using log rank test. P-value was set significant at 0.05 levels. ***(Kleinbaum, 2005).***

RESULTS:

The age of our group ranged from 2 to 156 months with a median and mean of 24 and 35.2 months respectively. There was a predominance of disease in males with male to female ratio 1.4:1.The majority of our group were of high risk category (65.1 %) and stage IV represented 63.5%. As a trial to assess the prognostic impact of FDG uptake levels, quantitative analysis was used where maximum counts of regions of interest were estimated over primary NB lesions and over liver activity in FDG images, then a Receiver operator characteristic (ROC) curve analysis marked **1.95 & 2.05** as cut off points for SUV max of lesion/liver SUV max ratio, &also for Lesion SUV max alone to discriminate between different patterns of response to therapy (Controlled & progression group)***(Figure 2,3)*** .Correlation between the cut off value of 1.95 in respect to different clinico-pathological prognostic factors was performed. As indicated in ***(Table 1),***No statistically significant difference demonstrated in maximum SUV of NB lesion / maximum SUV liver ratio using 1.95 as a cut-off point in respect to different clinico-patholgical parameters (18 mons was discriminator for age) , to response and survival (P-value >0.05), yet ,a part from age, & response to treatment, lesion SUV max / liver SUV max ratio > 1.95 showed higher prevalence among poor prognostic variables as it was revealed among 60 % of those with amplified N-myc gene, 53.7 % with unfavorable histology, 51 % with high M/K ratio, 53.7 % with high risk stratification and in 58.3 % of dead patients, However there is no significant statically difference in between both groups. As in case of lesion SUV max / liver SUV max ratio , correlation between the cut off value of lesion SUV max alone (2.05) in respect to different clinico-pathological prognostic factors revealed (apart from age & therapy response) higher prevalence of poor prognostic variables with levels of SUV max >2.05 as it was noted among 60 % of those with amplified N-myc gene, 51.9 % with unfavorable histology , 51 % with high M/K ratio, 51.2 % with high risk stratification and in 58.3 % of dead patients. Only statistically significant correlation was noted with Shimada classification (P-value 0.03), the restof the parameters did not show statistical significance (*P-value >0.05)* ***(Table 2).***

Table (1): FDG uptake level in correlation with individual & overall main clinico-pathological risk factors and outcome in 63 Neuroblastoma patients.

FDG Lesion/Liver / **Clinico-pathological**	**≤ 1.95 No. (%)**	**> 1.95 No. (%)**	***P-value***
Age:			
< 18 mons	9(47.4 %)	10 (52.6%)	*0.9*
≥ 18 mons	23(52.3%)	21(47.7%)	
N-myc gene:			
Amplified	8 (40 %)	12 (60 %)	*0.29*
Normal pattern	24(55.8%)	19 (44.2%)	
Histology:			
Favorable	7 (77.8 %)	2 (22.2 %)	*0.15*
Unfavorable	25(46.3 %)	29 (53.7 %)	
Mitosis/Karhyorrhexis			
High	25(49 %)	26 (51 %)	*1*
Intermediate	2 (66.7 %)	1 (33.3 %)	
Low	5(55.6 %)	4 (44.4 %)	
Risk stratification:			
Low & intermediate	13(59.1 %)	9(40.9%)	*0.43*
High	19(46.3%)	22 (53.7 %)	
Response:			
Controlled	24(49 %)	25 (51%)	*0.76*
Progression	8 (57.1%)	6 (42.9 %)	
Survival:			
Alive	27 (52.9%)	24(47.1%)	*0.54*
Dead	5 (41.7 %)	7 (58.3 %)	

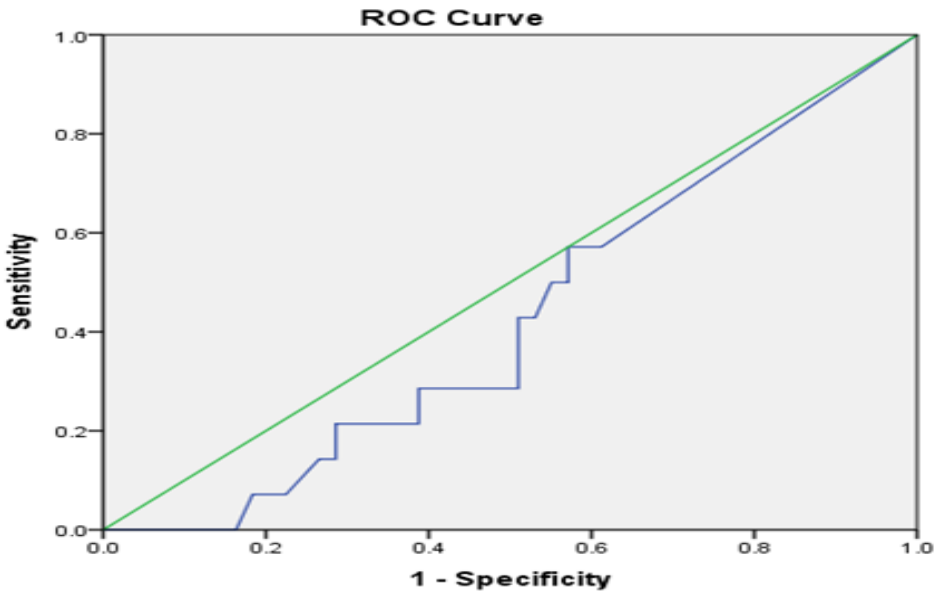

Fig. (2): ROC curve for FDG lesion uptake /liver uptake cut-off value between controlled & progressed groups in NB patients.

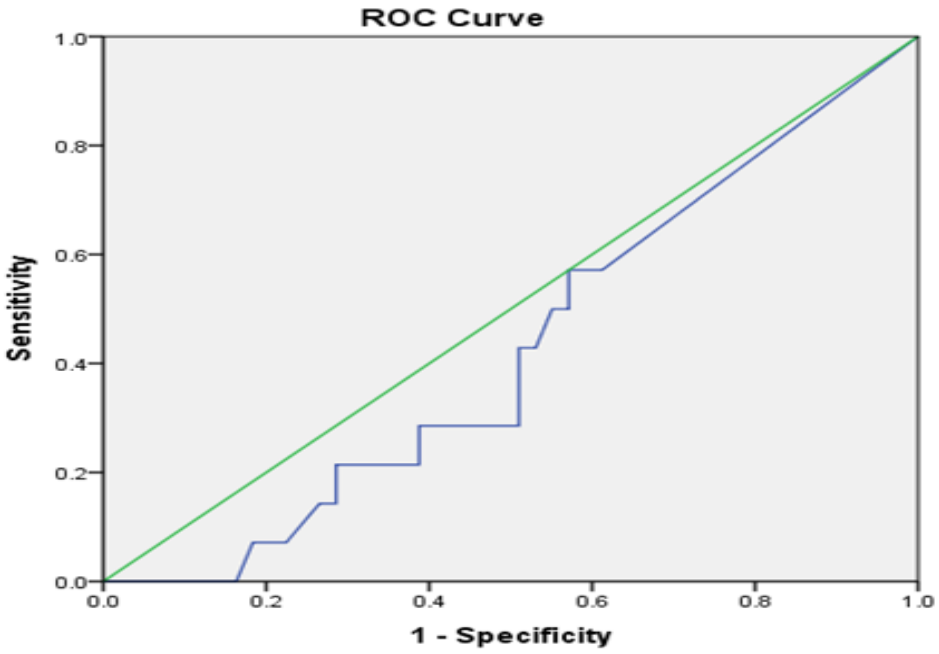

Fig. (2): ROC curve for FDG lesion uptake /liver uptake cut-off value between controlled & progressed groups in NB patients.

Table (2): Lesion maximum SUVCut off value in correlation to individual & overall main clinico-pathological risk factors and outcome in 63 Neuroblastoma patients.

SUV max / **Clinico-pathological**	**≤ 2.05 No. (%)**	**> 2.05 No. (%)**	***P-value***
Age:			
< 18 mons	9(47.4 %)	10 (52.6%)	*0.59*
≥ 18 mons	25(56.8%)	19(43.2%)	
N-myc gene:			
Amplified	8 (40 %)	12 (60 %)	*0.18*
Normal pattern	26(60.5%)	17 (39.5%)	
Histology;			
Favorable	8 (88.9 %)	1 (11.1 %)	***0.03***
Unfavorable	26(48.1%)	28(51.9 %)	
Mitosis/Karhyorrhexis			
High	25(49 %)	26 (51 %)	*1*
Intermediate	2 (66.7 %)	1 (33.3 %)	
Low	5(55.6 %)	4 (44.4 %)	
Risk stratification:			
Low & intermediate	14(63.6 %)	8(36.4%)	*0.29*
High	20(48.8%)	21 (51.2 %)	
Response:			
Controlled	24(49 %)	25 (51%)	*1*
Progression	8 (57.1%)	6 (42.9 %)	
Survival:			
Alive	29(56.9%)	22(43.1%)	*0.52*
Dead	5(41.7 %)	7 (58.3 %)	

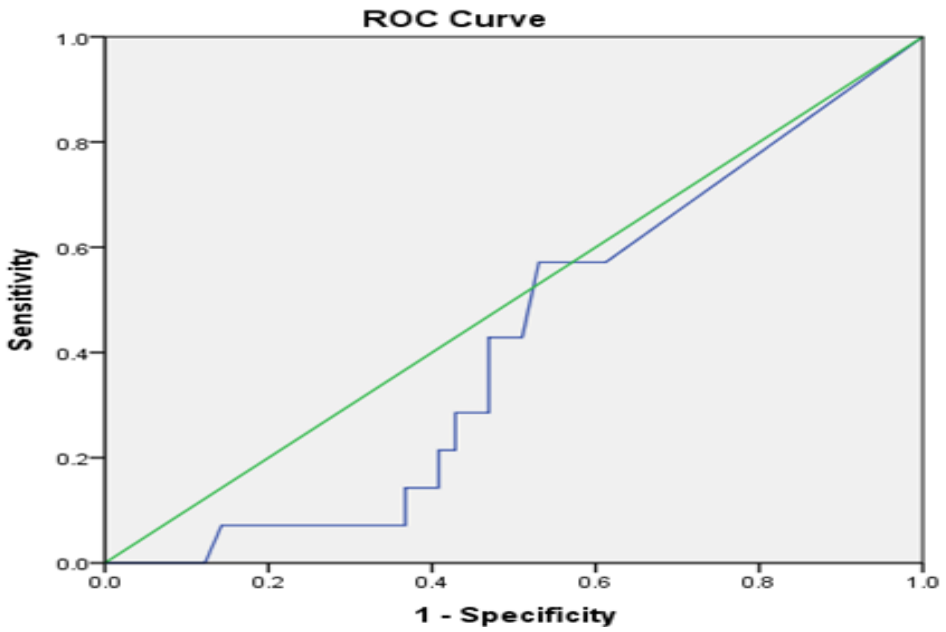

Fig. (3): ROC curve for maximum FDG lesion uptake (SUV max) cut-off value between controlled & progressed groups in NB patients.

Survival analysis: Overall survival was calculated from first visit date to death or last examination with range of 4 to 52.2 months. Twelve patients (19%) died during the observation period. Two years overall survival for the whole group of patients was 72 %.Log rank test was applied to check for the prognostic significance of the previously marked 1.95, & 2.05 cutoff values for maximum SUV lesion/ maximum SUV liver & maximum SUV of lesions in relation to overall survival.Significant correlation of maximum SUV lesion/ maximum SUV liver with 2 years overall survival , where higher (80.7%) 2 years overall survival was shown in those below the cut off value 1.95 compared to 64 % of those with lesions exceed the cutoff point of uptake ***(p-value=0.05)***. No significant correlation was found with lesion SUV max cut off value yet higher 2 years overall survival was noticed in those below the cut off value 2.05 in SUV max with 77.7 % of them showed higher 2 years OS versus 66.6% for those exceeding this cutoff value***(Table 3), Figures (4,5).***

Table (3): Prognostic significance of maximum SUV lesion/ maximum SUV liver & maximum SUV lesioncut-off values for 2 years OS.

Cut off values	**2 Yrs OS**	***P-value***
FDG Lesion/Liver Cutoff		
≤ 1.95	**80.7 %**	
> 1.95	**64 %**	***0.05***
SUV max of the primary lesion		
≤ 2.05	**77.7 %**	
> 2.05	**66.6 %**	***0.07***

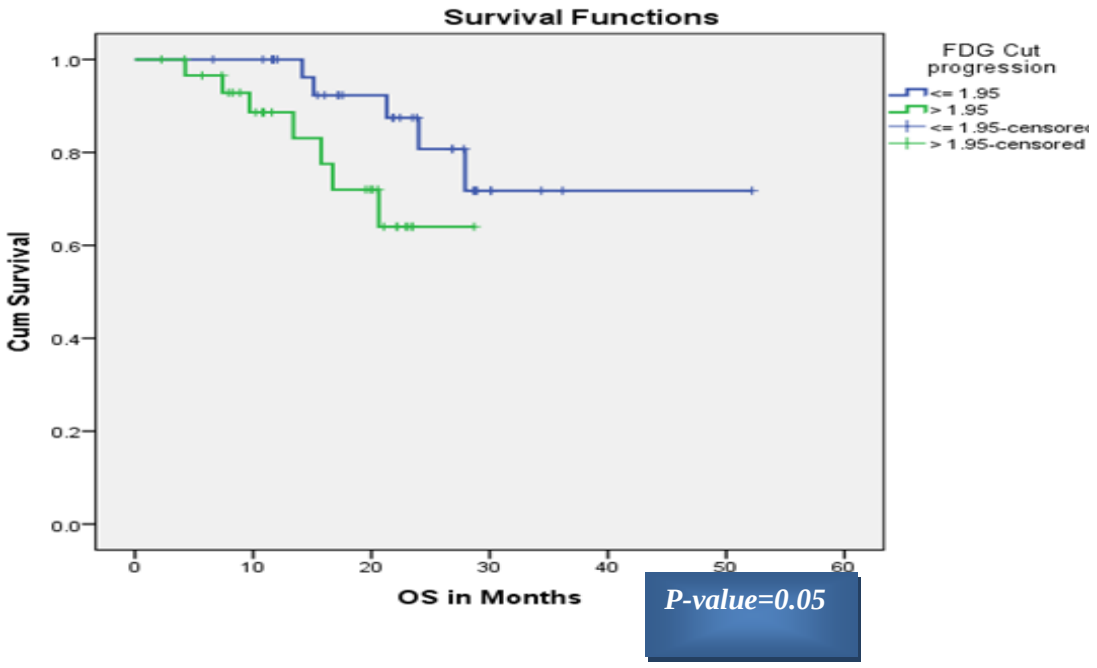

Fig.(4):Overall survival curves of patients with FDG avid lesions above the estimated lesion SUV max/ liver SUV max cut off value (1.95) (green line) correlated to those with less FDG avid lesions (≤ 1.95) (blue line).

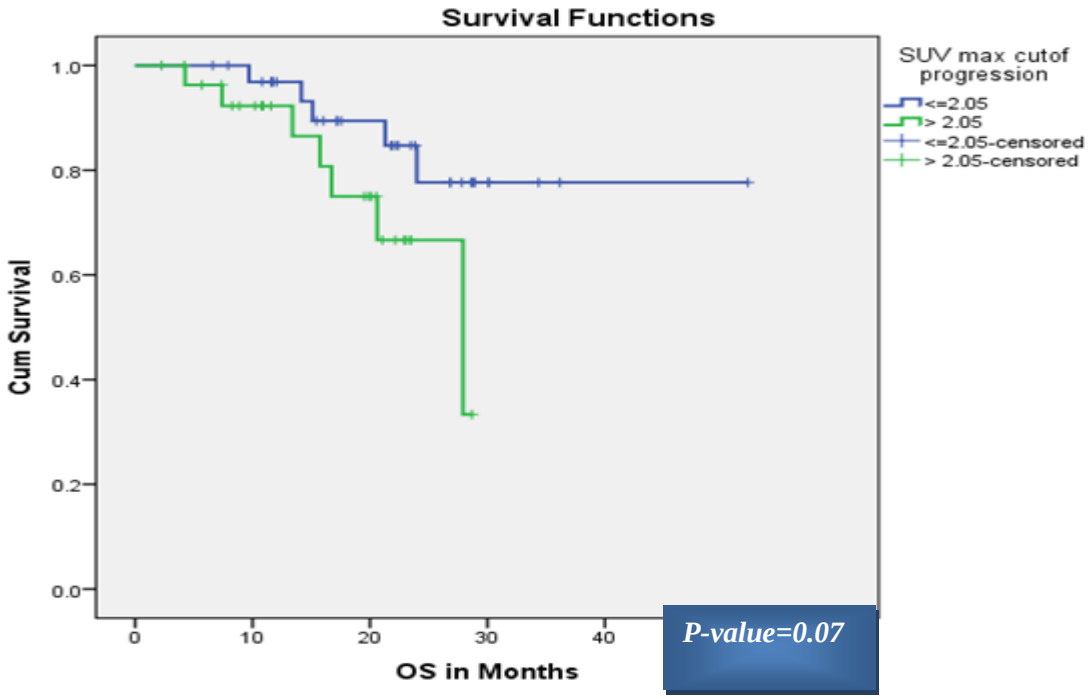

Fig. (5):Overall survival curves of patients with FDG avid lesions above the estimated SUV max cut off value (2.05) (green line) correlated to those with less FDG avid lesions (≤ 2.05) (blue line).

DISCUSSION:

Molecular imaging is changing diagnostic and treatment paradigms in patients of neuro-endocrinal tumors through its ability to non-invasively characterize disease, supplementing the traditional role of using imaging for localizing and measuring disease. With increasing range of therapies there was a need for their individualization to the specific subtype of tumor expressed, which varies in aggressiveness from well to poorly differentiated phenotypes. F-18 FDG/PET CT is now able to characterize these subtypes through its ability to quantify glycolytic metabolism. The ability to perform this as a whole body study is highlighting the limitations of relying on histopathology obtained from a single site (5, 6).Several publications have shownthat 18 F-FDG uptake correlates with high proliferative activity, cellular dedifferentiation, and aggressiveness of neuroendocrine tumors (7, 8, 9).In our study, FDG uptake level was expressed in terms of maximum standardized uptake of the

primary lesion against the maximum standardized uptake of the reference liver activity and maximum standardized uptake of the primary lesion stands alone where their marked cut off values are of 1.95 & 2.05 respectively (both are almost double the reference hepatic activity). Our cut-off values were tested in respect to the established clinico-pathological features and the disease outcome. Supported by the published data ,we found significant relationship between the Shimada classification and FDG uptake level ,using 2.05 (cut-off value of the max SUV of the primary lesion), where 88.9% of those with favorable histology exhibit low FDG tumor uptake , while on the contrary 51.9 % of those with unfavorable histology showed high FDG uptake level exceeding the cut-off value2.05.The rest of correlation of both cut-off values with the other clinico-pathological features showed prevalence of increased primary tumor uptake of FDG (almost equal to or above double the reference hepatic activity) among those with less favourableclinico-pathological features yet was not statistically significant. Intense 18 F- FDG uptake, and high standardized uptake value (SUV) have been accused for decreased survival and poor prognosis by ***Adams et al***&Kayani et al. (10, 11). ***Binderup et al***. revealed that FDG-PET, both in terms of positive/negative and quantified by SUVmax, was an independent prognostic factor for the prediction of survival for neuro-endocrinal tumor patients, exceeding the prognostic value of traditionally used parameters (12). In the present study, we tried to quantitatively evaluate impact of variable patterns of tracer accumulation on overall survival using the suggested cut off values. Our results revealed higher risk for lower 2 years overall survival with increased tumor accumulation of FDG which was statistically significant when using max SUV of the primary/ max SUV of the hepatic activity cut-off value (1.95) (p-value=0.05) and a higher SUV maxof the primary was also seen in

correlation with 2 Years overall survival the result was statically insignificant (p-value=0.07).

CONCLUSION:

PET-CT seems to be a valuable imaging technique in NB patients not only as a diagnostic tool but also as a prognostic indicator where higher tracer accumulation of F-18 FDG seems to be linked to unfavorable histology & lower survival.

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