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A CORRELATIONAL STUDY OF HISTOPATHOLOGY AND FDG-PET/CT IN THE DIAGNOSIS OF VARIOUS GRADES OF NON-HODGKIN LYMPHOMAS.

Oncopathology

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ABSTRACT

Lymphomas are a heterogeneous group of disorders arising from constituent cells of the immune system. The SUVmax (standardised uptake value) on PET/CT reflects the tumor's aggressiveness. In this study, we observe the SUVmax in FDG-PET/CT and correlate it with the histopathological diagnosis and proliferation index in various grades of non-Hodgkin lymphoma (NHL). 187 cases of NHLs received at the Department of Pathology during the years 2018–2020 were included in the study. The age, final histopathological diagnosis, Ki67 index, and SUVmax for each case were collected. Statistical analysis was performed using SPSS 23 to establish a correlation between histopathological diagnosis, the Ki67 index, and the SUVmax. There was a significant correlation between high-grade lymphomas and SUVmax (r = 0.416, P value 0.001) and also between SUV max and the KI67 proliferation index (r = 0.731, P value 0.001). The sensitivity and specificity of SUVmax were 70% and 76%, respectively. There is an acceptable correlation between the final histopathological diagnosis, SUVmax, and Ki67, thus suggesting that SUVmax can be used as an additional tool for the early detection of high-grade lymphomas, rapid transformation, and recurrence in a known case.

KEYWORDS

Non-Hodgkins lymphomas, SUVmax, Ki67 proliferation index

INTRODUCTION:

Lymphomas are neoplasms of the lymphoreticular system that can arise in lymph nodes and extranodal sites [1]. Non-Hodgkins lymphomas with an aggressive phenotype usually has a poor prognosis. Successful therapy for most NHLs requires an accurate pathologic diagnosis. The role of radiology in the management of lymphomas has increased in recent years due to the advent of PET/CT. Fluorine-18 fluorodeoxyglucose PET/computed tomography (FDG-PET/CT) is an emerging functional and metabolic technique for the molecular imaging of tumors [2]. Since the advent of FDG-PET/CT, the management of lymphomas has been made easier owing to its role in staging, restaging, prognostication, monitoring therapy, detecting bone marrow involvement and recurrence.

The 18F-FDG PET/CT method takes advantage of the fact that tumour cells have significantly increased glycolysis and therefore these cells process the administered 18F-FDG to a greater extent when compared to normal cells. Because of the diverse biological nature and metabolic processes in different histological subtypes of NHL, the intensity of 18F-FDG accumulation in lymphoma cells varies, but it also varies in individual patients with identical lymphoma subtypes [3]. In each patient, the intensity of 18F-FDG accumulation is determined semi-quantitatively by calculating the standardized uptake value (SUV) [4]. SUV max is affected by various clinicopathological factors including proliferation activity, aggressiveness, and glucose transporter expression [2]. SUV Max has been used to differentiate between indolent and aggressive lymphomas, as well as to detect Richter's transformation and extra-nodal involvement. [2,5]

Ki67 is associated with tumour cell proliferation and is used as a marker of aggressiveness. In this study, we attempt to correlate the Ki67 proliferation index with the SUVmax at the biopsy site in indolent and aggressive non-Hodgkin lymphomas.

METHODS:

We retrospectively analyzed patients with Non-Hodgkin lymphomas, diagnosed at HCG hospital, Bengaluru from January 2017 to December 2020. 187 patients who had undergone FDG-PET/CT were included in the study. All cases of nodal and extranodal NHLs, treatment naïve, progressive, and relapsed cases were included in the study.

Age, sex, site of biopsy, Ki67 proliferation index, and final histopathological diagnosis after immunohistochemistry were noted. The previous FDG-PET/CT reports of these patients were retrieved and the SUVmax at the site of the biopsy was included.

All lymph node core biopsies and whole node excisions received in the department of Pathology; HCG Bengaluru were processed in 10% Neutral buffered formalin. 3–4-micron thickness sections were taken and stained with Hematoxylin and Eosin. After the initial examination under the microscope, immunohistochemistry was carried out for all cases for categorization and typing. The final diagnosis was made in reference to the WHO classification of tumors of hematopoietic and lymphoid tissues, 2017 revised edition.

FDG-PET/CT: After fasting for 4-6 hours, with a blood glucose level of <150mg/dl, 18F-FDG is administered at 0.15 mCi/kg. The scan is carried out 60 mins after the administration of radioactive glucose.

A whole-body CT scan is carried out, followed by a whole-body PET scan and then the two sets of images are co-registered.

Statistical Analysis

Statistical analyses were performed using SPSS Version 23 (Statistical Package for the Social Sciences) software. Continuous data were expressed as mean ± standard deviation (SD), and quantitative values were expressed as numbers, ranges, and/or percentages. Receiver operating characteristic (ROC) curves of SUVmax and Ki 67 index were used for estimating the accuracy. A student's t-test was used to analyze differences between SUV Max in different parameters (between two groups). Correlations between SUVmax and Ki 67 were calculated using Pearson's correlation test. The correlations between SUVmax and High grade and low grade were calculated using Spearman's rank correlation test. When $r > 0$, correlations were considered relevant and statistically significant when $P < 0.05$.

RESULTS

Patient characteristics

There were 187 patients out of which 119 were males (64%) and 68 were females (36%) and 67% of them were older than 50 years. There were 134 (72%) nodal cases and 53 (28%) extranodal cases. Among the nodal lymphomas 83(61%) cases were cervical, 18(13%) were axillary, 5(3%) were inguinal, and 28 (23%) were abdominal group of lymph nodes. Ki67 index less than or equal to 40 was taken as cut off to distinguish low-grade and high-grade lymphomas. Based on this, 131(70%) cases were high-grade and 56(30%) cases were low-grade. NHLs included DLBCL(n=92, 49%), Follicular lymphoma(n=34, 18%), ALCL(n=3, 2%), B lymphoblastic lymphoma (n=3, 2%), T lymphoblastic lymphoma(n=5, 3%), PTCL(n=8, 4%), CLL/SLL(n=8, 4%), Mantle cell lymphoma (n=3, 2%), Marginal zone lymphoma(n=6, 3%), Primary mediastinal large B cell lymphoma(n=5, 3%), NK/T cell lymphoma(n=2, 1%), T cell rich B cell lymphoma(n=2, 1%), Burkitt's lymphoma (n=2, 1%), Plasmablastic lymphoma(n=2,1%), Primary cutaneous follicle centre lymphoma(n=1)

SUVmax in indolent and aggressive lymphomas

The SUVmax of 187 patients at the biopsy site was collected. For aggressive lymphomas, the mean±SD was 19.94±12.62, for indolent lymphomas the mean±SD was 10±7.14. There was a statistically significant correlation between high and low-grade lymphomas with SUVmax($p<0.001$) and a moderately positive correlation($r=0.416$). Among the NHLs, DLBCL was the most common with mean±SD being 70.35±19.9.

The mean±SD for the cervical group was 15.5±11.97, the axillary group 13.16±8, the inguinal group 10.94±5.08, the abdominal group 19.04±12.6 and the extranodal group 20.52±13.09.

Ki67 index in indolent and aggressive lymphomas

The mean±SD for indolent lymphomas and aggressive lymphomas were 70.02±17.58, 25.42±11.54 respectively. There was a strong statistically significant correlation between the Ki67 index and high-grade, low-grade lymphomas with a strong positive correlation($r=0.731$). There was a significant mean difference of Ki67 observed between high and low-grade groups.

Correlation between SUVmax and Ki67 in high-grade and low-grade lymphomas

The mean±SD for SUVmax and Ki67 index was 17±12 and 58±25 respectively. There was a statistically significant correlation ($p<0.001$) as well as a weak positive correlation($r=0.377$) between the two. The area under the ROC curve was 0.76(95% confidence interval: 0.691-0.830, $p<0.001$) and the sensitivity and specificity of SUVmax were 70% and 76% respectively.

DISCUSSION:

The efficacy of 18F-FDG PET in the initial staging of lymphoma has been validated in several studies. The primary advantage over anatomical imaging such as CT is that it can detect metabolic changes in the areas involved by the tumour before structural changes become visible 6. The sensitivity and specificity of FDG PET/CT have made it a basic imaging method for determining the stage and extent of non-Hodgkin lymphomas.4 Tumor cells have significantly increased glycolysis and hence use the administered FDG to a greater extent. However, NHL encompasses a variety of disease entities and the intensity of FDG accumulation in lymphoma cells may vary due to the disease's diverse biologic nature, different histological subtypes, or different tumor proliferation statuses7. Hence it has been found useful in differentiating indolent and aggressive lymphomas and also in the detection of Richters transformation.

According to Thandra et al, the average age at diagnosis is 67 years, with 57 % of diagnoses made in those above 65 years old, and the incidence is higher in males than females. The most common NHL being diagnosed was DLBCL which was observed in our study as well.8

While lymph nodes are the usual sites of involvement by NHL with the cervical group being the most common, up to 30% of the NHLs can be extranodal. 9 In the current study lymphoma involving the cervical group was most common and 25% of the cases were extranodal.

SUVmax has been found to be higher in aggressive lymphomas when compared to indolent lymphomas, although there has been considerable overlap between the two groups in the lower range of SUV.10, 5 This is concurrent with our study where within the histological subtypes of NHL, SUVmax was higher in DLBCL, ALCL, LBL, BL and lower in SLL, FL MCL, and MZL. In ROC curve analysis, the area under the curve was 0.76(95% confidence interval:0.691-0.830, $P<0.001$), and the sensitivity and specificity of SUVmax were 70% and 76% respectively.

A study by Hongling Li et al11 found the SUVmax cut-off value to be 8.5, above which the tumour was considered to have aggressive histology. The sensitivity and specificity were found to be 76.3% and 92% respectively. Another study by Ngeow et al said that a SUVmax cutoff value of >10 provided a sensitivity of 91% and specificity of 62%, and Schöder et al, reported that a SUVmax cutoff value of 10 yielded a sensitivity of 71% and specificity of 81% with regard to distinguishing between indolent NHL and aggressive NHL.5, 12

The Ki67 index which is expressed in all dividing cells demonstrates the proliferation potential of tumours which is used as a proliferation marker. It determines the speed of tumour growth and hence helps the clinician choose an appropriate chemotherapy regimen. Several studies have found a link between ki67 and clinical presentation in breast13, lung14, prostate15, cervical carcinomas16, and lymphomas17. A study by Watanabe et al17 included 36 cases of untreated lymphomas demonstrating a significant correlation between SUVmax and Ki67 at the biopsy site ($r=0.69$, $P<0.001$), another study by Hongling et al11 had similar findings ($r=0.813$, $p<0.001$) which is concordant with the findings of the current study ($r=0.377$, $p<0.001$). A study by Broyde et al18 included 268 newly diagnosed lymphomas with a Ki67 index cut-off of 45% between indolent and aggressive lymphomas (area under the curve = 0.877, $P < 0.001$), and cut off of 70% to discriminate good and bad prognosis in DLBCL (area under the curve = 0.65, $P = 0.004$)

A meta-analysis review by Meyer et al stated that FLT-PET/CT might be a better imaging modality compared to FDG-PET/CT, as FDG uptake depends on the GLUT transporters present on cell membrane whereas FLT depends on thymidine kinase 1 which is usually elevated during S phase. The study established a moderate correlation between FDG-PET/CT or FLT-PET/CT SUV max with the ki67 index.19

This study had seven cases of gastric lymphomas, six were diagnosed as DLBCL, and one as mantle cell lymphoma. The mean±SD for SUVmax was 22.44±12.62. A study by Hwang et al 20 showed that patients with SUVmax less than 5.2 in primary gastric lymphomas had better overall survival than others.

CONCLUSION

Imaging is a non-invasive modality for predicting tumour biology and behavior. Ki67 index in an invasive test and site-specific test. In lymphomas like DLBCL, where intratumoral heterogeneity is greater, a single biopsy is not representative of the whole malignancy. In such cases, imaging modalities that can accurately predict the Ki67 index can be used to bridge the gap.

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