ORIGINAL ARTICLE

Gülhane Med J 2017;59: 44-48

doi: 10.5455/Gulhane.271274

Utility of FDG-PET/CT in primary central nervous system lymphoma and its contribution to prognosis estimation

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SUMMARY

Aims: Primary central nervous system lymphoma (PCNSL) is an aggressive form of extra-nodal non-Hodgkin's lymphoma confined to CNS at initial presentation. The role of FDG-PET/CT in PCNSL is not fully defined and reviewed systematically. This study was conducted to summarize the utility of FDG-PET/CT in the management of PCNSL and show its contribution to predicting survival.

Materials and Methods: This study included 19 patients with PCNSL treated with high dose methotrexate between 2004 and 2015. We retrospectively examined PET/CT and outcome of the patients. Maximum standardized uptake value (SUVmax) was calculated.

Results: Mean overall survival (OS) and disease-free survival (DFS) was 22.7 months, 16.8 months, respectively. Mean SUVmax was 19.9 ± 6.7 in recurrent/metastatic group, 15.3 ± 7.2 in nonmetastatic (complete remission) group. There was a statistically significant difference between them according to SUVmax values (p=0.199). OS at 1st year was 84%, 58% at 2nd year. DFS at first year was 47%, 31.5% at second year.

Conclusion: The utility of FDG-PET/CT can be summarized as initial diagnosis, baseline staging and restaging, evaluation of treatment response and prognosis estimation in PCNSL. SUVmax derived from FDG-PET/CT is a strong predictor for progression and survival of the disease.

Key Words: *Primary CNS lymphoma, disease-free survival, overall survival, SUVmax, FDG-PET/CT.*

ÖZET

FDG-PET\BT'nin primer santral sinir sistemi lenfomasında yararı ve prognoz tahminindeki katkısı

Amaç: Primer santral sinir sistemi lenfoması (PSSSL) başlangıcında santral sinir sistemine hapsolmuş agresif bir ekstranodal non-Hodgkin lenfomadır. FDG-PET/CT'nin hastalıktaki rolü tam anlamıyla tanımlanmamış ve sistemik olarak gözden geçirilmemiştir. Bu çalışma, FDG-PET/CT'nin hastalığın yönetimindeki faydalarını özetlemek ve sağkalım tahminine katkısını göstermek için yapılmıştır.

Gereç ve Yöntem: Bu çalışma 2004-2015 yılları arasında yüksek doz metotreksatla tedavi edilmiş 19 PSSSL hastasını içermektedir. Geriye dönük olarak bu hastaların PET/CT sonuçlarını ve gidişatlarını inceledik. Maksimum standardize tutulum değerleri (SUVmax) hesaplandı.

Bulgular: Ortalama toplam sağkalım (OS) ve hastalıksız sağkalım (DFS) süreleri 22.7 ay ve 16.8 aydı. Ortalama SUVmax rekürrent/metastatik grupta 19.9 ± 6.7, nonmetastatik grupta 15.3 ± 7.2 idi. Bu iki grup arasında SUVmax değerlerine göre istatistiki olarak anlamlı bir fark mevcuttu (p=0.199). OS 1. yılda %84, 2. yılda %58; DFS 1. yılda %47, 2. yılda %31.5 idi.

Sonuç: FDG-PET/CT'nin PSSSL'deki kullanılabilirliği ilk teşhis, başlangıç ve yeniden evreleme, tedaviye yanıtın değerlendirilmesi ve prognoz tahmini şeklinde özetlenebilir. FDG-PET/CT görüntülerinden hesaplanan SUVmax, progresyon ve sağkalım tahmini açısından kuvvetli bir parametredir.

Anahtar Kelimeler: *Primer SSS lenfoması, hastalıksız sağkalım, toplam sağkalım, SUVmax, FDG-PET/BT.*

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Date submitted: Jul 03, 2017 • **Date accepted:** Sep 08, 2017 • **Online publication date:** June 30, 2017

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare, aggressive form of extra-nodal non-Hodgkin's lymphoma most commonly consisting of diffuse large CD20+ B-cell infiltrates confined to CNS at initial presentation (1). It accounts for only 3–5% of all primary brain tumors and affects all age groups, while peak incidence is seen in fifth to seventh decades (2). High dose methotrexate-based chemotherapy regimens are the current main therapy for newly diagnosed PCNSL with significant rates of complete response (3). Despite high initial complete remission rates with methotrexate-based regimens, over 50% of the patients relapse within 2 years after diagnosis (4). Unlike systemic diffuse large B-cell lymphoma (DLBCL), PCNSL doesn't have a plateau in progression-free survival rates; even patients, living a disease free life of more than 5 years, continue to carry recurrence risk (5).

Contrast-enhanced magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) are the preferred imaging methods for diagnosis and follow-up. Although CT and MRI are still the key imaging modalities in the diagnosis and management of PCNSL, FDG-PET is the latest attractive and widely used technique which evaluates tumor metabolism noninvasively. PCNSL is a very highly cellular tumor and its increased glucose metabolism is reflected by a homogenously marked FDG uptake (6), even if normally high physiological uptake in cerebral cortex, basal ganglia and thalamus sometimes may mask the presence of an underlying PCNSL.

As its clinical application is flourishing, the role of FDG-PET in PCNSL is not fully defined and reviewed systematically. This paper aims to review the usefulness of FDG-PET in initial diagnosis, baseline staging, restaging, evaluation of treatment response and survival analysis of PCNSL. The study was conducted to summarize the utility of FDG-PET in the management of PCNSL and show its contribution to predicting survival of these patients.

Material and Method

This retrospective cohort study included 19 patients with PCNSL of DLBC variant (14 newly-diagnosed) treated with high dose methotrexate between 2005 and 2015 at our institution. Inclusion criteria was: histologically confirmed CD20+ DLBCL jailed in the brain or cerebrospinal fluid, treatment with methotrexate regimens with or without rituximab, a follow-up period of at least two years, having an initial staging or control FDG-PET. Patients with systemic involvement of lymphoma outside CNS at initial presentation and immunodeficiency syndromes or immuncompromised conditions (AIDS) were

excluded. Patients who received alternative therapy regimens other than methotrexate as first line therapy protocol were also neglected from the analysis.

Primary staging FDG-PET (14 cases) or control (treatment response evaluation) FDG-PET (5 cases) were suggested for the patients. Imaging was performed according to previously described current international consensus-based guidelines. The patients were treated by high dose methotrexate. The files of 19 patients having PCNSL were looked over retrospectively. We examined baseline staging, restaging or control PET and outcome of the patients.

The semiquantitative parameter of maximum standardized uptake value (SUVmax) was calculated on FDG-PET. Overall survival (OS) was accepted as the time from initial diagnosis to death of any cause or last follow-up. Disease-free survival (DFS) was defined as the period from diagnosis to detection of first relapse or last follow-up. Informed consent was deemed as a retrospective study using records, documents and data of patients referred to our clinic for the test.

FDG-PET Imaging Protocol and Quantitative Assessment

FDG-PET was performed between 2005-2010 with a PET scanner (Siemens ECAT) and by an integrated PET/CT scanner (Discovery 690-GE Healthcare) since 2010. Patients had to be hungry for at least 6 hours and their blood glucose level must be below 150 mg/dl before the injection of an activity of 370-555 MBq of 18F-FDG calculated according to patient's body weight. Images were acquired 1 hour later from mid-thigh to the vertex of the skull in supine position with the arms raised over head by the same method which was described in previous studies (7,8). SUVmax was calculated by standard methods from the activity of most intense voxel in three-dimensional tumor region of transaxial whole body images.

Statistical analysis

The whole data were analysed by IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Number and percentage values were used for the description of categorical data; mean, median, standart deviation (SD), minimum (min) and maximum (max) values were used for the description of continuous data. Normality was checked with Shapiro-Wilk test. Student's t test was used for continuous variables (SUVmax) in the comparison between groups. The variables having a value of $p<0.2$ were accepted as statistically significant. ROC curve was drawn to evaluate the diagnostic accuracy of SUVmax and cutoff levels showing the best sensitivity and specificity for recurrence were determined. Sensitivities and specificities were calculated according to chosen cutoff values. Kaplan-Meier test was used for survival analyzes. Our institutional review board commitee approved this study.

Results

Mean age of the patients was 55.4 ± 11.6 years (34-73). 42% of the cases were male, 58% female (male / female ratio: 0.72). Mean SUVmax value 18.5 ± 7 (9.8-30.8). Mean OS and DFS was 22.7 months (3-55), 16.8 months (3-55), respectively. Patient characteristics, demography and outcomes of follow-up data are described in Table 1. Mean SUVmax was 19.9 ± 6.7 in recurrent/metastatic group, 15.3 ± 7.2 in nonmetastatic (complete remission) group. There was a statistically significant difference between them according to

TABLE 1: Patient characteristics, demography and outcomes of follow-up data.

Sex	Age (Years)	SUVmax	Ex Status	Recurrence	DFS (Months)	OS (Months)
M	56	14.2	-	-	55	55
F	41	9.8	-	-	29	29
M	49	16.2	+	+	6	9
F	66	9.8	-	+	9	30
M	64	13.7	-	-	28	28
F	40	17.5	-	+	3	27
M	45	22.3	+	+	3	3
F	34	15.6	+	+	9	11
F	50	29.1	+	+	14	24
F	45	12.2	+	+	18	24
F	66	29.8	-	-	26	26
M	73	27.1	+	+	7	13
F	47	13.4	-	+	12	26
F	66	30.8	+	+	9	13
M	57	22.2	-	+	22	30
M	71	14	-	-	25	25
F	63	17.6	+	+	11	19
M	67	10.8	-	-	27	27
F	53	25.4	+	+	7	13

M: Male, F: Female, - : Absent, + : Present, DFS: Disease-free survival, OS: Overall survival

TABLE 2: Cut-off values, related sensitivities and specificities of SUVmax according to diagnostic accuracy for recurrence.

Cutoff values	Sensitivity (%)	Specificity (%)	Area Under Curve (%95 Confidence Interval)
14	77	67	0.712 (0.43-0.99)
15	76	83	p=0.148

SUVmax values (p=0.199).

Complete remission was achieved in 6/19 of the cases (31.5%) and 9 patients (47%) died. 13/19 (68.5%) developed recurrence and/or metastasis in the follow-up. Median time to progression was 10 months. OS at 1st year was 84%, 58% at 2nd year. DFS at first year was 47%, 31.5% at second year.

ROC curve was drawn to evaluate the diagnostic value SUVmax (Figure 1). Cut-off values for recurrence, sensitivity and specificity of SUVmax were demonstrated in Table 2. Kaplan-Meier method compared DFS and OS of recurrent/metastatic and nonmetastatic groups. Kaplan-Meier curves were plotted for OS (Figure 2) and DFS (Figure 3).

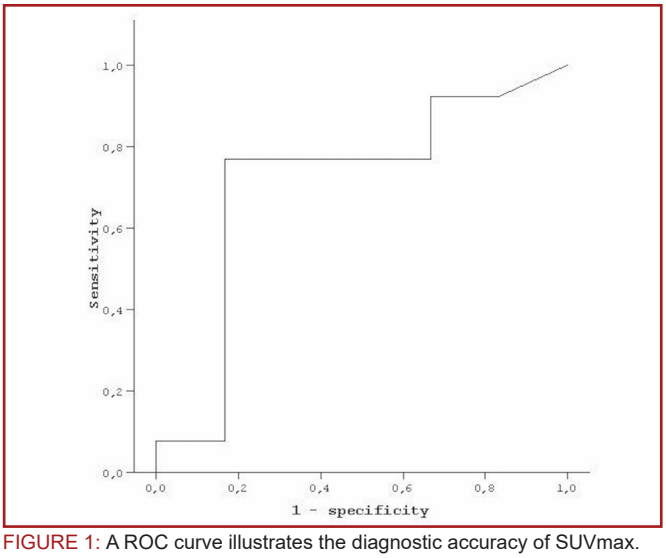

FIGURE 1: A ROC curve illustrates the diagnostic accuracy of SUVmax.

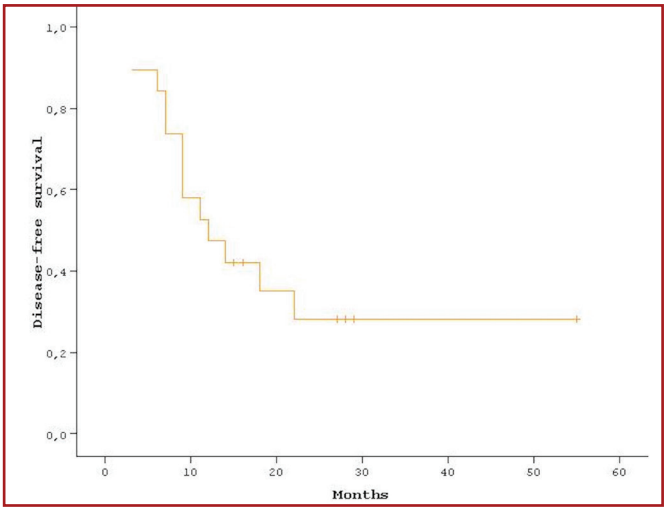

FIGURE 2: Kaplan-Meier curve represents the plot associated with overall survival.

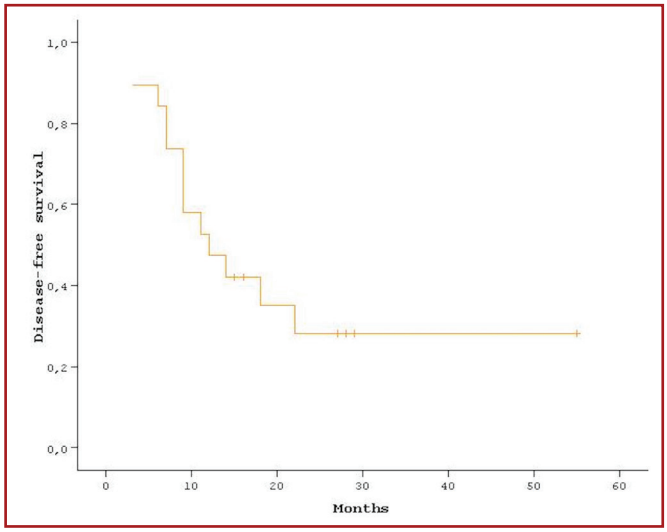

FIGURE 3: Kaplan-Meier curve showing disease-free survival in patients with primary central nervous system lymphomas.

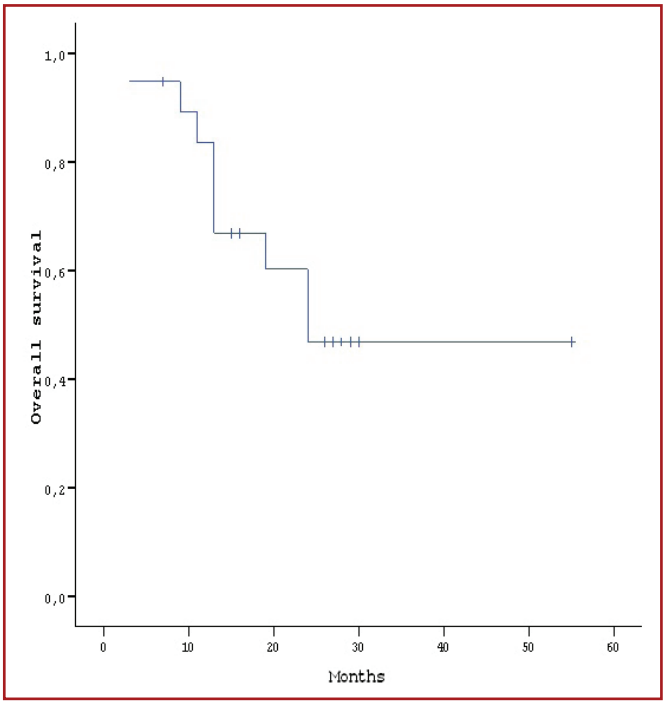

FIGURE 4:

Discussion

Mean age of our patient group was 55 years. This is congruent with literature, although it nears the lower limit of the range (2). It is hard to achieve a durable response in PCNSL. Up to 60% of the patients who obtain a complete remission will relapse in the first two years and at least 5% of them

metastasize outside CNS (9). 68% of our cases relapsed in the first two years.

Early diagnosis of PCNSL is essential to begin immediate treatment before the performance status of the patients has deteriorated. Clinical diagnosis is sometimes difficult; because initial symptoms such as focal signs, raised intracranial pressure, personality and behaviour changes especially in elderly patients are nonspecific (10). Radiological findings are not pathognomonic for PCNSL and cannot accurately differentiate PCNSL from other brain lesions (11). FDG-PET is very helpful in the diagnosis of typical PCNSL, usually showing prominent uptake in the tumor. FDG uptake pattern provides useful information to differentiate PCNSL from other malignant brain tumors, especially glioblastoma multiforme (12). PCNSL usually has a more homogeneous and markedly increased FDG uptake, higher SUVmax values than glioblastoma multiforme (11,12).

Whole body screening ability of FDG-PET depicts entire body for the detection of disease involvement. This establishes the correct diagnosis and stage of PCNSL. Combination of CT with PET also gives anatomic and functional information about the lesions. These superior advantages of this new hybrid imaging make it a unique and excellent method providing both accurate primary staging at initial diagnosis and restaging during the follow-up which can directly effect treatment strategy (13).

FDG-PET is also beneficial for assessing treatment response after initial chemotherapy and determining the therapy strategy at a very early stage (14,15). Pretreatment and posttreatment FDG uptake values can be considered as a predictor in patients with PCNSL. It was declared that about 10–35% of PCNSL are refractory to high dose MTX-based regimens and up to 60% of complete responders develop recurrence (16). High FDG uptake in tumors means high proliferative activity and is associated with poor patient outcome (17). PCNSL with high FDG uptake inclined to show poor treatment response compared to those with lower ones (18). Thus FDG uptake may have prognostic value to represent tumor aggressiveness and estimate treatment success in PCNSL. At the same time, FDG-PET shows the real nature of residual masses after chemotherapy. It distinguishes active foci from fibrotic tissue or inflammatory origin (19).

The semiquantitative FDG uptake parameter called maximum standardized uptake value (SUVmax) was reported to be between 14–22 in PCNSL (18). These values are nearly 2.5 times higher than the average SUV of normal gray matter (2). Current studies showed that pretreatment FDG uptake on baseline staging FDG-PET may have a prognostic value in several cancers and a recent paper confirmed this information in newly diagnosed PCNSL patients (18). OS in patients with low to moderate FDG uptake (SUVmax < 12) was significantly longer than that of patients with high FDG uptake (SUVmax ≥ 12) (18).

Recently, Kawai et al reported that a high SUVmax value was related with a decreased DFS and OS in univariate analyses (20). But the number of patients in their study was small (n=17). Kasenda et al investigated the potential predictive value of pretreatment FDG uptake regarding to tumor response, DFS and OS with SUVmax as a marker of clinical aggressiveness to visually evaluate primary CNS lymphoma metabolism (20). The sensitivity and specificity of SUVmax was calculated as 77%, 67%, respectively with a cutoff value of 14 in our study. We found SUVmax a valuable parameter indicating both recurrence and poor prognosis. All our results are in fully agreement with literature.

The inverse correlation between high FDG uptake measured by SUVmax and survival times in our study, as parallel to the notion that lymphoma aggressiveness is usually associated with high FDG uptake, suggests that pretreatment or posttreatment FDG-PET is a potential predictor in the management and outcome of PCNSL. The main limitation in our study are the small patient number and ignoring the effects of other treatments as previous studies in literature.

Conclusion

The utility of FDG-PET can be summarized as initial diagnosis, baseline staging and restaging, evaluation of treatment response and prognosis estimation in PCNSL. SUVmax between 14-15 seems like the best values for diagnostic accuracy in recurrence according to our results. SUVmax derived from FDG-PET is also a strong predictor for progression and survival of the disease.

Conflict of interest: None

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