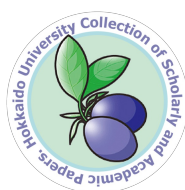




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The Diagnostic Role of 18F-FDG PET for Primary Central Nervous System Lymphoma

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Abstract

Objective

¹⁸F-FDG PET has become one of the most important methods for studying malignant lymphoma, but its diagnostic role for primary central nervous system lymphoma (PCNSL) has not been established. The aim of this study is to determine the appropriate cut-off values of FDG uptake and to investigate how corticosteroid administration influences PCNSL.

Methods

We retrospectively reviewed 82 patients with contrast-enhanced brain tumors who underwent an FDG PET scan at onset, including 19 PCNSLs. FDG uptake of the lesion was assessed by the maximum standardized uptake value (SUVmax) and the ratio of tumor to normal contralateral cortex activity (T/N ratio). Receiver operating characteristic (ROC) curves were generated from the SUVmax and T/N ratios. To investigate the influence of corticosteroid application before a FDG PET scan, we evaluated the association between the FDG uptake of the lesion and the cumulative dose of corticosteroid administration on 13 PCNSL patients who had received steroid treatment before an FDG PET examination.

Results

The mean FDG SUVmax and T/N ratio of PCNSLs were 22.6 and 2.79, respectively, and these values were significantly higher than that of the other malignant brain tumors. ROC analysis indicated that the evaluation of FDG uptake using the T/N ratio was more reliable than the SUVmax with respect to the differential diagnosis. When PCNSL patients went without steroid application before FDG PET, the accuracy of the T/N ratio with a cut-off point of 2.0 was 91.1%, the sensitivity was 94.7%, and the specificity was 87.3%. Although there are no significant differences in the FDG T/N ratio for PCNSL patients with or without steroid treatment, a negative correlation was found between the T/N ratio and cumulative dose of corticosteroid before PET study ($r = 0.71$, $p = 0.032$).

Conclusions

We concluded that the T/N ratio was superior to SUVmax for FDG uptake assessment as for distinguishing PCNSLs from other malignant brain tumors; the appropriate T/N ratio cut-off point was 2.0. In addition, FDG uptake could be influenced by cumulative

doses of corticosteroid before a PET scan, and thus this fact should be taken into consideration when evaluating FDG PET for PCNSL diagnosis.

Keywords

Brain tumor, Corticosteroid, 18F-FDG PET, Primary central nervous system lymphoma, ROC curve

Introduction

Incidences of primary central nervous system lymphoma (PCNSL) have increased over the last two decades in Japan [1-3]. Initial evaluation for the diagnosis of PCNSL routinely involves brain magnetic resonance imaging (MRI). Histopathological confirmation of PCNSL by stereotactic biopsy from intracranial lesion or vitrectomy in patients with intraocular involvement is standard procedure. PCNSL lesions on an MRI nearly always display contrast enhancement and no necrosis. Cerebral edema is usually larger than the area of contrast enhancement and is thus responsible for the apparent mass effect. The diffusion weighted scans are consistent with the increased diffusivity of water protons [4]. Even if these MRI features of PCNSL are recognized, differentiating it from other diagnoses—including malignant gliomas, metastases, and inflammatory disorders—is not always easy [5].

Therefore, in diagnosing PCNSL, another supportive radiological finding is desirable. Metabolic imaging with ¹⁸F-FDG (FDG) PET is one of the better candidates for diagnosing PCNSL, because the tumor has an extremely high FDG uptake compared to other brain tumors, such as high-grade gliomas [6]. In fact, due to its difficult diagnosis PCNSL occasionally presents atypical MRI findings [7]. FDG PET can improve the ability to distinguish between PCNSL and GBM with similar MRI findings [8] (Figure 1). The presence of positive FDG uptake in the tumors reliably represents active disease in PCNSLs, and at present the maximum standardized uptake value (SUVmax) is reported as the most accurate parameter for distinguishing lymphomas [8-11]. However, since the SUVs of FDG PET significantly vary among individuals, the SUVmax appear to be of limited value as clinical tool for the characterization of brain tumors [12, 13].

In this report, to evaluate the role of FDG PET for PCNSLs as a clinical diagnostic tool, we retrospectively reviewed the FDG PET appearances of primary intra-axial brain tumors, including PCNSLs, high-grade gliomas, and metastatic brain tumors. One aim of this study is to present the evaluated method of FDG uptake and provide the appropriate cut-off value to distinguish PCNSLs from other brain tumors. In addition, we evaluated the influence on FDG uptake of corticosteroid therapy in PCNSLs, as suspected PCNSL patients may have already been prescribed corticosteroid. To the best of our knowledge, this is the first report to investigate the influence of corticosteroid before FDG PET study in patients with PCNSLs. Exhibiting a clear association between FDG uptake and corticosteroid therapy may contribute to a better interpretation of FDG PET in the diagnosis of PCNSLs.

Patients and Methods

Patients

We retrospectively reviewed patients with brain tumors who underwent an FDG PET scan at the time of presentation at Hokkaido University Hospital from 2007 to 2013

From these, we selected patients using several criteria: (a) intra-axial tumors, (b) tumors with gadolinium enhancement on conventional MRI, and (c) tumors without any previous treatment. Excluded from this study were patients with high blood sugar, which was defined as more than 150 mg/dl at the time of FDG PET examination, and the patients suffering from uncontrolled diabetes. Eighty-two patients matched these criteria, with 19 PCNSLs, 6 metastatic brain tumors, and 57 high-grade gliomas (HGGs)—including 33 Glioblastomas, 10 anaplastic astrocytomas, 8 anaplastic oligodendrogliomas, and 6 anaplastic oligoastrocytomas.

In addition, to evaluate the influence of corticosteroid treatment on the FDG PET, we reviewed 13 PCNSLs that had been given corticosteroid before the FDG PET examination. Patients who had already received chemotherapy or radiotherapy were not included in this study. We assessed the cumulative doses of corticosteroid administration before the FDG PET study, as well as the interval between the day of last steroid application and the FDG PET examination. Corticosteroid dosage was converted to prednisolone. Patient characteristics are shown in Table1. Appropriate informed consents were obtained from all eligible patients. The Ethics Committee of Hokkaido University Hospital approved the study.

PET protocol

All the patients underwent the same protocol of PET acquisition. Following a blood glucose test excluding hyperglycemia, a 4.5 MBq/kg of FDG was intravenously injected, and the whole brain was scanned one hour later. The images were acquired using either a stand-alone PET scanner (ECAT HR+ scanner; Asahi-Siemens Medical Technologies Ltd., Tokyo, Japan) operated in a three-dimensional mode, or an integrated PET-CT scanner (Biograph 64 PET-CT scanner; Asahi-Siemens Medical Technologies Ltd., Tokyo, Japan).

The image acquisition for ECAT HR+ PET scanner consisted of ten-minute emission scanning and following three-minute transmission scanning with ⁶⁸Ge/⁶⁸Ga retractable line sources. The Biograph 6 PET-CT scanned for ten minutes of emission and used a CT dataset for attenuation corrections. Attenuation-corrected radioactivity

images for both scanners were reconstructed, using filtered back projection with a Hann filter of 4 mm full width at half maximum. The reconstruction matrix was 256×256 , and the FOV was 33 cm in diameter.

PET image analysis

A circular region of interest 10 mm in diameter was placed in the lesion at the area corresponding to the MRI abnormality. Slices displaying maximum tumor activity were selected. Regional uptake of FDG was expressed as a standardized uptake value (SUV), calculated as (tissue activity [Bq/ml]) $\times$ (body weight [g]) / (injected radioisotope activity [Bq]). Maximum SUV (SUVmax) of tumors was sampled from the single pixel showing highest FDG accumulation. The T/N ratio was defined as the ratio of the SUVmax of the lesion to the SUV of contralateral normal gray matter at the same axial plane. If the patients had multiple lesions, the lesion showing the highest SUVmax was selected in this analysis. If the lesion was located in a central location, such as the brain stem or the hypothalamus, the average SUV of both sides of gray matter was adopted as normal SUV.

Statistical analysis

All statistical analyses were performed by R statistical environment v3.0.2. SUVmax and the T/N ratios of each group were expressed by mean value with standard deviation (SD). For comparison of mean values among each group, the F-test was used in univariate analysis. The mean SUVmax and T/N ratio between two groups were compared by Tukey test as the post-hoc determination. To evaluate for the diagnostic performance of ^{18}F -FDG PET, as well as to determine the optimal cut-off values for PCNSL diagnosis, receiver operating characteristics (ROC) curves were generated from SUVmax and T/N ratio using the Epi package with the "ROC" function. Accuracy was provided by the area under ROC curves. The optimal cut-off values were determined by the closest point to the upper left-hand corner in the ROC curves. The correlation between the FDG T/N ratio and the applied dose of corticosteroid before the PET examination was analyzed, using Spearman's rank correlation test. P-values less than 0.05 were considered statistically significant.

Results

Difference of FDG uptake between PCNSLs and other contrast-enhanced brain tumors

In terms of the evaluation of FDG uptake in brain tumors, two parameters were used in

previous reports: the maximum value of SUV in the lesion (SUVmax), and the tumor to normal brain uptake ratio (T/N ratio). Since the FDG uptake of the cortex is completely different from that of white matter, we selected the SUV value of contralateral cortex as normal region when we calculated the T/N ratio of the lesions. Figure 2 shows the SUVmax and the T/N ratio of PCNSLs, as well as HGGs and metastatic brain tumors in our series. The mean $\pm$ standard deviation of the SUVmax of HGGs, metastatic brain tumors and PCNSLs are 9.12 ± 5.75 , 9.25 ± 3.63 , and 22.6 ± 12.6 , respectively. The mean $\pm$ standard deviation of the T/N ratio of HGGs, metastatic brain tumors, and PCNSLs are 1.40 ± 0.90 , 1.44 ± 0.47 , and 2.79 ± 0.91 , respectively. As clearly shown above, these FDG uptake values of PCNSLs was significantly higher than that of HGGs and metastatic brain tumors in both the SUVmax ($p < 0.001$ and $p = 0.001$, respectively) and the T/N ratios ($p < 0.001$ and $p = 0.004$, respectively).

Next, to compare the reliability of FDG uptake parameters as diagnostic tools for PCNSLs, we generated the ROC curves from each parameter in all 82 cases (Figure 3). The ROC curves indicated that the accuracy of the SUVmax with a cut-off point of 12.3 was 89.9%, the sensitivity was 84.2% and the specificity was 84.1%, whereas the accuracy of the T/N ratio with a cut-off point of 2.0 was 91.1%, the sensitivity was 94.7% and the specificity was 87.3%.

This ROC analysis demonstrated that the evaluation of FDG uptake values using the T/N ratio was more reliable than the SUVmax with respect to the differential diagnosis for PCNSLs and other contrast-enhanced brain tumors. Ideal cut-off values of the T/N ratio should be 2.0 when the patients have not received steroid treatment.

Influence of corticosteroid therapy in 18F-FDG PET

Since it is well-known that PCNSLs often respond to corticosteroid administration, we tested whether or not corticosteroid therapy influenced the FDG uptake. Thirteen corticosteroid-treated PCNSLs underwent FDG PET before high-dose Methotrexate (MTX) or radiation therapy. There were no statistical significant differences in blood sugar level of these patients at the FDG PET examination compared to the patients without corticosteroid administration (Table 1, $p = 0.59$). The mean T/N ratio of these cases was 2.51 ± 1.10 . Figure 4 shows the mean and distribution of the T/N ratio for the PCNSLs with and without steroid administration. The difference of the mean T/N ratio was statically insignificant. However, when 2.0 was applied as the diagnostic cut-off value for the T/N ratio, only one (5.3%) out of 19 tumors had a T/N ratio less than 2.0 in PCNSLs without steroid administration, whereas 5 (38.5%) out of 13 PCNSLs with steroid administration had a T/N ratio less than 2.0. Next, we assessed the influence of

FDG uptake by steroid dose as well as by the washout period for the steroids before the PET examination. An FDG PET was performed on 9 out of 13 patients, without a washout period for the steroids. Four out of 13 patients had washout period for the steroids, and after the last steroid administration these intervals were from 5 to 20 days, including two patients who received steroid-pulse treatment. Figure 5 shows the trend of negative correlation between the steroid dose and the T/N ratio, especially concerning the PCNSLs with continued steroid therapy at the time of PET examination ($r = -0.71$, $p = 0.032$). Interestingly, the T/N ratios for the two patients that received steroid-pulse therapy before PET study were relatively high (2.6 and 1.92, Figure 5) compared to the expected values.

Discussion

One of the main purposes of this study is to discern the cut-off values between PCNSLs and other intra-axial tumors with contrast enhancement for differential diagnoses. Based on our ROC analysis, which was generated in 82 intra-axial tumors with contrast enhancements on MRIs, we propose a T/N ratio of 2.0 as the appropriate cut-off value for differential diagnosis of PCNSLs from other malignant brain tumors, when the patients have not received steroid treatment. In this study, we observed a significantly higher FDG uptake in lymphomas than in the others. The molecular mechanisms remain to be clarified, because histological studies addressing the expression of glucose-related proteins in PCNSL are lacking. However, several reports regarding lymphomas in other organs have addressed this question, and they found correlations of FDG uptake with glucose metabolism molecules such as glucose transporter (GLUT) -1 [14-16], GLUT-3 [14], and hexokinase-II [17]. We could speculate that PCNSLs have shown FDG avidity possibly due to over-expression of one or more above molecules. In addition, the majority of PCNSLs are diffuse large B-cell lymphomas. It is well-known that FDG uptake on diffuse large B-cell lymphoma is higher than that on other types of lymphoma [18], and this characteristic feature could be helpful in differentiating between B-cell lymphoma and other histological tumors. Likewise, in the brain tumors, previous reports clearly demonstrate that PCNSL has an extremely high FDG uptake compared to other brain tumors, such as anaplastic astrocytoma and glioblastoma [13, 19]. This study would also suggest that FDG PET could be a valuable pretreatment diagnostic examination for intra-axial brain tumor.

Recently, several studies presented the cut-off values of PCNSL diagnosis on FDG PET, using SUVmax [8-11]. Makino et al. reported that the accuracy of SUVmax

by itself for distinguishing PCNSL from GBM (cut-off point 12) was 86%, sensitivity was 100%, and specificity was 71.4% [8]. However, SUV measurement of the brain should be influenced by various factors, such as the plasma glucose level [12, 13].

On the other hand, the activity ratio, which is calculated by the ratio of the tumor SUV to the contralateral cortex SUV, would be a more useful parameter with respect to the characterization of brain tumors. This ratio should not be influenced by individual factors such as plasma glucose level, age, dosage level, or body weight [12]. From our ROC analysis, we demonstrate that the accuracy of the T/N ratio is superior to that of the SUVmax for PCNSL diagnosis.

The mean T/N ratio of PCNSLs of this series was 2.79, which is slightly higher than the ratio reported previously. Karantanis et al. reported that the mean T/N ratio was 2.45 in 13 PCNSLs at primary diagnosis [20]. Palmedo et al. reported that the mean T/N ratio was 2.36 in 6 PCNSLs before initiation of chemotherapy [21]. Both reports did not mention steroid treatment; thus, there is a concern about the possible influence of corticosteroid application before the FDG PET study. Given such a background, another intriguing question in terms of the role of FDG

PET in PCNSLs is whether or not FDG PET is still useful for diagnosis after corticosteroid administration. Since at presentation patients sometimes have severe neurological deficits and an elevation of intracranial pressure, steroids are frequently prescribed to PCNSL patients before the biopsy. It is recognized that the effects of corticosteroid can interfere with histopathological diagnosis on PCNSLs by lympholytic effect [22]. Unexpectedly, in our series the mean T/N ratio of these tumors was 2.51 with no significant difference from PCNSLs without steroid administration in our series ($p = 0.46$). We considered that this unexpected result might be influenced by the cumulative dose of corticosteroid and the washout period. In actuality, except for two cases in which the patients received steroid-pulse treatment, the mean cumulative dose of corticosteroid was 375 mg (range from 50 mg to 810 mg) in 11 patients, indicating that the cumulative steroid doses were relatively low in our group. Moreover, four patients had a washout period for corticosteroid before FDG PET.

Nevertheless, we demonstrate that the T/N ratio showed negative correlation for the dose of corticosteroid in the PCNSLs with continued steroid therapy at the time of the PET examination (Figure 5). Since it is known that FDG uptake is influenced by blood sugar levels and that corticosteroid treatment could induce high blood glucose levels, we investigated the correlation between FDG uptake and blood glucose level. We were able to clarify that blood glucose level were not influenced in the FDG T/N ratio in PCNSLs (data not shown). Therefore, we confirmed that whether or not the

FDG T/N ratio is predominant depends on the cumulative dose of corticosteroid administration before the FDG PET examination. This also suggests that the diagnostic accuracy of FDG PET is also highly influenced by steroid treatment, which is similar to histopathological diagnosis.

On the other hand, it is potentially significant that T/N ratios were relatively high in the PCNSLs with the steroid washout period, which indicates that the diagnostic accuracy of FDG PET might improve if the suspected PCNSL patients with steroid therapy could have a washout period for corticosteroid before their examination.

In conclusion, our analyses may be summarized as follows: first, in the assessment of FDG uptake in PCNSLs, the tumor-to-normal cortex ratio (T/N ratio) is superior to the maximum SUV values in the lesion; second, appropriate and convenient cut-off T/N values between untreated PCNSLs and other malignant brain tumors are 2.0; third, FDG uptake of PCNSLs might be reduced by steroid administration in a cumulative dose-dependent manner; fourth, a washout period of corticosteroid before FDG PET study may improve the reliability and potency of FDG PET for PCNSL diagnosis.

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Figure Legends

Fig. 1

A case illustrating the usefulness FDG PET for PCNSL diagnosis (69-year-old female). Although T1-weighted with contrast enhanced MRI showed atypical faint enhancement (a), the lesion was detected by remarkable FDG uptake compared to contralateral normal cortex (SUVmax was 19.1 and Tumor-to-Normal ratio was 2.1) (b).

Fig. 2

Stripchart of FDG uptake according to histopathology shown by maximum SUV value of FDG uptake of tumor (SUVmax) (a) and by FDG uptake ratio of tumor compared to that of normal contralateral gray matter (T/N ratio) (b). The mean $\pm$ standard deviations are represented by horizontal bars and error-bars. Both SUVmax and T/N ratio of PCNSLs are significantly higher than that of other tumors.

Fig. 3

ROC curves generated from the SUVmax (gray solid-line) and T/N ratio (black dot-line) measured in all 82 eligible cases of this series. With SUVmax cut-off point of 12.3, accuracy is 89.9%, sensitivity is 84.2% and specificity is 84.1%. With T/N ratio cut-off point of 2.0, accuracy is 91.1%, sensitivity is 94.7%, and specificity is 87.3%. ROC analysis indicates that the diagnostic accuracy of T/N ratio is superior to that of SUVmax.

Fig. 4

The differences and distribution of FDG T/N ratio between PCNSLs without any previous treatment (left) and PCNSLs that had received steroid application (right). Mean T/N ratio was 2.79 ± 0.91 in PCNSLs without treatment, and 2.51 ± 1.10 with steroid application. There are no significant differences ($p = 0.46$). Blue dot-bar indicates the cut-off value provided by our ROC analysis.

Fig. 5

Scatterplot shows the association between T/N ratio and applied steroid dose before PET examination in PCNSLs that received steroid treatment before PET examination. Circle plots represent the tumors with continued steroid therapy at the time of PET examination, whereas triangle plots represent the tumors with washout period for steroid. The number next to triangle plots represents the interval day after the last

steroid application. X-axis is logarithm scale. In the PCNSLs with continued steroid therapy (circle plots), FDG T/N ratio shows significant negative correlation with the dose of steroid administration (bar, $r = -0.71$, $p = 0.032$). Blue dot-bar indicates the cut-off value provided by our ROC analysis.

Table 1 Patient Characteristics

		HGG (n=57)	Metastatic BT (n=6)	PCNSL (n=19)	PCNSL w/ steroid (n=13)
Age (mean $\pm$ sd)		58 $\pm$ 16	57 $\pm$ 11	66 $\pm$ 12	67 $\pm$ 9
Sex					
	Male	34	5	9	6
	Female	23	1	10	7
Tumor location					
	Supratentorial	51	5	13	5
	Infratentorial	3	1	1	3
	Multistyle	3	0	5	5
Diabetes Mellitus					
	No	54	5	18	13
	Yes	3	1	1	0
Blood Sugar (mean $\pm$ sd)		104 $\pm$ 19	107 $\pm$ 13	107 $\pm$ 22	103 $\pm$ 16

Abbreviations: BT; brain tumor, HGG; high-grade glioma, PCNSL; primary central nervous system lymphoma, sd; standard deviation

Acknowledgements

The authors declare that they have no financial interests in this article.

Figure 1

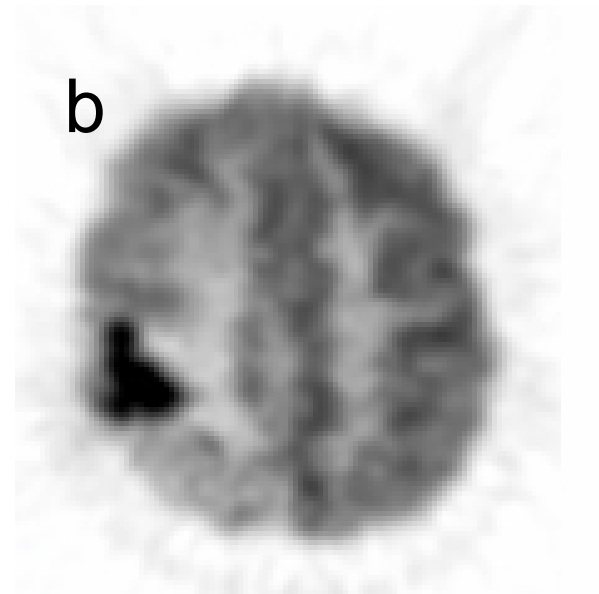
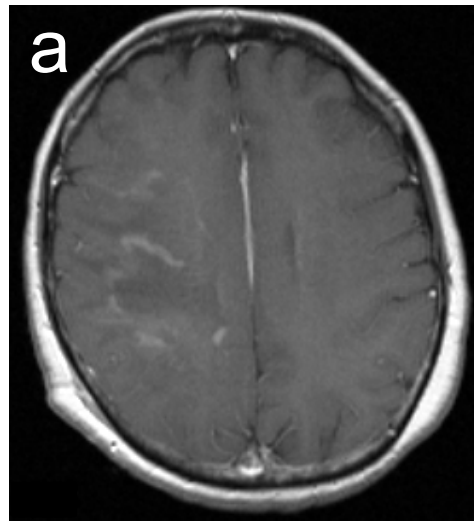


Figure 2

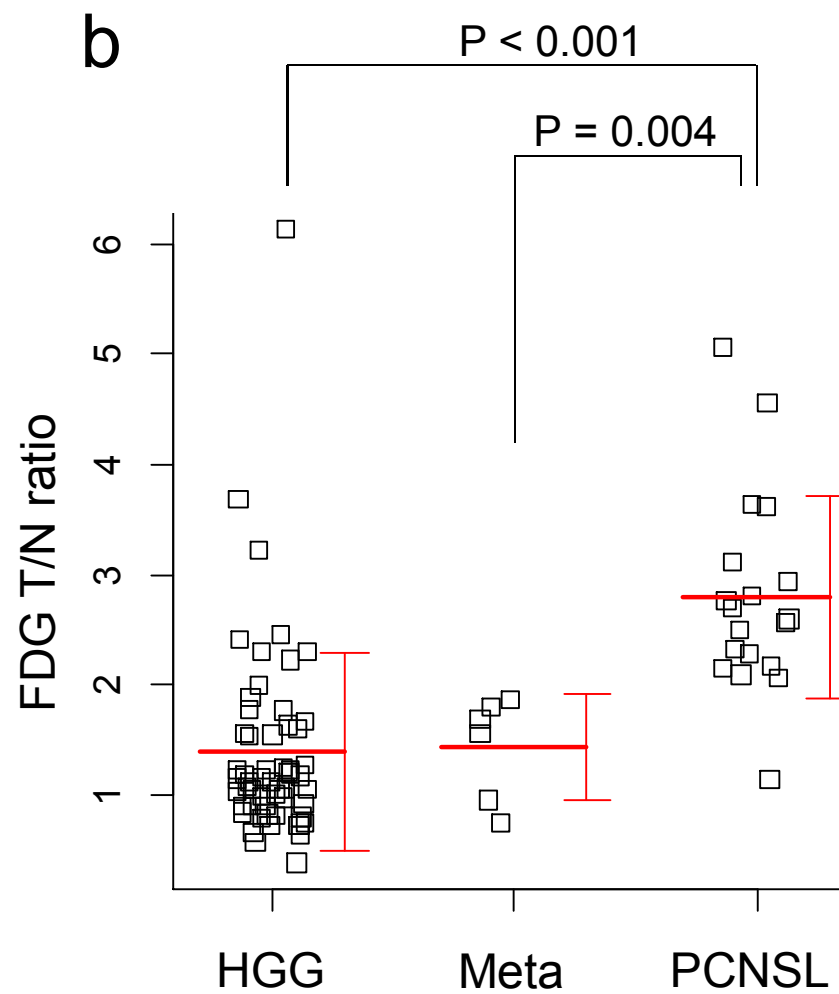
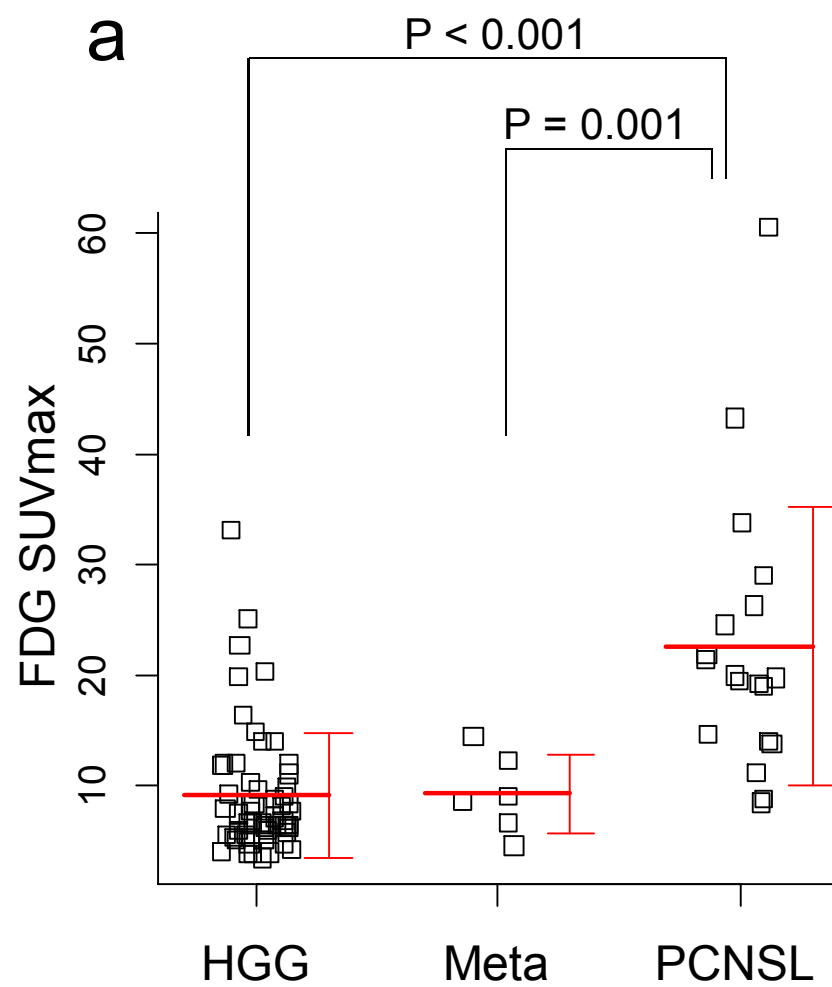


Figure 3

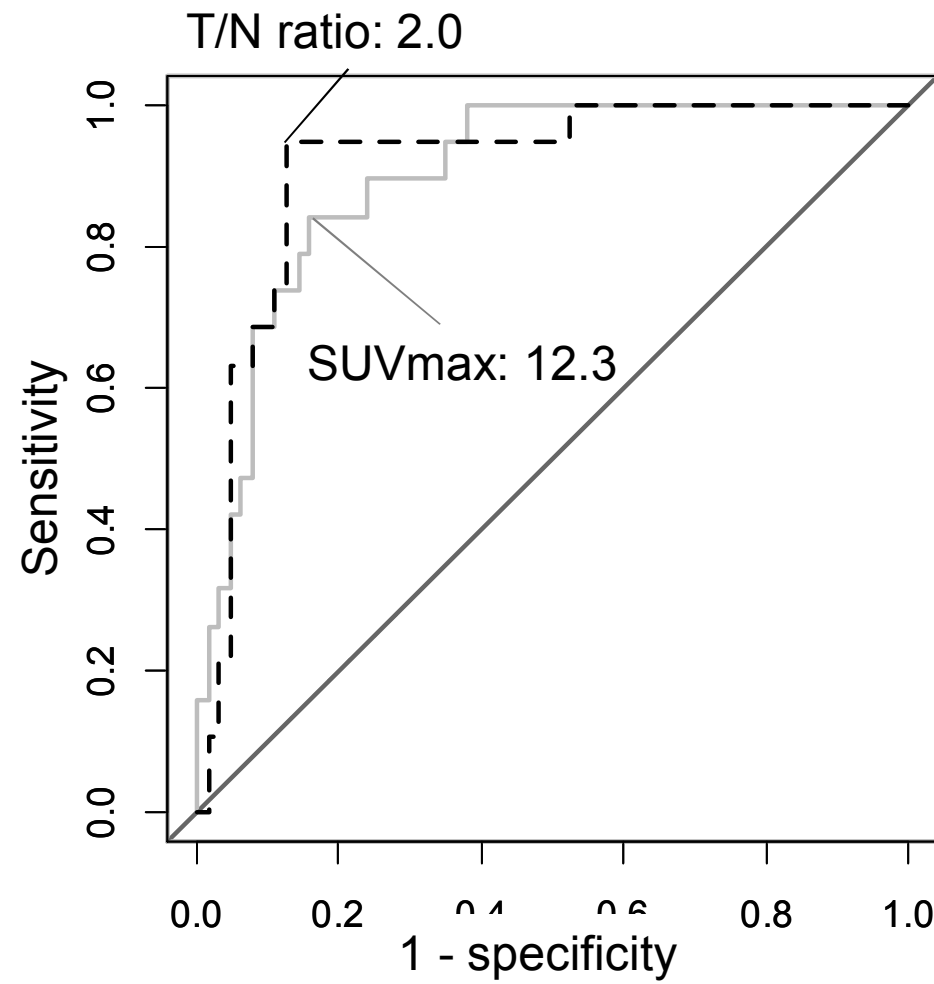


Figure 4

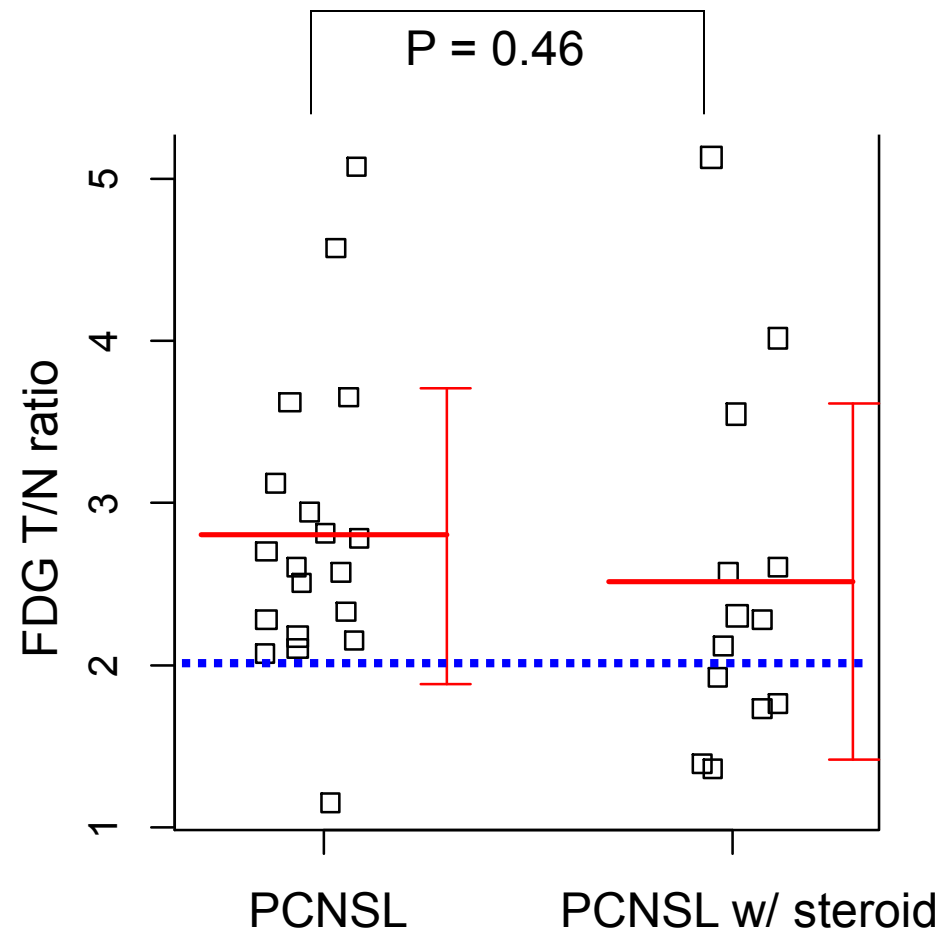


Figure 5

