Fluoromethylcholine PET/CT for CNS lymphoma assessment: a new tool [version 1; peer review: awaiting peer review]

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Abstract

Background
Central nervous system (CNS) lymphomas are a rare subset of lymphoma, which are associated with a poor outcome. The gold standard for CNS imaging is with gadolinium-enhanced magnetic resonance imaging (MRI); however, there are a number of limitations, including some patients with small persistent abnormalities from scarring due to focal haemorrhage or from a previous biopsy, which can be difficult to discern from residual tumour. [(18)F]Fluoromethylcholine positron emission tomography–computed tomography (FCH-PET/CT) uses an analogue of choline, which due to the upregulation of choline kinase in tumour cells, allows increased uptake of FCH. As there is minimal background grey matter uptake of FCH, FCH-PET/CT can be used in CNS imaging and provide a useful tool for response assessment.

Methods
This is a cohort study, where we identified 40 patients with a diagnosis of primary or secondary CNS lymphoma between 1st November 2011 and 10th October 2019.

Results
26 of the 40 patients (65%) had concordant results. Of the discordant results, 11 out of 14 had partial response (PR) on MRI but showed a metabolic complete response (mCR) on FCH-PET. The overall response rates (ORR) were similar between the two modalities (90% for MRI versus 95% with FCT-PET/CT).

Conclusion
We conclude that FCH-PET/CT is a reasonable alternative mode of imaging to gadolinium-enhanced MRI brain imaging, providing a new tool for assessment of CNS lymphoma.
Keywords
CNS lymphoma, imaging, response assessment.

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare type of B cell lymphoma, accounting for 1–2% of all lymphomas and approximately 4% of newly diagnosed CNS tumours. Secondary CNS involvement occurs in 2.3–10% of patients with systemic diffuse large B-cell lymphoma (DLBCL) but can also occur in other lymphoma subtypes.

Despite recent advances in treatment, with the addition of thiotepa to the methotrexate-cytarabine backbone, prognosis for PCNSL remains poor with 2-year overall survival rates of between 42 and 69%, and only a fifth of patients being alive at 5 years. For secondary CNSL, the prognosis is even more dire, with median OS of 10 months. It is challenging to decipher which patient will do poorly, as only age and performance status having an impact on prognosis. Unlike other lymphoma types, most noticeably Hodgkin’s lymphoma, metabolic imaging has no role in response assessment and the associated prognostic impact and is confined to diagnostic staging to exclude concurrent systemic disease.

The gold standard for CNS imaging is with gadolinium-enhanced magnetic resonance imaging (MRI). However, MRI has its limitations. When used in end-of-treatment (EOT) imaging, some patients will have small persistent abnormalities from scarring due to focal haemorrhage or from a previous biopsy, which be difficult to discern from residual tumour and is currently classified as unconfirmed complete response (CRu). There have also been recent safety concerns over exposure to gadolinium-based contrast agents (GBCAs) with case reports of the development of nephrogenic systemic fibrosis, as well as gadolinium deposits in other organs. This led to the European Medicines Agency (EMA) restricting or suspending the use of linear gadolinium products in 2017.

Choline positron emission tomography–computed tomography (PET/CT) uses analogues of choline as a radiotracer. Choline can be labelled with either [18F] fluoromethyl (18FCH) or [11C] carbon (11CH3). FCH was first developed as a radiotracer for PET imaging in 2000. Choline is a precursor of phospholipids, which upon entry to the cell, is phosphorylated by the enzyme choline kinase. The expression of choline kinase is upregulated in tumour cells and allows increased uptake of the choline tracer. There is evidence that MYC, which regulates lipid metabolism and can be overexpressed or translocated in high-grade lymphomas, plays a part in the increased uptake. MYC over-expression a poor prognosis in PCNSL with patients having a 5-fold higher 5-year risk of progression and/or death than those without. When Bcl-2 is also over-expressed (so called double expressor) the risk is 13-fold higher.

As there is minimal background grey matter uptake of the tracer, FCH-PET/CT can be used to detect tumours with a high lesion-to-CNS background ratio and has been used in diagnosis and follow up imaging in brain tumours, particularly high-grade gliomas. There are case reports of both systemic and CNS lymphoma showing FCH-PET/CT avidity, including incidental lymphoma picked up during imaging for prostate cancer and histology proven CNS lymphoma in brain tumour series. This contrasts with the lack of utility of the 2-deoxy-2-[18F]fluoro-D-glucose (FDG) PET/CT for CNS lymphoma analysis, due to high FDG physiological activity levels within the grey-white matter. Although high-grade CNS lymphomas do have a standard uptake value maximum (SUV_max) greater than background grey-white matter at diagnosis (average SUV_max 13.5±5.4 compared to background SUV_max of 5.3±1.2), for interim and EOT scanning the higher physiological background levels limit accurate detection of residual active disease.

Our centre has been using FCH-PET/CT alongside MRI for CNS lymphoma assessment since 2011 following approval by the Administration of Radioactive Substances Advisory Committee (ARSAC). Our primary objective to to assess concordance between FCH-PET/CT and MRI.

Methods

To assess concordance between FCH-PET/CT and gold standard MRI, our centre conducted a retrospective cohort analysis of patients who had EOT response assessment conducted using both modalities between 1st November 2011 and 10th October 2019 at the Royal Marsden Hospital, London. Approval for this study (approval number 782), including
ethical approval was obtained from the Committee for Clinical Review (CCR). Patients with a histopathological or
specialist neuroradiological (where biopsy was not feasible) diagnosis of primary or secondary CNS lymphoma who
had an EOT MRI and FCH-PET/CT were identified from a radiology database. Patients who did not complete treatment,
or had the imaging performed after consolidative therapy were excluded. Patient characteristics, clinical information,
and survival data were collected from the electronic patient recorded (EPR). MRI and FCH-PET/CT reports were
collected from EPR and PACS. EOT response was classified as either complete response (CR) for MRI/metabolic
complete response (mCR) for FCH-PET/CT, partial response (PR), stable disease (SD) or disease progression (PD). MRI
response was reported as per the International Primary CNS Lymphoma Collaborative Group (IPCG).4 For FCH-PET/
CT, PR is defined as reduction in activity (SUV_{max}), PD is an increase in SUV_{max}, SD as no change in SUV_{max}, and mCR
is defined as no activity. Statistical analysis was performed using IBM SPSS version 27 (RRID:SCR_019096), JASP
(RRID:SCR_015823) is an open-access alternative. Survival analysis was evaluated using log-rank test.

Results
A total of 40 patients met the inclusion criteria. Patient characteristics are shown in Table 1. PCNSL was the most
common type of CNS lymphoma, and MATRix regimen the most common type of chemotherapy used. 16 patients (40\%)
were consolidated after EOT imaging, with autologous stem cell transplant (ASCT) being the preferred method.

14 patients (35\%) had discordant results on EOT imaging. The majority of discordant cases (11 out of 14) were patients
who had PR on MRI but showed CMR on FCH-PET/CT. In the remaining discordant three cases, two had PD on MRI
with PR on FCH-PET/CT and one had CR on MRI and PR on FCH-PET/CT. Figure 1 shows examples of two concordant
cases and one discordant case.

For the whole cohort, the overall response rates (ORR) were similar between the two modalities. The ORR for MRI was
90\%, with 16 patients (40\%) achieving CR and 20 (50\%) achieving PR. FCH-PET/CT had a slightly higher ORR of 95\%,
with 26 (65\%) patients achieving mCR and 12 (30\%) achieving PR.

| Table 1. Patient characteristics. |
|----------------------------------|
| Age at diagnosis: Median 59, Range 19-77 |
| Gender: Male 21 (52.5\%), Female 19 (47.5\%) |
| Diagnosis: PCNSL 24 (60.0\%), SCNSL 1 (2.5\%), Relapsed PCNSL 6 (15.0\%), CNS relapse of systemic lymphoma 6 (15.0\%), Other 3 (7.5\%) |
| Chemotherapy: MATRix 15 (37.5\%), Methotrexate and cytarabine 7 (17.5\%), Rituximab, methotrexate and cytarabine 11 (27.5\%), TIER 3 (7.5\%), Rituximab, cytarabine and thiotepa 2 (5.0\%), Other 2 (5.0\%) |
| Consolidation: Yes 16 (40.0\%), No 24 (60.0\%) |
| Radiotherapy: Yes 5 (12.5\%), No 35 (87.5\%) |
| Autologous stem cell transplant: Yes 11 (27.5\%), No 29 (72.5\%) |

Abbreviations: PCNSL = primary central nervous system lymphoma, SCNSL = secondary central nervous system lymphoma, MATRix = methotrexate, cytarabine, thiotepa and rituximab, TIER = thiotepa, ifosfamide, etoposide and rituximab, PD = progressive disease.
A total of 17 patients subsequently progressed (47%). The progression-free survival (PFS) was 78% at 100 days and 51% at 2 years. Overall survival (OS) was 61%.

Discussion

To our knowledge, this is the first published study for FCH-PET/CT imaging in CNS lymphoma.21 Our results showed a concordance rate of 65% between FCH-PET and MRI. 11 out of 14 discordant cases were in patients who achieved a PR by MRI, but were in mCR on FCH-PET/CT. This group had a clinical course similar to the patients who achieved a CR/mCR on both. One theory is that the residual enhancement seen on MRI was scarring or post-treatment changes and may have been better classified as CRu.

There are no studies with direct comparison. A similar study by Ahn et al.22 looked at the prognostic value of metabolic imaging, using 11C-methionine (11C-MET) rather than FCH as a tracer. Imaging was done after four cycles.
of methotrexate-containing chemotherapy and again after completion of chemotherapy. The concordance at interim imaging between $^{11}$C-MET PET/CT and MRI was 89%, with four cases achieving CMR on $^{11}$C-MET PET/CT who had residual lesions on MRI. There are limited studies looking at the effect of FDG-PET/CT on prognosis. Bursen et al.\textsuperscript{23} showed PET negativity (defined as SUV uptake below physiologic background uptake) after two cycles of methotrexate-containing chemotherapy is associated with improved PFS but not OS. This conflicts with results from Jo et al.\textsuperscript{24} who showed improved PFS only with EOT and not interim scanning. Again, there was no difference in OS.

Our study does have limitations. Our numbers are small and consist of a combination of primary and secondary CNSL as well as relapsed cases, which have different expected outcomes. There was also considerable variation in treatment and consolidation regimens, with the addition of thiopeta from 2016 onwards for young, fit patients. Therefore, the prognostic value of FCH-PET/CT could not be studied using this cohort. Further work is being done by our group to assess the prognostic value of FCH-PET/CT in patients with PCNSL who undergo ASCT.\textsuperscript{25}

We conclude that FCH-PET/CT is an important new tool for assessment of CNS lymphoma. At the current time, its use may be limited to patients who have a contraindication to MRI.\textsuperscript{26} Further studies are warranted evaluating the potential role for FCH-PET/CT in CNS lymphoma, including assessment of whether FCH-PET/CT is superior to MRI in predicting persistent disease or identifying patients that need consolidation therapy.

**Data availability**

**Underlying data**

OSF: Underlying data for ‘$^{[18]}$F Fluoromethylcholine PET/CT for CNS lymphoma assessment: a new tool’ https://doi.org/10.17605/OSF.IO/KTNDG.\textsuperscript{27}

The project contains the following underlying data:

Data file 1: Patient database.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

**Consent**

Written informed consent for publication of the patients’ details was obtained from the patients.

**Author contributions**

KM wrote the initial draft of the manuscript. KM, SC, FS, EG, BS collected data. AA provided histopathology images. BS, SC, FS, EG provided radiology images. All authors contributed to design, review and redrafting of the manuscript.

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