Evaluation of children with craniopharyngioma using carbon-11 methionine PET prior to proton therapy

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Background. Fluorine-18 (18F) fluorodeoxyglucose (FDG) positron emission tomography (PET) is limited in its evaluation of brain tumors due to the high basal activity of the cerebral cortex and white matter. Carbon-11 methionine (11C MET) has little uptake under normal conditions. We prospectively investigated the uptake of 18F FDG and 11C MET PET in patients with craniopharyngioma prior to proton therapy.

Methods. Ten patients newly diagnosed with craniopharyngioma underwent PET imaging using 18F FDG and 11C MET. PET and MRI studies were registered to help identify tumor volume. Measurements of maximum standardized uptake value (SUVmax) were taken of the tumor and compared with noninvolved left frontal background white matter using a paired t-test. Uptake was graded using a 4-point scale.

Results. Median patient age was 9 years (range 5–19). Seven patients were diagnosed by pathology, 1 by cyst fluid aspiration, and 2 by neuroimaging. Median FDG SUVmax for tumor and background were 2.65 and 3.2, respectively. Median MET SUVmax for tumor and background were 2.2 and 1, respectively. There was a significant difference between MET tumor SUVmax and MET background SUVmax ($P = .0001$). The difference between FDG tumor SUVmax and FDG background SUVmax was not significant ($P = .3672$).

Conclusion. 11C MET PET uptake is significantly greater within the tumor compared with noninvolved background white matter, making it more useful than FDG PET in identifying active tumor in patients with craniopharyngioma. Future work will focus on using 11C MET PET to discriminate between active and inactive tumor after irradiation.

Keywords: craniopharyngioma, fluorodeoxyglucose, FDG, methionine, positron emission tomography, proton therapy.
also for phospholipid synthesis through intermediate compounds. In contrast to $^{18}$F, $^{11}$C has a shorter half-life (20 min) and must be synthesized in close proximity to the site of use. There is little uptake of MET under normal conditions in the brain. Slight elevations in MET uptake due to pathologic conditions may be more readily detected, making it an attractive PET tracer for the evaluation of brain tumors. This study reports on the use of $^{11}$C MET PET prior to irradiation in patients diagnosed with craniopharyngioma.

**Materials and Methods**

Ten patients with newly diagnosed craniopharyngioma underwent PET imaging using $^{18}$F FDG and $^{11}$C MET prior to proton therapy as part of a prospective institutional review board–approved protocol (ClinicalTrials.gov identifier: NCT00840047). Informed consent was required and obtained. The MET PET scans were considered investigational and were not used for treatment planning. The approximate total doses for the FDG PET CT and MET PET CT were estimated to be 6.5 mSv (millisievert) and 3.4 mSv, respectively. This was based on a patient age of 10 years and the following information: FDG PET scan, 5.1 mSv; CT for dose attenuation of FDG PET scan, 1.4 mSv; MET PET scan, 2 mSv; CT for dose attenuation of MET PET scan, 1.4 mSv.

The PET scans were registered to an MRI brain study performed within a few days of the PET studies to help identify tumor volume (Figure 1). Measurements for either examination, and no patient refused the appropriate imaging. If both examinations were performed on successive days. Because the physical half-life of $^{11}$C is short, only 20 min, both studies could be performed in a single session after allowing enough wait time between injections to conduct the appropriate imaging. If both examinations were performed in a single session, the process would involve administrating $^{11}$C, imaging, and waiting 3 h. After that period of time, there would be 1/512 of the original activity. The examiner would inject the patient with FDG and perform imaging 1 h later, at which time the remaining MET would be about 1/4000 of the original activity. If the examiner waited only 2 h after MET to inject FDG 2, when imaging 1 h later, there would be only 1/512 of the original activity of MET present. In our series, there was no problem with fasting or quiet period requirements for either examination, and no patient refused...

For MET PET CT examinations, participants fasted for at least 4 h. Patients were then given intravenous injections of 740 MBq (20 mCi) of $^{11}$C MET per 1.7 m$^2$ of body surface area (maximum prescribed dose, 740 MBq). Transmission CT images for attenuation correction and lesion localization and PET images were obtained ~5 min later using the same GE Discovery 690 PET/CT system. Emission images were acquired for 15 min in 3D. FDG and MET PET images were reconstructed in multiple planes using a vendor-supplied 3D iterative reconstruction algorithm. Both the FDG PET and MET PET emission images were spatially registered to the transverse fluid attenuated inversion recovery MRI on a Hermes workstation.

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**Fig. 1.** $^{18}$F FDG (left side) and $^{11}$C MET (right side) PET images (upper) with MRI registration (lower).
Patient characteristics are shown in Table 1. Median age was 9 years (range 5–19). Seven patients were diagnosed with pathologically confirmed craniopharyngioma. Two patients were diagnosed by neuroimaging and 1 patient by cyst fluid aspiration. All patients who were diagnosed by pathology had a subtotal resection. Three patients required multiple surgeries. The median pre-op gross tumor volume (GTV) and post-op GTV were 18.5 cc (range 3.2–226.2) and 9.0 cc (range 3.2–24.6), respectively.

SUVmax measurements for the FDG and MET PET scans taken from the tumor and background white matter for each patient are shown in Table 2. Median MET SUVmax for tumor and background were 2.2 (range 0.9–3.5) and 1.0 (range 0.6–1.7), respectively. Median FDG SUVmax for tumor and background were 2.65 (range 1.3–7.4) and 3.2 (range 2.3–5.4), respectively. There was a significant difference between MET tumor SUVmax and MET background SUVmax (P = .00013). This difference was not significant for FDG PET (P = .36718).

Tumor uptake grades are shown in Table 3. MET uptake was graded as 3 in 9 patients and 2 in 1 patient. FDG uptake was graded as 3 in 2 patients, 2 in 1 patient, and 1 in 7 patients. Nine of the 10 patients had tumor uptake greater than background with MET PET. Two patients had tumor uptake greater than background for both MET and FDG PET scans.

### Discussion

Craniopharyngioma is a central nervous system tumor that requires multimodality imaging for diagnostic and treatment planning purposes. CT is useful because calcifications are pathognomonic for craniopharyngioma and can be used to differentiate between gross total and subtotal resection. Multisequence and gadolinium-enhanced MRI are required to differentiate between cystic and solid tumor components and to monitor response to therapy. There is a need to further characterize residual disease for the purpose of target planning and predicting response to therapy. Identifying residual disease may be difficult after attempted radical surgery,
for tumors adjacent to bony structures and at the base of skull, or interfaces between normal brain parenchyma and CSF-containing structures. No current imaging method is capable of predicting response to therapy including the potential for cyst progression in response to radiation therapy or ultimately disease control after radical surgery or limited surgery and radiation therapy.

This study shows that 11C MET has significantly greater uptake within the tumor compared with noninvolved background white matter. This was not the case for FDG, as there was no difference in uptake between the tumor and noninvolved background white matter. This can be explained by the relatively low background uptake of MET under normal circumstances.

Nine of the 10 patients were graded as having MET uptake greater than background, with 1 patient having MET uptake approximately equal to background. FDG uptake was present but less than noninvolved background white matter in 7 patients and approximately equal to background in 1 patient. Two patients had FDG uptake greater than background. Only one patient in our series was diagnosed by cyst fluid aspiration.

Previous studies have shown a similar advantage of MET PET over FDG PET in pediatric patients with primary brain tumors; however, none has focused on craniopharyngioma. One study looked at 27 patients—19 with low-grade and 8 with high-grade tumors (17 supratentorial, 10 infratentorial)—and compared MET PET with FDG PET. Overall, 22 of 23 (96%) tumors studied with MET PET were graded as hypermetabolic. Of the FDG PET tumors, 11 of 21 (52%) were graded as hypermetabolic, 8 (38%) as eumetabolic, and 2 (10%) as hypometabolic. There was higher MET accumulation in tumor than in normal adjacent brain but no difference between low-grade and high-grade tumors.

Another study looked at the use of both MET and FDG PET for directing stereotactic biopsy in children with newly diagnosed gliomas. In this series, there were 10 glioblastomas, 12 anaplastic astrocytomas, and 10 low-grade gliomas. All 32 tumors had abnormal MET uptake, while 27 tumors showed abnormal FDG uptake. There were a total of 70 stereotactic trajectories. Of those, 61 were directed to an area of increased MET uptake, while 27 tumors showed abnormal FDG uptake. A tumor diagnosis was made in all cases, with 25% being nonglial tumors despite having a brainstem glioma appearance on MRI. PET guidance improved the diagnostic yield of stereotactic biopsies and allowed a reduction in the number of samples taken to 1 trajectory in eloquent brain areas. Upon comparing FDG with MET, it was concluded that MET was a better choice for PET guidance because it was more specific to tumor tissue, targeted anaplasia as well as FDG, and avoided risk of low FDG uptake. Similar results were shown in children with low-grade brain tumors in which MET PET guidance improved tumor delineation, leading to an increased number of total resections and amount of tumor removed. Studies done on adult patients with primary and metastatic brain tumors using external beam radiotherapy and stereotactic radiosurgery have shown that MET PET can be used to differentiate between tumor recurrence and radiation necrosis.

Should MET PET prove useful for targeting, the benefit to the patient would include the ability to further restrict the highest doses of radiation to the volume at risk and reduce the risk of complications. Should MET PET prove useful in predicting response to therapy, those at risk for tumor progression might be identified early and spared the morbidity of symptomatic recurrence. These potential rewards must be balanced against the cost of providing additional diagnostic procedures and the access logistics associated with a procedure that includes a short half-life isotope such as 11C. The dose associated with the administration of both isotopes represents less than 1/3000 the dose prescribed to the tumor and adjacent normal tissue.

**Conclusion**

11C MET uptake is significantly greater within the tumor compared to noninvolved background white matter, making it more effective than FDG PET in identifying active tumor in patients with craniopharyngioma. Future work will be focused on using MET PET to discriminate between active and inactive tumor after irradiation, an important distinction that remains difficult with both FDG and MRI imaging.

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References