Pilot Study of ^{11}C-Choline (^{11}C-CH) PET in assessing post-treatment true tumor progression from pseudo-progression in high-grade gliomas.

PROTOCOL FACE PAGE FOR
MSK NON THERAPEUTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a pilot study evaluating the ability of ^{11}C-choline (^{11}C-CH) PET imaging to evaluate ^{11}C-CH distribution in the head and to distinguish pseudo-progression from true tumor progression in high-grade gliomas treated with radiation. Distinguishing true tumor progression from pseudo-progression in gliomas remains a challenge with conventional gadolinium-enhanced MRI and FDG PET. Radiographic and FDG PET changes in pseudo-progression are often indistinguishable from those related to true tumor progression. Thus, current advanced imaging techniques are not sufficient in distinguishing these two processes. With a more accurate and an earlier understanding of the pathology of evolving radiographic changes following treatment of high-grade gliomas, more effective treatment decisions could be made earlier on in the course of treatment and may lead to improved patient outcomes.

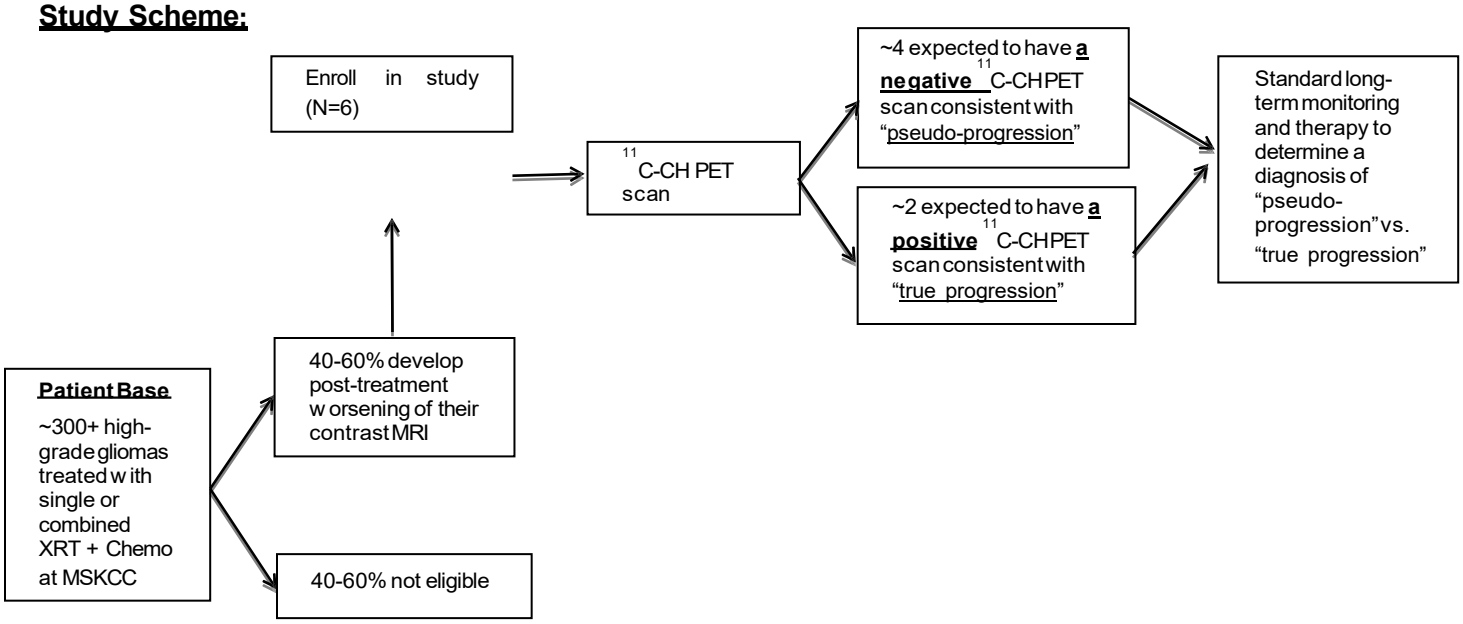
Here we propose to study the biodistribution of ^{11}C-CH using PET imaging and to obtain pilot data as to whether ^{11}C-CHcan differentiate lesions primarily composed of recurrent tumor versus inflammation associated with treatment. ^{11}C-CH PET is a nuclear imaging modality that has been used for the detection of proliferating cells as opposed to inflammation.[7] This is particularly relevant to brain tumors, where ^{11}C-CH has a very low background uptake, contributing to high sensitivity for identifying neoplasia.

In this small plot study of 6 patients, we seek to determine the uptake and biodistribution of ^{11}C-CH with the purpose of correlating SUV measures with evolving MRI findings consistent with a diagnosis of tumor progression versus pseudoprogression.

Our central hypothesis is that ^{11}C-CH PET imaging will delineate those lesions with a large fraction of tumor cells, consistent with true progression, from those with inflammatory cells as seen in pseudo-progression. This pilot study will not be considered definitive, but rather will be used to gather preliminary data in support of a larger, definitive study.

The ^{11}C-CH will be used in this trial, strictly in concordance with the requirements of the Radioactive Drug Research Committee (RDRC). The RDRC permits the study of up to 30 human subjects with a research radiotracer prior to an IND application provided: (1) the radiotracer is not a first in man study, (2) the agent is administered at doses below that which will produce a pharmacologic effect and (3) the projected radiation dose falls within defined limits; namely <3cGy for eyes, bone marrow and testes per injection and <5 cGy per annum; for all other organs <5cGy per injection or <15 cGy per annum. This trial will investigate the distribution of a research agent. The trial is intended to discover where the agent distributes within the head (RDRC justification), as well as address objectives 1 and 2. The individual patient results from this study will not be used for disease diagnosis or to assess treatment response or to change treatment decisions.

Study Scheme:



2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective:

(a) To determine the distribution of ^{11}C-CH in high-grade glioma lesions with MRI findings concerning for pseudoprogression vs true tumor progression following radiotherapy (with or without concurrent therapy).
(b) To investigate the correlation between ^{11}C-CH SUV measures and MRI follow-up outcomes in patients with high-grade glioma lesions with changes concerning for pseudoprogression vs true tumor progression following treatment with radiation (with or without concurrent therapy).

Hypothesis: ^{11}C-CH PET imaging has high uptake in "true tumor progression" (recurrent tumor) relative to evolving treatment related inflammatory changes following radiation and/or chemotherapy ("pseudo-progression").

3.0 BACKGROUND AND RATIONALE

What is post-treatment glioma "pseudo-progression"? Glioma pseudo-progression occurs in 28-66% of all glioblastoma (GBM) patients undergoing chemoradiation and typically presents as an increased area of contrast enhancement and surrounding T2/FLAIR hyperintense signal.[1] These findings are often indistinguishable from those related to true progression of tumor on standard MRI. The radiographic changes of pseudo-progression range from mild to dramatic, may or may not result in neurologic symptoms, and typically occur within 3-6 months of standard combined radiation and temozolomide therapy.[1, 2] Patients with tumors harboring promoter methylation of the repair enzyme O-6-methyl guanine DNA methyltransferase (MGMT) appear to be at greater risk for pseudo-progression, with up to 91% (21 of 23 patients) of such patients developing early radiographic changes in one study.[3] The pathophysiology of glioma pseudo-progression is not fully understood. It is most likely induced by a pronounced local tissue reaction with an

inflammatory component, edema, and abnormal vessel permeability causing new or increased contrast enhancement on MR imaging examinations. Most important, there may be an association between the incidence of pseudo-progression and increased survival, suggesting pseudo-progression represents an active "inflammatory" response against the tumor.[3]

Why is it clinically important to differentiate between "true progression" and "pseudo-progression". Differentiating between true progression and pseudo-progression provides critical information to guide patient management decisions. In patients with pseudo-progression, the imaging findings represent treatment-related inflammatory changes secondary to a robust response to therapy and continued treatment is appropriate and beneficial. For patients in whom pseudo-progression is suspected, continued therapy with close monitoring is recommended as the contrast enhancement will typically remain stable or improve.[4] For patients who are symptomatic from a growing lesion in an eloquent portion of the brain, observation is not feasible, and the prompt diagnosis of tumor progression versus pseudo-progression is imperative to ameliorate and prevent further disability. Tumor recurrence needs to be managed more aggressively to prevent growth, and early identification of recurrence could impact a patient's overall prognosis and survival. An accurate assessment of treatment response is also fundamental in clinical trials and is becoming increasingly relevant with the growing interest in immunotherapies for high-grade gliomas.

Diagnosis of pseudo-progression. Distinguishing pseudo-progression from tumor progression radiographically remains a challenge. Conventional gadolinium enhanced MRI is currently the standard method of evaluating response to chemoradiation, and the Macdonald Criteria are the most widely used response assessment guidelines for high-grade gliomas.[5] These are based on 2D tumor measurements on MRI, in conjunction with clinical assessment, and corticosteroid dose. The Macdonald Criteria define tumor progression as any increase of >25% in the size of the contrast-enhancing lesion, but are limited as only the enhancing portion of the tumor is measured. The revised RANO criteria attempt to address this and account for the nonenhancing component of the tumor in assessing response.[6] They are also more stringent in defining true progression within 12 weeks after radiation only with pathologic confirmation or with the presence of a new lesion outside the radiation field. Comparing these two criteria, it is clear that tumor progression is "over-diagnosed" using the Macdonald criteria, resulting in a subsequent diagnosis of pseudo-progression of 24% for Macdonald and 13% for RANO criteria.[7] Even with the modified criteria, current imaging techniques are not sufficient in reliably distinguishing tumor progression from treatment related changes. Although limited retrospective data suggest perfusion MR may be useful, its sensitivity is comparable to FDG-PET, which is low or disputed in some studies.[4, 8-12] Furthermore, most studies utilize the first MRI following chemoradiation to determine radiographic progression, limiting our understanding of the timeline of treatment-related inflammatory changes. Indeed, some investigators have considered pseudo-progression up to 6 months post-radiation, with one study demonstrating 33% of pseudoprogression cases occurring 3-6 months following treatment initiation [13], highlighting the poorly defined measures used in the diagnosis of this entity.[13-15]

Choline Metabolism: Choline is a quaternary (hydrophilic) amine and is an "essential" nutrient that must be obtained from the diet. Choline is predominantly utilized for the synthesis of essential lipid components of cell membranes (e.g., phosphatidylcholine (PtdylC) and sphingomyelin), the production of potent lipid mediators (such as platelet-activating factor and lysophosphatidylcholine), and for the synthesis of the cholinergic neurotransmitter acetylcholine (ACh). PtdylC is the most important metabolite of choline and accounts for approximately one-half of total membrane lipid content and is the largest fraction of choline metabolites.[16]

Choline is initially transported into the cell and then phosphorylated by choline kinase, forming phosphocholine (PCho). Choline transporters and choline kinase are frequently overexpressed in malignancy.[17-23] PCho is readily detected by ^{31}P magnetic resonance spectroscopy (MRS),

and elevated levels of "choline" $(C\text{-}NH_3)_3$ moieties are detected by ^1H MRS. These measures have been used as surrogate markers for tumors, but elevated levels are also found in many rapidly dividing cells. MRS imaging of elevated choline has been shown in numerous studies of breast, brain, and prostate tumors and is a marker of malignancy.[24-29]

Fluorocholine imaging: ^{18}F-FCH has demonstrated utility for imaging a variety of neoplasms, including those of the breast, prostate, liver and brain. Imaging metastatic and primary brain tumors with ^{18}F-FCH has also been demonstrated (**Figs. 1-3, Table 1**). The results summarized in **Table 1** demonstrate that ^{18}F-FCH uptake in primary brain tumors is very high, and most important, that uptake is very low in "benign" brain inflammatory lesions (e.g. demylinating disease and radiation necrosis), as well as in normal brain tissue.[30]

Table 1. ^{18}F-FCholine PET data [30]

Parameter	High-grade Gliomas (*n*-13)	Benign Lesions (*n*-9)	*P* Value
SUVmax*	1.89±0.78	0.59±0.31	<.0001
White matter SUV	0.40±0.13	0.46±0.20	.58
Lesion/Brain Ratio*	5.15±2.51	1.28±0.32	<.0001

l pairwise comparisons were significant.

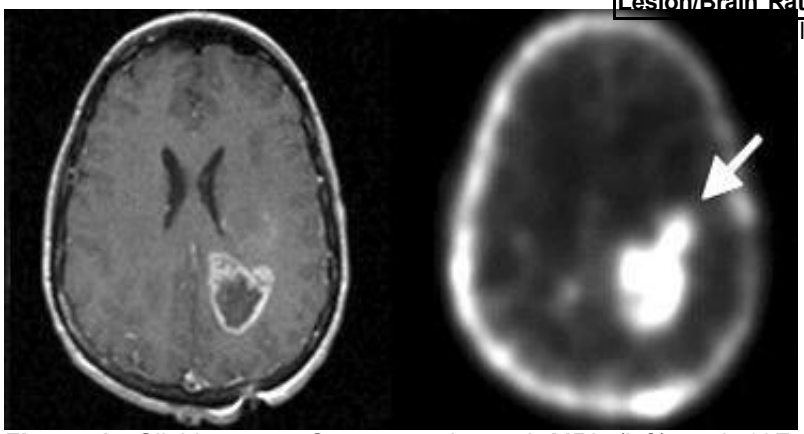


Figure 1. Glioblastoma: Contrast enhanced MRI (left) and 18F-FCholine PET (right). Note visualization of an infiltrating portion of the tumor on the FCH PET image (arrow), that is not seen on the contrast enhanced MRI. Also note the low background activity in non-tumor normal brain regions [20].

Comparison to ^{11}C-Choline: The imaging characteristics (e.g., tumor/brain) of ^{18}F-FCH and ^{11}C-Choline are similar (**Fig. 2**). Although there are advantages to ^{18}F-FCH, including the longer physical half-time of ^{18}F ($t_{1/2}$=110 min) compared to ^{11}C ($t_{1/2}$=20 min) and the slightly greater *in vivo* stability of ^{18}F-FCH[31, 32], radiation exposure (dosimetry) is significantly less with ^{11}C-Choline (approximately 1/5 that of ^{18}F-FCH), allowing repetitive ^{11}C-Choline studies. In addition, ^{11}C-CH is produced frequently (several times each week) for prostate cancer imaging studies at MSKCC. Furthermore, an IND for ^{11}C-CH PET imaging has been approved for these studies.

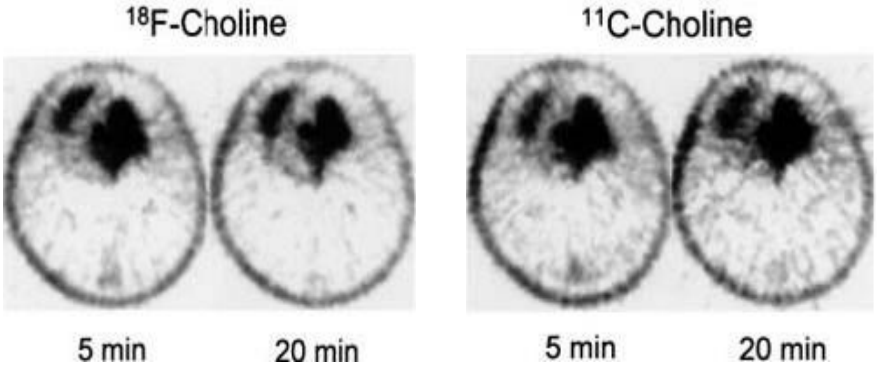


Figure 2. ^{18}F- and ^{11}C-Choline PET scans were similar at 5 and 20 minutes post-injection in a glioblastoma. However, the Tumor/Brain ratio (T/B) of ^{18}F-FCholine increased with time, whereas the ratio of ^{11}C-Choline was constant. As a consequence, the T/B ratio of ^{18}F-FCholine at 20 minutes post-injection was higher, ranging from 13.2 to 21.1 (16.2 +/- 2.6, seven cases) in glioblastoma [31].

Comparison to ^{18}F-FDG. FDG is avidly accumulated by many tumor cells and is widely used to stage many malignancies. FDG has also been used in the past in an attempt to differentiate tumor recurrence from radiation necrosis. However, FDG accumulates avidly in inflammatory lesions, where white blood cells and macrophages have high rates of glycolysis. Non-neoplastic applications of FDG-PET were recently reviewed in 16 articles published in the Annals of the New York Academy of Sciences.[33] In fact, there are many reports where FDG-avid brain lesions have subsequently been shown to be non-malignant inflammatory lesions, including radiation necrosis with an inflammatory infiltrate.[17-23] Reports on the sensitivity and specificity of FDG-PET to distinguish recurrent tumor from radiation necrosis, involving 363 patients in 12 studies varied widely (9 reviewed in reference [34], [11, 35]). Since 1988, sensitivity and specificity values ranged from 65-86% and 22-94%, respectively, although a recent small (n=25) dual phase study reported values of 90-95% and 95-100% respectively.[11, 34-36] Thus, FDG-PET is inconsistent in identifying radiation necrosis and is less frequently used in current clinical management. Furthermore, the background level of FDG in normal brain tissue is high, which further minimizes sensitivity and complicates its ability to distinguish active, progressive brain tumors from other inflammatory brain diseases.

Comparison to ^{18}F-FLT. Comparing ^{18}F-FCH to ^{18}F-fluorothymidine (FLT) (and amino acid uptake) may be more appropriate, because both tracers have relatively low brain background. However, there are no published head-to-head ^{18}F-FCH and ^{18}F-FLT (or radiolabeled amino acid) comparisons for primary or metastatic brain tumors. A comparison can be made between two different studies involving patients with high-grade gliomas. The FLT SUV_{max} and LNR (lesion-to-normal brain ratio) values (1.33 ± 0.75 and 3.54 ± 1.03, respectively) were slightly lower compared to those for ^{18}F-FCH.[30,37] These differences are small and were not statistically significant. No comparable SUV_{max} or LNR values for FLT uptake in brain metastases or radiation necrosis have been reported. FLT has been reported to have low uptake in inflammatory lesions, and FLT is consistently better than FDG in distinguishing tumor from inflammation.[38-40] However, FLT uptake in BCG-induced granulomas was comparable to that in KDH-8 hepatomas (2.2±0.5 vs. 2.6±0.8 lesion/blood). FLT uptake in turpentine-induced inflammation was slightly lower (1.4±0.2 lesion/blood) than that in granulomas, but significantly above baseline.[40] One recent abstract reports a comparison of FLT- and FDG-PET in differentiating recurrent tumor from radiation necrosis in 15 patients with primary brain tumors.[41] Sensitivity/specificity FLT Ki_{max} was 91/75% (p=0.0071), whereas sensitivity/specificity for FDG SUV_{max} was 82/100% (p=0.0016); visual distinction between recurrent tumor and radiation necrosis was statistically significant for

FDG (p=.007), but not for FLT (p=.066). These differences reflect some inconsistency in the published literature.

Comparison to radiolabeled amino acids. Similar to FLT, many radiolabeled amino acids (^{11}C-methionine and ^{18}F-fluoroethyltyrosine [FET]) have relatively high tumor and low brain uptake. However, normal brain uptake of the amino acids is higher than that of ^{18}F-FCH, whereas tumor uptake of ^{11}C-Choline and ^{18}F-FCH is greater than that of ^{11}C-methionine and other amino acids.[3] Several relevant studies have been reported.[42-47] One recent study of 29 patients (33 lesions) using ^{11}C-methionine to distinguish brain tumor recurrence from radiation necrosis,[43] reports a SUV_{max} sensitivity, specificity, and accuracy of 68.2% (15/22), 72.7% (8/11) and 69.7% (23/33), respectively.[43] These values reflect those reported in other amino acid imaging studies.[42, 44-47]

Comparison to MRI perfusion. MRI perfusion provides physiologic information about brain tissue biology, allowing the in *vivo* measurement of increased tumor microvascularity and permeability. There is growing evidence that MRI perfusion can improve the diagnosis of brain tumors over conventional imaging alone. DCE MRI perfusion is a T1 technique with excellent spatial resolution and is relatively insensitive to susceptibility artifacts due to hemorrhage and bone/air interfaces. DCE MRI perfusion provides measurements of plasma volume and Ktrans. Although small retrospective and prospective studies have suggested a role for MRI perfusion in distinguishing tumor progression from treatment related changes, there still remains considerable overlap between these two disease entities.[4, 8-10, 48, 49] There is an open protocol at MSKCC (IRB 12-067) comparing MRI perfusion and FDG-PET/CT to distinguish between radiation injury and tumor progression.

Comparison to spectroscopy (MRS). MRS in combination with standard MRI sequences is clearly better than MRI alone in distinguishing treatment related changes from recurrent tumor. Using ^{1}H MRS, resonances from choline ($C\text{-}NH_3)_3$ moieties (Cho), creatine+phosphocreatine (Cr), N-acetyl-aspartate (NAA), lactate (Lac), and free fatty acids can be resolved well enough to assist in the diagnosis under routine conditions, and PCho is readily detected by ^{31}P MRS. These measures and combination of measures (e.g., Cho/Cr ratio) have been used as surrogate markers of brain, breast, prostate and other tumors in numerous studies,[24-29] and are considered to be a marker of malignancy. In contrast, other combinations (e.g., Lac/Ch) have been used as a marker of necrosis. Small studies have been reported in primary brain tumors.[49-54] However, no large comprehensive efficacy studies have been performed.

Preliminary Data. This proposal is based on observations that gliomas have a much higher uptake of ^{18}F-FCH and ^{11}C-CH than non-proliferative brain lesions and surrounding normal brain tissue, thus providing a clear distinction between the two processes (**Table 1**).[30] MSK has recently been funded to study whether ^{18}F-FCH PET imaging can distinguish between post-stereotactic radiosurgery (post-SRS) induced radionecrosis versus recurrent tumor (R21; IRB-13-199). The results have been very encouraging (see **Fig. 3**).

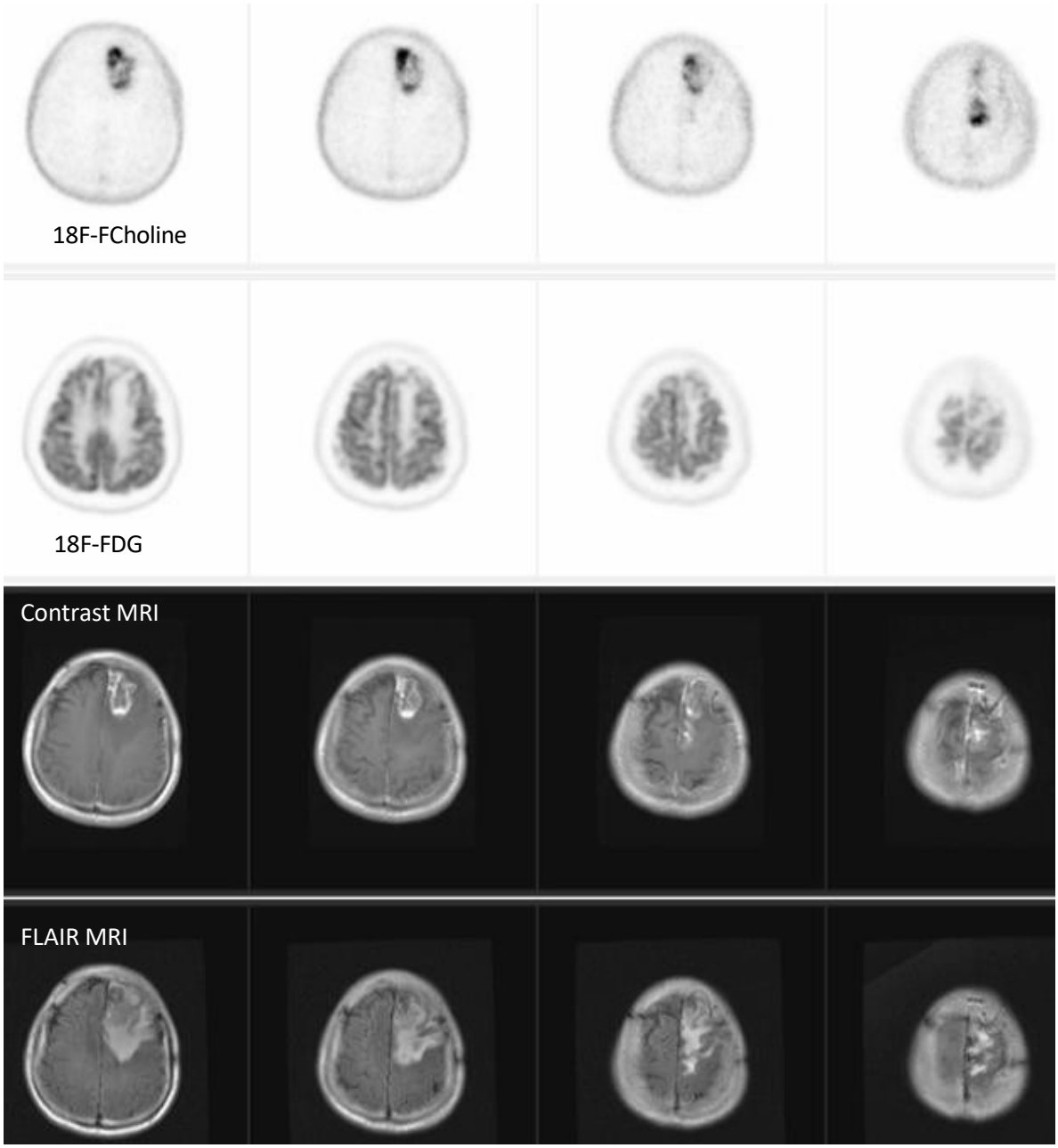


Figure 3. A patient at MSKCC with an evolving brain lesion following stereotactic radiosurgery for a left frontal lobe lung adenocarcinoma metastasis. The patient was scheduled for surgical resection based on clinical grounds, prior to enrollment in the 18F-FCholine PET study (protocol 13-199). Panel A shows foci of high 18F-FCholine uptake in the lesion. Panel B shows some irregular 18F-FDG uptake around the lesion (the level of uptake is between cortex and white matter), which is difficult to interpret. The official reading attributed the findings to radiation necrosis and less likely viable tumor. Panel C shows the lesion with irregular contrast enhancement. Panel D shows a FLAIR signal well beyond the margins of contrast enhancement, suggesting the presence of significant brain edema. The official pathologic diagnosis of tissue removed at time of surgery was consistent with metastatic adenocarcinoma.

Investigational Use of ^{11}C-CH. This study involves the use of an investigational radiotracer ^{11}C-CH that will be performed under the MSKCC Radioactive Drug Research Council (RDRC) and, therefore, will comply with the requirements of the committee as specified on page 4 of the protocol. The purpose of this research study is to discover where the agent distributes within the head (RDRC justification), and explore whether ^{11}C-CH can distinguish between true tumor progression and psuedoprogression and evaluate the biodistribution of ^{11}C-CH in these lesions. No clinical decisions will be made on the basis of the ^{11}C-CH PET scan. A total of 6 patients will be enrolled on this study. The administered activity of ^{11}C-CH has been determined to ensure that the radiation dosimetry falls below the limits required by RDRC.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a non-therapeutic pilot study performing ^{11}C-CH PET imaging of patients with high-grade gliomas who develop MRI findings consistent with recurrent tumor and/or pseudo-progression within 24 weeks after completion of treatment with radiation (with or without concurrent therapy). The objective of this trial is to correlate ^{11}C-CH PET SUV measures with MRI follow-up outcomes. Each patient will be followed up for at least 11 months after completion of the PET scan to confirm MRI changes as representing pseudoprogression or true tumor progression. This study will not be used to make a clinical diagnosis or to change treatment decisions. Six patients will be enrolled on this study over a 1 year period.

4.3 Intervention

This study will enroll patients with a histologically confirmed diagnosis of a high-grade glioma. Eligible patients must have undergone standard radiation (typically 60Gy in 30 fractions), with or without concurrent drug therapy, and have MRI findings consistent with tumor progression and/or pseudoprogression within 24 weeks after completion of radiation. Eligible patients will undergo an ^{11}C-CH PET study within 2 weeks of the standard of care MRI that shows changes concerning for tumor progression vs. pseudoprogression. All patients will then be followed with surveillance brain MRI with and without contrast as per standard of care for a period of 11 months, to assess further progression or stabilization of the lesion. Initial MRI changes are considered to represent pseudoprogression/treatment related changes if the lesion stabilizes or becomes smaller without a change in tumor-related therapy. Otherwise, it will be considered a recurrence should there be progessive radiographic changes.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the subject population.

5.1 Subject Inclusion Criteria

- Age ≥ 18 years
- Patient is able to provide written informed consent prior to study registration
- Histologically-confirmed high-grade glioma
- Completion of treatment with standard radiation (with or without concurrent therapy).

- Standard gadolinium-enhanced MRI changes that are considered indeterminate for tumor progression vs. treatment-related changes by the neuroradiologist or clinician within 24 weeks of completion of radiation.

5.2 Subject Exclusion Criteria

- Inability to undergo or cooperate with an MRI or PET scan (e.g., claustrophobia, metal implant)
- Renal insufficiency with recent (<3 month old) creatinine > 2.0 mg/dL
- Pregnant or nursing female

6.0 RECRUITMENT PLAN

Patients for this study will be recruited by physicians from the Departments of Neurology. Approximately 300 patients with high grade gliomas treated with radiation with or without concurrent therapy are seen a year. Approximately 30-40% will develop progressive radiographic changes on MRI brain concerning for tumor progression, typically within the first 24 weeks following completion of treatment with radiation. Of those patients approximately 30-40% with have pseudoprogression as opposed to true tumor progression. A small percentage of these patients will require surgical intervention for symptom management. We expect to enroll 6 patients over a one year period who require surgical resection of the lesion for management of progressive symptoms or if there is clinical need to establish a histologic diagnosis. Additional patients may be enrolled to replace a previously enrolled patient should surgical resection not yield adequate tissue to complete the histopathologic metrics required for the second objective of the study.

All adult patients ≥18 years are eligible for participation regardless of sex or race. Every effort will be made to encourage eligible women and minorities to enroll in this study. Prior to study entry, the study staff will explain to each potential subject the research objectives, risks and benefits of study participation, alternative treatments available, and the subjects' rights and responsibilities. If the patient agrees to participate in the study, informed consent will be obtained by a consenting individual on the study. All patients must sign written informed consent prior to being registered on this protocol.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team.

The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log.

7.0 ASSESSMENT/EVALUATION PLAN

7.1 PRE-IMAGING EVALUATION

The following tests and procedures need to be performed within 14 days of study registration unless stated otherwise:

- History and Physical exam, including Neurologic exam
- MRI brain with/without contrast with findings consistent with radiographic progression versus pseudoprogression.
- Laboratory studies obtained as part of standard clinical care
  - Serum creatinine
  - Serum pregnancy test (women of childbearing potential) within 7 days of the first PET scan

7.2 ^{11}C-CH PET imaging and injection

All patients will undergo a single head PET/CT scan, measuring ^{11}C-CHradioactivity. This PET scan will be performed within 2 weeks of the brain MRI that demonstrates radiographic findings concerning for true tumor progression vs pseudoprogression. Various metrics derived from this data (including simple threshold SUV values) will be assessed for their ability to differentiate between pseudoprogression and recurrent tumor as confirmed by the evolution of the lesion on subsequent standard of care surveillance MRIs.

Radiographic changes will be defined as progression rather than pseudoprogression within that 24 week window per modified RANO criteria. However, unlike the RANO criteria, the protocol will allow for a broader window of 24 weeks after completion of radiation instead of 12 weeks to maximize enrollment. Progression can only be defined using diagnostic imaging less than 24 weeks after completion of radiation if there is new enhancement outside the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor or histopathologic sampling (ie, >70% tumor cell nuclei in areas, high or progressive increase in MIB-proliferation index compared with prior tissue, or evidence for histologic progression or increased anaplasia in tumor). Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 24 weeks after completion of radiation. Follow-up brain MRI with and without contrast per standard of care will be used in the assessment of the evolution of these lesions. Further increase in enhancement in subsequent MRI warranting a change in therapy per the treating physician will define progression unless proven otherwise by a histopatholigcally confirmed diagnosis. Lesions that stabilize or reduce in size will be deemed consistent with pseudoprogression.

Radiation Exposure (dosimetry). Radiation exposure from ^{11}C-CH PET imaging study has been estimated and published.[55, 56] The critical organ exposures are: kidney 0.64, bladder wall 0.36, and liver 0.26 cGy/mCi with all other organs receiving less than 0.25 cGy per mCi injected. Doses to the most radiation sensitive tissues red marrow, testes and ovaries are 0.075, 0.057, and 0.067 cGy/mCi respectively. The RDRC requires that the administered activity result in <30mSv to the

radiosensitive tissues that include the lens of the eye, gonads, bone marrow, and GI tract, and <50mSv for all other organs per administration. Dosimetry data for lens of the eye was not available (visual uptake of F-choline was not observed for this organ). Additionally, if more than one administration of the radiotracer will be given, then the study must ensure <50mSv for the radiosensitive organs and <150mSv for all other organs within a single year. These factors taken together influenced the selection of a total administered activity of not more than 14mCi for this study in order to be within compliance with the RDRC dosimetry regulations. The organ dose estimates from this study are provided in Table 3.

Radiosynthesis and Specific Activity of ^{11}C- CH. The ^{11}C-CH drug product will be manufactured in compliance with the current Good Manufacturing Practices (cGMP) requirements at the MSKCC Radiochemistry and Molecular Imaging Probes Core Facility, using the ORA Neptis automated synthesizer. The synthesizer cassettes, and reagents and materials will be supplied by ABX Advanced Biochemical Compounds (Radeberg, Germany). 11C-choline injection contains 30 mCi to 400 mCi in approximately 10 ml of 11C-choline at EOS (End of Synthesis) calibration time in aqueous 0.9% sodium chloride solution. The patient unit dose will consist of 10-20 mCi of 11C-choline. With a molecular weight of 104, 20 mCi of 11C-choline corresponds to 104 mg/mmol x 2x10-6 mmol = 200x10-6 mg = 2x10-4 mg of administered. All manufactured ^{18}F-FCH drug product batches will be Quality Control (QC) tested to ensure conformance with the acceptance specifications for pH, appearance, radiochemical purity, radiochemical identity, radionuclidic identity, endotoxin levels, sterilizing filter integrity, and residual solvent levels prior to release for patient administration. Sterility testing will performed post release.

^{11}C-CH Delivery to the MITS Radiopharmacy from Radiochemistry (RMIP) Core. ^{11}C-CH dose will be delivered by Radiochemistry (RMIP) Core to MITS Clinical Radio-pharmacy in Nuclear Medicine. MITS Clinical Nuclear Pharmacist receives the delivery from RMIP Core and ensures that the study drug is handled, inventoried, stored properly, labeled and dispensed as per AU MITS Physician prescription order. The ^{11}C-CH dose will be drawn and measured in a Dose Calibrator by a MITs Nuclear Pharmacist prior to dispensing. Then, the syringe will be placed in a shielded Carrier and handed over to AU MD or designee for administration. After the dose administration the AU MD returns the Syringe for Residual Measurement by MITS Nuclear Pharmacist. All MITS Radiopharmacy activity will be documented by MITS Nuclear Pharmacist.

PET imaging Protocol. Patients will undergo PET scanning following intravenous administration of up to 10-20 mCi (6-20mCI to permit for decay*)* of ^{11}C-CH under the regulation and approval of the MSKCC RDRC. 10-20 mCi of 11C-choline will be administered intravenously as a bolus, followed by 10-30 mL of normal saline flush, with the patient already placed on the bed of the scanner unit. Imaging will begin approximately 5 minutes after injection of 11C-choline.We will accrue 6 evaluable research subjects with the purpose of determining the biodistribution within the evolving lesion. No information gleaned from the PET images or biodistribution data shall be used to affect patient management.

Patients will be set up for a static single field of view (15 cm) head scan by means of a scout and low-dose CT scan. ^{11}C-CH will be administered as an intravenous slow bolus with simultaneous initiation of the scan sequence. The patient will be positioned in the PET/CT in the scan ready position prior to the radiopharmacy dispensing the ^{11}C-CH activity. In this way the activity administered to the patient is within 10% of the prescribed activity as required by research PET studies. ^{11}C-CH, for intravenous bolus injection, is a PET imaging agent with a half-life of 20.4 min. Prior studies have shown that tracer uptake plateaus within 15-20 minutes post-injection. A single PET scan will be performed for up to a maximum of 40 min to ensure capture of the uptake.

PET Imaging Analysis. The procedures described above will yield a number of parameters that individually or in specific combinations will be assessed in their ability to distinguish treatment related changes from recurrent tumor. A positive ^{11}C-CH PET study, one which is believed to indicate recurrent tumor, is one in which there are visible focal “hot spots” (a focus of lesion/normal white matter ratio >1.4) of ^{11}C-CH.

8.0 TOXICITIES/SIDE EFFECTS

The recommended daily dietary intake of choline is 500mg per day and the maximum safe level of choline is 3.5 g/day. The amount of ^{11}C-CH to be administered will be at tracer micrograms levels, which are orders of magnitude below the safety limits for choline. Therefore chemical toxicity is not expected. No toxicities associated with "tracer doses" of ^{11}C-CH have been reported. The dose-limiting toxicity is therefore associated solely with the radiation emissions emanating from the ^{11}C radiolabel. The activities of ^{11}C-CH that shall be administered will be up to 10-20 mCi (approximately 6-20mCi). The expected radiation doses from this maximum administration level of 20 mCi is given in total dose column of the table below, which also includes the 0.9 cGy contribution from the low-dose CT (Table 3). Exposure falls within the constraints imposed by an RDRC protocol.

While toxicities are not anticipated on this trial, all patients will have a follow up toxicity assessment by a member of the reasearch team (MD, NP, or RN), either in person or over the phone, 1-3 days following the research scans. The participants will be asked whether they have suffered any adverse events and these will be documented.

Table 3. Radiation Dosimetry Estimates

^{11}C-Choline and Head CT Dosimetry

		^{11}C-Choline			
		Imaging: rad / **10.0** mCi	**Pre-surgical:** rad / **2.0** mCi	**Low-dose Head CT** [1]	**Total Dose**
Target Organ	rad/mCi			rad	**rad**
Adrenals	0.0630	0.630	0.126	0	**0.819**
Brain	0.0290	0.290	0.0580	0.9	**1.28**
Breasts	0.0310	0.310	0.0620	0	**0.403**
Small Intestine	0.0480	0.480	0.096	0	**0.624**
Large Intestine	0.0480	0.480	0.096	0	**0.624**
Stomach Wall	0.0480	0.480	0.096	0	**0.624**
Kidneys	0.289	2.89	0.578	0	**3.76**
Liver	0.207	2.07	0.414	0	**2.69**
Lungs	0.0410	0.410	0.0820	0	**0.533**
Muscle/Other Tissue	0.0370	0.370	0.0740	0	**0.481**
Pancreas	0.0590	0.590	0.118	0	**0.767**
Red Marrow	0.0370	0.370	0.0740	0.9	**1.38**
Bone surface	0.0560	0.560	0.112	0.9	**1.63**
Skin	0.0290	0.290	0.0580	0	**0.377**
Spleen	0.111	1.11	0.22	0	**1.44**
Gonads	0.0340	0.340	0.0680	0	**0.442**
Thymus	0.0370	0.370	0.0740	0	**0.481**
Thyroid	0.0350	0.350	0.0700	0.9	**1.36**
Urinary Bladder Wall	0.107	1.07	0.214	0	**1.39**

1 For bone surfaces, red marrow, and thyroid, the low-dose CT absorbed doses are conservatively estimated as if they were completely in the CT

field of view. All other organs were assigned a CT dose of 0, since they would receive only a negligibly small scatter dose.

9.0 PRIMARY OUTCOMES

We will assess ^{11}C-CH tracer biodistribution within high-grade glioma lesions with MRI findigns concerning for pseudoprogression vs. true tumor progression after treatment with radiation. PET imaging metrics will be collected; peak SUV values in the lesion and the tumor to background ratio will be compared to clinical follow-up outcomes based on MRIs.

We expect that there will be low uptake of ^{11}C-CH in perilesional normal brain tissue and SUV measures will correlate with clinical follow-up outcomes, thus supporting more definitive investigation of ^{11}C-CH PET to noninvasively distinguish recurrent tumor (true tumor progression) from necrosis and inflammation (pseudoprogression) in post-treatment MRI-evolving brain lesions.

10.1 CRITERIA FOR REMOVAL FROM STUDY

- Inability to undergo PET/CT scan.
- Found to be ineligible for the protocol as described in the section on Criteria for Patient/Subject Eligibility.
- Patient and/or legal representative requests to withdraw from study for any reason
- Referring physician requests to have patient withdrawn from study for any reason, including believing that it would be in the patient's best interest.

11.0 BIOSTATISTICS

This trial is a pilot study to determine the distribution of ^{11}C-CH using PET imaging in progressive high-grade glioma lesions suspected to represent true tumor progression vs pseudo-progression, following treatment with a course of radiation. The purpose of this trial is to correlate SUV measures from ^{11}C-CH PET with evolving changes on brain MRI in high-grade glioma after radiotherapy. In a small subgroup of patients required surgery, tissue will be analyzed for histopathologic correlate. The data gathered will not be considered definitive, but rather will be used to as preliminary data in support of a larger, definitive study.

The biodistribution of ^{11}C-CH will be measured using PET as a basis for dosimetry. This will be performed with region of interest analysis. The first objective is to determine the organ/tissue uptake and tumor localization following intravenous injection of ^{11}C-CH in patients with high-grade glioma with radiographic progression concerning for progression versus pseudoprogression following treatment with radiation with or without chemotherapy. The group for this analysis comprises 6 high-grade glioma patients who appear to have progression vs pseudoprogression on standard MRI with contrast. Standardized uptake values (SUV) in the brain will be measured and summarized for each patient to describe the organ and tissue uptake of the tracer. The mean SUV along with SUVmax value will be estimated in normal and tumor tissue, and lesion-to-normal brain ratio (LNR) values will be obtained. All patients will then we followed with surveillance brain MRI per standard treatment over a period of 11 months for evolving changes that will confirm the diagnosis of progression versus pseudoprogression as defined in the protocol.

It is anticipated that 1 patient every 2 months will be accrued to this study and the study will be completed in approximately 12 months.

12.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process, registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligibile to enroll in the study.

Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

12.3 Randomization

No randomization will occur in this study.

13.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

13.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

13.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials,” which can be found at:

http://www.cancer.gov/clinicaltrials/conducting/dsm -guidelines /page1.

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs: the *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and IRB.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

14.1 PROTECTION OF HUMAN SUBJECTS

Risks: There are no expected additional risks to the patients who participate in this study. Patients will receive the current standard of care for their disease. PET/CT is considered a minimal risk procedure. FDG PET/CT is a standard diagnostic test utilized in the management of patients with high grade gliomas. ^{18}F-FCH PET is not standard but poses no risk other than a very minimal radiation exposure as detailed above. No additional risks have been reported in patients receiving ^{18}F-FCH PET scans. Patients may experience pain and/or discomfort related to the IV catheter, but they would commonly require IV contrast for their routine scans in any case.

Costs: The patient and/or patient's insurance will be responsible for all charges, which are part of the standard of care. No financial reimbursement or other financial incentive will be provided for patients to enroll in this study. There will be no charge for the ^{18}F-FCH PET/CT studies or the tissue analysis of radioactivity levels.

Benefits: We do not expect patients to derive any clinical benefit from this clinical trial. We hope that in the future, knowledge from this trial will help better evaluate diagnostic procedures for these diseases.

All patients will sign informed consents and have all their questions fully addressed before enrolling in this study. During the informed consent process, it will be made clear to the potential patient that participation is entirely voluntary, and will not impact the care that they receive at MSKCC. Potential patients will be advised of alternatives to the proposed study, including not participating in the study. All the data will be held confidential, maintained in a password protected electronic database, and comply with all HIPAA guidelines.

14.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

14.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

14.2.1

This is not an Industry or Cooperative group protocol. This protocol does not have an IND.

15.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In

addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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