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Confidential

Evaluation of Response to Chemoradiation Therapy in Patients With Locally Advanced Head and Neck Cancer using 3'-Deoxy-3'-[F-18] Fluorothymidine Positron Emission Tomography (FLT PET)

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1. ABSTRACT:

Squamous cell cancer of the head and neck affects over 40,000 Americans each year. Treatment options for these cancers currently include surgery, radiation and chemotherapy either alone or in combination. These cancers and their treatment can have a profound impact on the ability to eat, speak, breath and other important functions. Current treatment approaches are not uniformly successful, but all treatments produce significant morbidity. One key challenge to improving care for patients with this type of cancer is to use a treatment most likely to produce cure and least likely to produce toxicity for any individual patient. No test is available to determine which treatment approach is likely to help an individual patient. Treatment efficacy is currently determined months after completion of therapy. Preclinical and clinical data suggest changes in cell cycle kinetics following a brief exposure to radiotherapy, either alone or with chemotherapy, can be used to determine ultimate treatment efficacy in terms of locoregional control, disease free survival and overall survival. Determining changes in cell cycle kinetics involves infusion of potentially toxic analogs of DNA precursors and multiple biopsies, precluding routine assessment. Preclinical data also suggests that cell cycle kinetics can be inferred from the degree of avidity or uptake of radiolabeled DNA precursors. Work with one such precursor, 3′-deoxy-[F-18] fluorothymidine (FLT), suggests that rapidly dividing tissues have a higher avidity for FLT. **The hypothesis of this proposal is that changes in FLT uptake by the tumor early during chemoradiotherapy serve as predictors of ultimate response. This hypothesis will be examined in a clinical trial by specific aims designed to test imaging after 3-5 and 13-15 days (out of a total of 7 weeks of therapy) of radiation therapy combined with cisplatinum-based chemotherapy.** Dynamic FLT PET imaging will be obtained concurrently with serial venous and arterial blood sampling to ensure accurate FLT kinetic data in head and neck tumors. Degree of change in FLT uptake will be tested for predictive value for locoregional control and progression free survival in these subjects.

2. BACKGROUND AND SIGNIFICANCE:

2.1 Current Imaging Evaluation of Response to Chemoradiation in Patients with Head and Neck Cancer:

Approximately 40,000 cases of squamous cell cancer of the head and neck (HNSCC) are diagnosed annually in the United States. Roughly two thirds of patients are diagnosed with locoregionally advanced disease, with either locally invasive cancers or with spread to adjacent regional cervical lymph nodes. Patients with locoregionally advanced disease are typically treated with combined modality therapy involving either surgical resection and post-operative irradiation or combined chemotherapy with radiation therapy. In many cases, the efficacy of resection and radiotherapy is comparable to combined chemoradiotherapy. For patients with aggressive features found after resection, combined chemoradiotherapy is recommended after resection. Increasing the intensity of therapy, by using more aggressive combinations of chemotherapy with radiotherapy, has led to modest increases in locoregional control and overall survival. Unfortunately, more aggressive therapy also results in greater toxicity, with some studies showing a significant increase in treatment related deaths. Each treatment option carries a range of significant morbidities. Surgical management may include a laryngectomy with resulting decreased ability for speech and social interactions. Chemoradiotherapy also has toxicities, including loss of swallowing function, aspiration risk and feeding tube dependence. Even with these aggressive approaches, cure for any individual is not certain. Although outcome expectations vary significantly based on stage, site and other factors, roughly half of all patients with locoregionally advanced disease will ultimately succumb to their disease (Garden 2004).

One important step necessary to improve outcome for this disease is to select which patients have tumors that are likely to respond to chemoradiotherapy and which tumors need alternative approaches including either surgery or more aggressive radiotherapy or chemotherapy regimens. Current means to assess response are all performed after completion of therapy. Conventional imaging with CT and MRI, which rely on structural changes, are not reliable for early evaluation of response to chemoradiation because treatment related changes in normal tissue planes and nonspecific contrast enhancement significantly reduce the accuracy of these imaging modalities in post-treatment setting. Metabolic imaging with F-18 fluorodeoxyglucose positron emission tomography (FDG PET) is significantly more accurate in assessment of residual or recurrent disease. In the largest published study including 143 patients with suspected recurrence, who were imaged with FDG PET after an average of 6.9 months of completion of treatment, Wong et al reported a sensitivity and specificity of as 96% and 72% for recurrent disease (Wong 2002). In a meta-analysis including all studies published between 1999-2003, the sensitivity and specificity for FDG PET for detection of residual / recurrent disease was 86% and 73% respectively, compared to 56% and 59% for CT and/or MRI (Klabbers 2003).

A critical issue with FDG PET imaging in head and neck cancer is the timing of the scan. Greven et al have reported that detection rate for residual disease of a 1-month post-treatment PET scan was only 59% compared to 100% for 4-month post-therapy PET (Greven 2001). Our experience with 53 patients imaged with FDG PET at 3 months post-treatment is in concordance with the earlier study by Greven in terms of the

negative predictive value of PET (100%), however the specificity of PET in our group was significantly lower at 43% (Yao 2005). Because of potential false positive FDG uptake in postradiation inflammatory changes, FDG PET is usually not performed for 2-4 months after completion of radiotherapy. It would be however highly desirable to check the efficacy of therapy earlier, preferably before the full treatment is completed, to modify the radiation treatment or the chemotherapy regimen in nonresponsive patients. Our proposal is to test F-18 fluorothymidine in this clinical setting based on the published preclinical evidence that FLT uptake in the tumor reflects response to radiotherapy (Apisarnthanarax 2006).

2.2 Labeling index as a prognostic indicator:

Tumor growth and proliferation markers have been investigated for their potential to predict response to treatment. Pretreatment measures of tumor cell cycle kinetics have been associated with poor local control and survival for patients with head and neck squamous cell cancer (HNSCC). Specifically, tumors showing high proliferative potential, short doubling times, overexpression of cell cycle progression activities (such as cyclins and cyclin dependent kinases) appear to have higher failure rates. For example, Giri and coworkers (Giri 2006) studied gene expression in patients with either no recurrence or distant metastases following resection and radiotherapy. They found expression of a cluster of 205 genes, including several cell cycle regulatory genes such as MCM4, RBL1 and HDAC2 were overexpressed in tumors from patients who developed distant metastases.

Rapidly growing tumors may respond differently to radiotherapy than slow growing tumors. Efforts to determine if pre-treatment proliferation rates determine radiation response rates are of considerable interest because radiotherapy schedules can be adjusted to increase toxicity in rapidly growing tumors. For example, shortening treatment time theoretically allows less time for rapidly proliferating tumors to grow, or repopulate, during the course of treatment. The strategy of shortening treatment time to avoid repopulation is termed accelerated therapy. Tumor growth kinetics can be determined by infusing a halogenated thymidine analog, such as bromodeoxyuridine or iododeoxyuridine, into a patient with a head and neck cancer. If their cancer is biopsied after a brief period following infusion, typically 4 to 6 hours, the proportion of cells that have taken up the label (labeling index) can be determined (Wilson 1999). Several large studies have been conducted examining the efficacy of accelerated radiotherapy, with most showing a modest benefit to shortened radiotherapy. Some of these studies have included measures of cell cycle kinetics prior to initiating therapy (Dobrowsky 2003). Faster proliferating tumors do appear to benefit most from accelerated treatment schedules. However, this finding is not uniformly consistent. Some investigators have found no correlation between pretreatment cell cycle kinetics and outcome.

2.3 Change in LI as a prognostic indicator:

One of the most important cellular responses to ionizing radiotherapy appears to be cell cycle arrest. Cell cycle arrest in G2 following radiotherapy is thought to be critical to allow for repair, recovery and survival following radiation exposure. While many genetic alterations affecting cell cycle kinetics have been described in HNSCC, pretreatment measures of cell cycle time has not proven a universally reliable measure of outcome. A more relevant determinant of outcome may be how the cell cycle is affected by ionizing radiation. Few studies have investigated changes in cell cycle parameters during the

course of radiotherapy. One study examined IUdR uptake into DNA of head and neck cancers prior to radiotherapy and BrUdR uptake one week after initiating radiotherapy (Zackrisson 2002). They found most cancers had a decrease in thymidine analog uptake following radiation exposure. However, some cancers continued to synthesize DNA, as evidenced by continued high rates of BrUdR incorporation into DNA. These authors found that a decrease of 10% in the labeling index with the onset of radiotherapy predicted a better outcome for patients. Indeed, when also considering DNA ploidy, the change in labeling index was very predictive. Patients with diploid tumors that showed a decrease of 10% or more in their labeling index had a 90% chance of survival at 5 years. In contrast, none of the patients with aneuploid tumors and no decrease in labeling index survived 5 years.

Other groups have found similar results. Silvestini and co-workers examined changes in tritiated thymidine uptake into tumor DNA before therapy and after 10Gy of treatment in 35 patients with squamous cell cancer of the oral cavity (Silvestrini 1984). They found no association between pretreatment labeling properties and eventual outcome. However, they did find a significant correlation between changes in tritiated thymidine uptake and eventual outcome. Subjects with tumors that showed a decrease in DNA labeling following 10Gy radiotherapy had a better outcome. A decrease of more than 70% in the labeling index was significantly correlated with long-term clinical outcome at 36 months in terms of the probability of local recurrence, with 82% of patients with a decrease in LI showing locoregional control and all patients with LI decrease less than 70% showing local recurrence.

Valente et al. examined Ki67 staining in oral squamous cell cancers pretreatment and again after 10Gy radiotherapy (Valente 1994). Ki67 is a cellular antigen marker associated with S-phase of the cell cycle; tumors with high levels of Ki67 have high proliferation rates. Work by Valente found no correlation between pretreatment Ki67 staining and outcome. 29 of 31 patients had a decrease in the amount of Ki67 staining after 10Gy, with a median 32% decrease in the number of Ki67 positive staining cells. Patients with tumors showing a decrease of greater than 32% had a better outcome. Eight of 13 patients with a decrease of 32% or larger in their LI showed a complete response, whereas only 3 of 18 with a lesser decrease in LI achieved a complete response.

Predictive tests have the most value if they are able to influence on therapeutic decisions. Using a change in labeling index following the first few radiotherapy sessions may allow prediction for the entire treatment course early enough to make adjustments if needed. Chemoradiotherapy for head and neck cancers can be delivered in a variety of ways. For example, rapidly proliferating tumors may respond better to accelerated radiotherapy to minimize tumor cell repopulation. Alternatively, higher doses of radiotherapy could be delivered to potentially resistant regions of disease. Various chemotherapy schedules and agents have been used concurrently with radiotherapy. A mid-treatment test may provide information regarding the success of the chosen agents with enough time left over to change the treatment approach. Alternatively, if a tumor is responding very poorly to chemoradiation, surgical resection may be the preferred treatment option, despite the morbidity. Currently, no test is available to conveniently and accurately distinguish which patients would specifically benefit from more aggressive radiotherapy or other treatment options.

Determining cancer cell kinetics in patients requires an invasive approach and specialized labeling and analysis techniques. Also, only a small portion of the tumor can be sampled. Thus, while multiple studies have suggested the utility of cell cycle kinetics and their response to radiotherapy as useful prognostic information, technical challenges have limited the widespread use of these kinetic studies. The main goal of this proposal is to extend translational research data collected over the last 20 years highlighting the importance of tumor proliferation characteristics by developing the 18F-FLT PET scan as an imaging method to determine proliferation responses to chemoradiotherapy. If successful, the 18F FLT PET scan could become an important tool allowing more individualized and specific cancer therapy.

2.4 Positron Emission Tomography with FLT:

Radiolabeled fluorothymidine (FLT) is a thymidine analog where the 3′-OH group is replaced with fluorine-18; a positron emitter with a physical half-life of 110 min. Thymidine is one of the four bases that comprise the backbone of DNA and is unique to DNA. A cell not undergoing division has a very low intracellular concentration of thymidine and the enzymes required for synthesis and utilization are not expressed. When cellular division begins, the cell obtains the thymidine necessary for DNA synthesis by two routes. The first is *de novo* synthesis where the enzyme thymidylate synthase converts deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). The second is the "salvage" pathway when thymidine is transported from the circulation into the cells and then phosphorylated by thymidine kinase. Thymidine phosphate (dTMP), from either pathway, then undergoes further phosphorylation to the triphosphate, which is incorporated into DNA. Thus, externally delivered thymidine is retained in the tissue as a function of thymidine kinase activity present in the cell.

FLT is an excellent substrate for thymidine kinase, but unlike thymidine FLT does not undergo metabolic degradation. Thus, tissue retention of FLT should reflect the thymidine kinase activity (Shields 1998). Preliminary reports have documented the utility of this agent to identify proliferating tissues such as bone marrow, spleen, and tumor. FLT retention correlates with Ki67 expression in lung and colon cancers (Vesselle 2002; Buck 2003; Francis 2003). FLT uptake has been demonstrated in 15/17 histologically proven laryngeal primary or recurrent cancers with a tumor-to-nontumor ratio of 1.5 and average SUV of 1.6 (Cobben 2004). Currently, no clinical data is available on changes in FLT retention following initiation of radiotherapy for any cancer.

2.5 Preclinical and clinical data supports the use of FLT in monitoring the effects of cancer treatment:

A noninvasive study able to predict the outcome of toxic anti-cancer therapy would be extremely valuable to increase the specificity of treatment. Our group has used FDG PET scans as an assessment tool following chemoradiation for stage III and IV squamous cell cancer of the head and neck. Following chemoradiation, sites of bulky disease often leave a residual mass detectable by CT or physical exam. We have found that sites formerly harboring cancer that show reduced FDG uptake to an SUV of 3.0 or lower do not contain histologic evidence of cancer following salvage resection. This finding may suggest a treatment management decision to observe patients with CT adenopathy that has low FDG uptake, resulting in fewer salvage neck dissections and sparing patients the toxicity of post-chemoradiation resections (Yao 2004).

The use of imaging studies early in the course of treatment could have a profound impact on tailoring therapy to improve outcome. Since proliferation determines 18F FLT uptake and retention, it may serve as a more rapid indicator of response to anticancer treatments. Also, the uptake of 18F FDG can be increased by inflammation to normal tissues in the treated area, obscuring tumor response. The potential value of 18F FLT relative to 18F FDG in determining response to radiotherapy has yet to be fully investigated. No human clinical data have yet been reported using 18F FLT to examine response to radiotherapy. Preliminary evidence from preclinical animal research supports the superiority of 18F FLT over 18F FDG in determining response to radiotherapy. Sugiyama, et al. examined the use of 18F FLT and 18 F FDG scans after single dose irradiation of C3H mice harboring autologous SCCVII squamous cell cancers (Sugiyama 2004). Grafted tumors were treated with a single, 20 Gy dose. Both types of scans were able to demonstrate decreased activity following irradiation. However, the FLT analysis showed a more dramatic and more rapid change in uptake and retention compared to FDG. Tumor uptake of FLT was decreased 6 hours after irradiation and remained low for 3 days after treatment. Tumor uptake of FDG decreased after irradiation, but the decrease was much more gradual, and became significantly lower than pre-irradiation only after 3 days.

Barthel also described changes in 18F FLT and FDG uptake in tumors after cytotoxic treatment (Barthel 2003). Their report examined changes in tracer uptake following treatment with 5-fluorouracil (5-FU) for either 24 or 48 hours. They found that both FDG and FLT uptake in RIF fibrosarcomas growing as implanted tumors in C3H mice decreased following treatment. However, the decrease in FLT uptake was more significant at the earlier time point and reached lower levels than for FDG. The same model system was used by Leyton et al. to examine the effects of cisplatinum on tumor growth and FDG and FLT uptake (Leyton 2005). Cisplatin was toxic to these tumors and resulted in a decrease in tumor size and kinetic measures such as degree of PCNA labeling. These authors also found that 18F FLT imaging provided a superior measure of tumor cell proliferation, and the changes in proliferation caused by cisplatin treatment. Our review of the literature has revealed only one report using 18F FLT to judge response to cancer therapy. Pio et al studied FDG and FLT scans in breast cancer patients prior to and following initiation of chemotherapy (Pio 2006). The changes in FLT uptake after one cycle of chemotherapy were more closely correlated with response judged by changes in tumor marker CA27.29 than were changes in FDG uptake. Their findings again suggest FLT may allow response assessment following a brief course of therapy.

2.6 Significance of the Proposed Project:

The ***significance*** of this work is to develop a tool to individualize cancer therapy. If successful, the FLT PET scan can be used to identify patients that require either more aggressive and more toxic treatment to cure their cancers or less aggressive and less toxic therapy resulting in high cure rates without the significant life long side effects that can follow aggressive chemoradiotherapy.

3. SPECIFIC AIMS / OBJECTIVES:

The immediate objectives of this proposal are 1) to examine the predictive value of FLT imaging during early and mid cycle during chemoradiation therapy and immediately at the completion of treatment for determining eventual long-term outcome and 2) to establish image acquisition and analysis parameters for routine clinical implementation of FLT imaging in patients with advanced head and neck cancers. The **hypothesis** of this project is that changes in FLT uptake imaged with PET early in the course of radiotherapy will predict the treatment outcome in terms of locoregional control and progression-free survival in patients with advanced head and neck cancer. This hypothesis will be tested by developing and obtaining FLT imaging before and early during chemoradiation therapy and immediately at the completion of treatment.

Primary aim:
Determine the value of baseline FLT uptake and changes with therapy for predicting the outcome in terms of locoregional control and progression-free survival.

Secondary aims:
(1) Compare different methods of image analysis to provide the most reliable assessment of therapeutic response. Quantitative (e.g., Patlak graphical analysis) and semi-quantitative (e.g., standardized uptake value (SUV)) techniques for analysis of FLT uptake will be evaluated and compared in order to determine the most dependable indicator of metabolic change.
(2) Evaluate the detection rate of primary and metastatic squamous cell head and neck cancer sites with FLT-PET in comparison to conventional work-up that includes physical exam, direct laryngoscopy and nasopharyngoscopy, CT/MRI and FDG PET.

4. RESEARCH AND DESIGN METHODS:

4.1 Experimental Design and Study Flow

The central hypothesis of this proposal is that 18F-FLT uptake, retention and metabolism as measured by PET prior to initiating treatment after a brief course of treatment will provide a rapid indication of tumor response to (chemo) radiotherapy and predict locoregional control in head and neck cancer. Testing this hypothesis will be performed by measuring the uptake of 18F FLT (1) prior to treatment, (2) very early during therapy, following 6-10 Gy (out of a total of 70Gy) radiation and one cycle of cisplatinum-based chemotherapy and (2) following 26-30 Gy of radiation and three cycles of cisplatinum-based chemotherapy. Patients will be followed closely for 2 years to determine locoregional control rates and progression-free survival following therapy and to assess if changes in FLT uptake prior to therapy and after 6-10 or 26-30 Gy of treatment correspond to treatment outcome. The study flow is summarized in Figure 1.

Study Flow

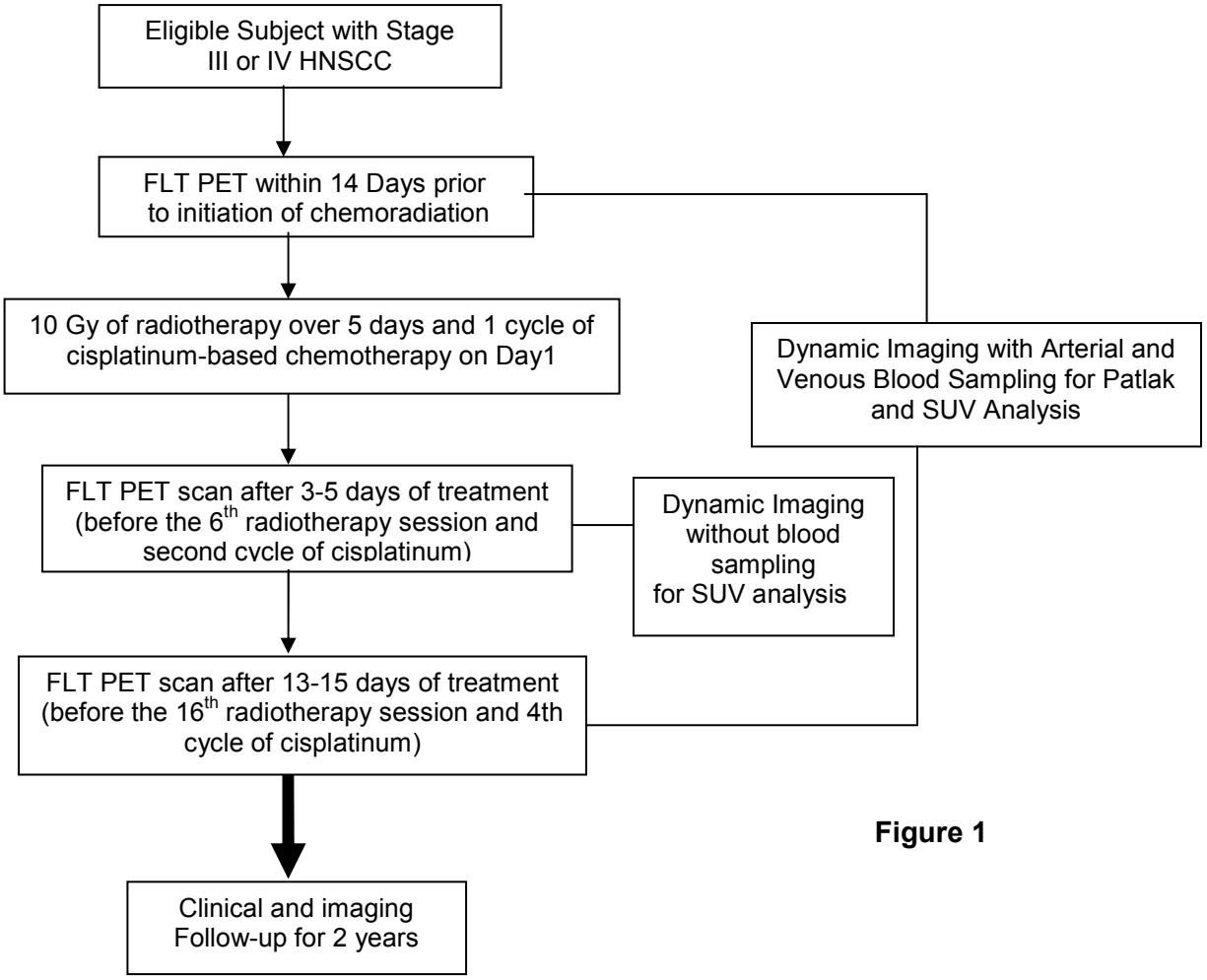

Figure 1

The chemoradiotherapy treatment for these patients will be standard of care. Patients will be staged using physical exam, computerized tomography (CT) and FDG PET imaging and appropriate means of biopsy. Additional staging studies will be performed as needed. Treatment recommendations will be made by the responsible otolaryngologist, radiation oncologist and medical oncologist together with review at a weekly multidisciplinary tumor board. Most patients with stage III or IV squamous cell cancers of the tongue base, tonsil, hypopharynx and larynx are treated with chemoradiotherapy at the University of Iowa. The details of radiotherapy have been described elsewhere (Yao 2005) and consist of intensity modulated radiation therapy (IMRT). The target and avoidance structures for IMRT will be defined by the staging studies described above but will not be influenced by the FLT scan. Chemotherapy will be based on a recent report from the RTOG (Garden 2004) and includes low dose weekly cisplatin during the course of radiotherapy. A total of 70 Gy is delivered in 2Gy daily fractions over 35 treatments or 7 weeks. Sites of high risk regions that do not bear gross tumor are treated concurrently at lower doses per day.

4.2 Subject Eligibility Criteria:

4.2.1. Inclusion Criteria:

1. Ability to understand and willingness to sign a written informed consent document.
2. Subject must have Stage III or IV squamous cell carcinoma of the head and neck. Carcinoma must be staged using the American Joint Committee on Cancer (AJCC) staging criteria version 6.
3. Subject must be scheduled to receive combined chemo-radiotherapy treatment for their standard cancer care. Treatment decisions will be made by the treating otolaryngologist, radiation, and medical oncologists.
4. Male or females 18 years of age. Squamous cell cancer of the head and neck is exceedingly rare in children and not generally applicable to the pediatric population.
5. Karnofsky 60% at time of screening.
6. Life expectancy of greater than 6 months.

4.2.2 Exclusion Criteria:

1. Subjects who have had chemotherapy within 6 weeks of the FLT scan.
2. Subjects with a Karnofsky score of below 60.
3. Pregnant women are excluded from this study. FLT PET has potential for teratogenic effects. Because there are potentially unknown risks for adverse events in nursing infants secondary to treatment of the mother with FLT, breastfeeding should be discontinued if the mother is imaged with FLT and may not resume for 48 hours after the FLT imaging.
4. Subjects taking 5-FU or other nucleoside analog medications such as those used as antiretroviral agents.

4.3 F-18 Fluorothymidine (FLT) Production

FLT is produced based on the previously described method of Machulla et al (Machulla HJ 2000). Fluorine-18 is prepared by bombarding oxygen-18 enriched water with 16 MeV protons. Fluoride is trapped on an anion exchange resin and subsequently eluted with potassium carbonate solution. [2, 2, 2] Kryptofix in 2 ml's of acetonitrile is added and the acetonitrile is evaporated by heating under vacuum to a 100º C. The majority of the water is removed by this evaporation. Two more additions and evaporation of 2 ml portions of acetonitrile from addition vessels 3 and 4 are performed to remove the last traces of water. When the F-18 fluoride solution is dry, 20 micromoles Anhydrothymidine benzoate dissolved in 1 ml of dimethyl sulfoxide is added and the solution heated for 10 minutes at 170º C. At this point the fluoride performs a nucleophillic displacement on anhyrothymidine and is incorporated into the organic molecule. Addition of 0.2 N HCl removes the benzoate protecting groups to give the F-18 FLT. This solution is loaded onto a semi-prep C-18 HPLC column through an alumina cartridge and the column eluted at 7 ml/min with an eluant that is 10% ethanol in isotonic saline.

4.4 FLT PET Imaging and Image Analysis:

All subjects will be imaged at baseline (i.e., prior to beginning any therapy for their head and neck cancer) and after 3-5 days and 13-15 days of chemoradiotherapy (i.e., 6-10 Gy radiotherapy one course of cisplatin-based chemotherapy and 26-30 Gy and three courses of chemotherapy).

4.4.1 FLT PET scans at baseline and 13-15 days after initiation of therapy: Imaging will initially consist of a full dynamic sequence for the first 60 minutes post FLT (0.07 mCi/kg IV) administration followed by a whole-body scan. The subject will be positioned for the dynamic scan with the field-of-view (FOV) centered over the primary lesion and including as many known metastatic lesions as possible. Transmission imaging will precede the dynamic sequence. Dynamic imaging (5 frames at 1 minute/frame + 11 frames at 5 minutes/frame = 16 frames/60 minutes) will begin at the start of the infusion. Subjects will be instructed to lay still and may sleep while images are acquired. At the end of the dynamic sequence, a whole body scan (T+E mode at 5 minutes/bed position) will be acquired from the base of the brain to the proximal thighs. The exact administered dose, time of administration and the subject's weight will be recorded and entered into the image header file for automatic calculation of standardized uptake values (SUV). Arterial and venous blood samples will be obtained 1, 2, 5, 15, 30, 40, 50, and 60 min the 60-min venous sample will be analyzed for glucuronide using a Sep-Pak (Waters, Accell Plus QMA 6 cc cartridge) (Shields 2005). All samples will be assayed for radioactivity concentration in the whole blood and in the plasma by counting in a previously calibrated well counter. The fraction of unchanged FLT in the plasma versus time will be fit to a single exponential curve. This function will be applied to metabolite-correct the arterial plasma samples. The images will be imported into an image analysis program (PMOD, PMOD Technologies, Ltd. Zurich) for the generation of time-activity curves (TAC) over tissues of interest. Tissue-based time-activity curves and metabolite-corrected arterial input functions will be used to generate influx rate constants, Ki, based on Patlak Graphical Analysis (Patlak 1985). Maximum pixel standardized uptake values (SUV) for each time point as well as during the whole-body imaging will also be acquired for these same tissues. Interim analysis for correlation of Ki and SUV at 25-30 min and Ki and SUV at 55-60 min will be performed after five subjects have completed the FLT scans. Blood sampling and dynamic imaging may be reduced or eliminated depending on the correlation of SUV's and Ki. This honing of the protocol will be an essential component of the research since the translational value of this research is linked to the development of a clinically-feasible imaging procedure that produces valuable prognostic information critical to therapeutic monitoring for the refinement of treatment regimens.

4.4.2 FLT PET scan 3-5 days after initiation of therapy: Whole body imaging will not be obtained for this scan as no significant changes in whole body FLT distribution are expected compared to the baseline study. To reduce the risks and discomfort associated with placement of arterial lines, this study will be also acquired without arterial and venous blood samples. A static image over the area of the tumor will be obtained at 55-60 min to calculate the maximum pixel standardized uptake values (SUV).

4.5 Reference Standard

Locoregional control and progression free survival will be assessed using clinical exams including fiberoptic nasopharyngoscopy and direct tumor visualization, every 2-4 months, for 24 months. In addition, subjects will undergo imaging with CT and FDG PET

imaging at 3 months, 12 months and 24 months post-therapy and more often as clinically indicated. Any indication of recurrence will be further assessed by biopsy.

5. Data Management, Quality Control, and Data Security

In order to protect confidentiality the subject will be assigned an identification number. This number will be used on all specimens from the subject and will be used for documentation purposes. Data management for the optimal entry, processing, storage, and retrieval for this protocol's data will be accomplished by the principal investigator. The database will be located on a computer or in a locked cabinet in a locked office. This computer will be secured, accessible only by the research team. There will be more than one copy of the database. The second, secured, copy of the protocol data will be stored in a locked room accessible only by the research team. For quality control, auditing, and checking data for integrity, there will be a regular accounting of data periodically performed.

6. Adverse Events Reporting

6.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Abnormal results of diagnostic procedures are considered to be adverse events (AEs) if the abnormality: (1) results in study withdrawal (2) is associated with a serious adverse event (3) is associated with clinical signs or symptoms (4) leads to additional treatment or to further diagnostic tests (5) is considered by the investigator to be of clinical significance.

6.2 Definition of Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence that: (1) results in death, or (2) is life-threatening (at the time of the event), or (3) requires inpatient hospitalization or prolongation of an existing hospitalization, or (4) results in persistent or significant disability or incapacity, or (5)is a congenital anomaly/birth defect.

Adverse Event Grading:
Grade is used to denote the severity of the adverse event.

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

Adverse Event Attribution:
Attribution is used to determine whether an adverse event is related to a study treatment or procedure.

Attribution categories are:
Definite – AE ***is clearly related*** to the study treatment or procedure.
Probable – AE ***is likely related*** to the study treatment or procedure.
Possible – AE ***may be related*** to the study treatment or procedure.
Unlikely – AE ***is doubtfully related*** to the study treatment or procedure.
Unrelated – AE ***is clearly NOT related*** to the study treatment or procedure.

6.3 Expected Adverse Events from FLT PET

Expected Adverse Events from injection of FLT and Arterial Line:

Bruising;
Bleeding;
Phlebitis;
Infection at the site of injection;
Allergic-type or other adverse reaction to FLT.

Expected Adverse Events from PET scan:

Discomfort;
Claustrophobia.

6.4 Reporting of Adverse Events

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and/or nurse engaged in clinical research. An adverse event report should be submitted to IRB if there is a reasonable suspicion of the medical treatment or imaging procedure.

Since this is a diagnostic study that does not involve any experimental forms of cancer therapy, adverse event reporting will be minimal. All expected and unexpected adverse events considered possibly, probably, or definitely related to FLT PET scan and serious adverse events will be documented in the study participant's case report form. All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse events are otherwise explained. Any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may be reasonably be related to the study imaging effect should be reported.

The following table summarizes the reporting requirements for AEs for the Trial:

Adverse Events that occur during study participation (from the first study procedure and up to 30 days after the last study procedure)	Type of Report		
	Routine Reporting	Expedited Written in 10 days	Telephonic Report to IRB within 24 hours of knowledge of AE
Grade 3 (Attribution of possible, probable, or definite)	X Expected and Unexpected		
Hospitalization/Prolongation of hospitalization** (Attribution of possible, probable, or definite)	X Expected and Unexpected	X Unexpected	
Grade 4 (Attribution of possible, probable, or definite)	X Expected and Unexpected	X Unexpected	
Grade5/Death (Attribution of possible, probable, or definite)	X Expected and Unexpected	X Expected and Unexpected	X Expected and Unexpected

**All unexpected hospitalizations (or prolongation of existing hospitalization) for adverse events with the severity (intensity) level of CTCAEv3.0 Grade 3, 4, 5 with attribution of possible, probable, or definite.

7. Statistical Considerations:

Primary Aim: *To determine the value of changes in FLT uptake with therapy for predicting the outcome in terms of locoregional control as assessed by progression-free survival (PFS) in patients with head and neck cancer*.

Most recurrences of head and neck cancers are locoregional failures and >90% of recurrences occur within 2 years following completion of therapy. In this study, the sensitivity and specificity of different cut-off values of change in FLT uptake measured with SUV will be calculated for diagnosis of recurrent disease within 2 years of completion of therapy. In the primary analysis for this aim, an ROC curve will be estimated and used to determine the optimum cut-off value of change in SUV that distinguishes responders from nonresponders to treatment. The estimation of the ROC curve will account for the potential for censored observations in PFS data (Heagerty 2005). In a secondary analysis, the predictive value of the change in FLT uptake will also be examined by deriving and comparing Kaplan-Meier estimates of PFS for patient groups defined by their dichotomized change in FLT uptake,

Secondary Aim 1: Compare different methods of image analysis to provide the most reliable assessment of therapeutic response. Quantitative (e.g., Patlak graphical analysis) and semi-quantitative (e.g., standardized uptake value (SUV)) techniques for analysis of FLT uptake will be evaluated and compared in order to determine the most dependable indicator of metabolic change.

Correlation analysis will be performed to assess agreement between the semi-quantitative measure (SUV) of metabolic change and the quantitative measure (Ki). After a graphical exploration of the relation between the two measures, Pearson correlation and rank correlation coefficients and 95% confidence intervals will be reported. Regression modeling will also be used to asses the agreement between the two measures. ROC curves will be generated for different cut-off values of change in Patlak coefficient and SUV between baseline scan and the third FLT PET scan. The area under the ROC curves will be compared to determine which measure is more accurate for assesment of therapeutic response.

Secondary Aim 2: *Evaluate the detection rate of primary and metastatic squamous cell head and neck cancer sites with FLT PET against the battery of reference standard tests which consist of clinical exams, other imaging studies and biopsy.*

Baseline FLT images will be visually assessed and compared to a combination of conventional tests including physical exam, direct laryngoscopy and nasopharyngoscopy, CT/MRI and FDG PET to calculate a lesion-based sensitivity for FLT PET.

Considerations for Sample Size Analysis:

Projected accrual in this protocol will be 48 patients. Recruitment is expected to take 2 years. Each patient will be followed for a minimum of two years. Based on past experience we project that 2-year progression free survival in these patients will be approximately 70%. Thus we project 34 patients will be free of progression at 2 years and 14 will have progressed.

Under these assumptions, the projected sample size will be adequate to ensure that the following expected half-length of the 95% confidence interval for the area under the ROC curve (AUC)

True AUC	0.7	0.75	0.8	0.85	0.90
Half-length of 95% CI	017	0.16	0.15	0.13	0.11

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Bibliography and References Cited:

Apisarnthanarax, S., Alauddin, M. M., Mourtada, F.*, et al.* (2006). "Early detection of chemo radioresponse in esophageal carcinoma by 3'-deoxy-3'-3H-fluorothymidine using preclinical tumor models." Clin Cancer Res 12(15): 4590-7.

Barthel, H., Cleij, M. C., Collingridge, D. R.*, et al.* (2003). "3'-deoxy-3'-[18F] fluorothymidine as new marker for monitoring tumor response to antiproliferative therapy in vivo with positron emission tomography." Cancer Res 63(13): 3791-8.

Blasberg, R. G., Roelcke, U., Weinreich, R.*, et al.* (2000). "Imaging brain tumor proliferative activity with [124I]iododeoxyuridine." Cancer Res 60(3): 624-35.

Buck, A. K., Halter, G., Schirrmeister, H.*, et al.* (2003). "Imaging proliferation in lung tumors with PET: 18F-FLT versus 18F-FDG." J Nucl Med 44(9): 1426-31.

Cobben, D. C., van der Laan, B. F., Maas, B.*, et al.* (2004). "18F-FLT PET for visualization of laryngeal cancer: comparison with 18F-FDG PET." J Nucl Med 45(2): 226-31.

Dobrowsky, W., Dobrowsky, E. and Wilson, G. D. (2003). "In vivo cell kinetic measurements in a randomized trial of continuous hyperfractionated accelerated radiotherapy with or without mitomycin C in head-and-neck cancer." Int J Radiat Oncol Biol Phys 55(3): 576-82.

Francis, D. L., Freeman, A., Visvikis, D.*, et al.* (2003). "In vivo imaging of cellular proliferation in colorectal cancer using positron emission tomography." Gut 52(11): 1602-6.

Garden, A. S., Harris, J., Vokes, E. E.*, et al.* (2004). "Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase ii trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck." J Clin Oncol 22(14): 2856-64.

Giri, U., Ashorn, C. L., Ramdas, L.*, et al.* (2006). "Molecular signatures associated with clinical outcome in patients with high-risk head-and-neck squamous cell carcinoma treated by surgery and radiation." Int J Radiat Oncol Biol Phys 64(3): 670-7.

Greven, K. M., Williams, D. W., 3rd, McGuirt, W. F., Sr.*, et al.* (2001). "Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer." Head Neck 23(11): 942-6.

Heagerty P, Zehng Y. Survival model predictive accuracy and ROC curves. Biometrics, 2005;61:92-105

Hsieh, F. Y. and Lavori, P. W. (2000). "Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates." Control Clin Trials 21(6): 552-60.

Khan, N., Oriuchi, N., Ninomiya, H.*, et al.* (2004). "Positron emission tomographic imaging with 11C-choline in differential diagnosis of head and neck tumors: comparison with 18F-FDG PET." Ann Nucl Med 18(5): 409-17.

Klabbers, B. M., Lammertsma, A. A. and Slotman, B. J. (2003). "The value of positron emission tomography for monitoring response to radiotherapy in head and neck cancer." Mol Imaging Biol 5(4): 257-70.

Leyton, J., Latigo, J. R., Perumal, M.*, et al.* (2005). "Early detection of tumor response to chemotherapy by 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography: the effect of cisplatin on a fibrosarcoma tumor model in vivo." Cancer Res 65(10): 4202-10.

Machulla HJ, B. A., Kuntzsch M, et al. (2000). "Simplified labeling approach for synthesizing 3'-deoxy-3'-[18F]fluorothymidine ([18F]FLT)." J Radioanal Nucl Chem 24: 843–6.

Patlak, C. S. and Blasberg, R. G. (1985). "Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations." J Cereb Blood Flow Metab 5(4): 584-90.

Pio, B. S., Park, C. K., Pietras, R.*, et al.* (2006). "Usefulness of 3'-[F-18] fluoro-3'-deoxythymidine with positron emission tomography in predicting breast cancer response to therapy." Mol Imaging Biol 8(1): 36-42.

Ponto, L. L., Graham, M. M., Richmond, J. C.*, et al.* (2002). "Contamination levels in blood samples drawn from the injection intravenous line." Mol Imaging Biol 4(6): 410-4.

Silvestrini, R., Molinari, R., Costa, A., Volterrani, F. and Gardani, G. (1984). "Short-term variation in labeling index as a predictor of radiotherapy response in human oral cavity carcinoma." Int J Radiat Oncol Biol Phys 10(7): 965-70.

Shields, A.F., Grierson J.R., Dohmen B.M. *et al.* (1998) Imaging proliferation in vivo with [F-18] FLT and positron emission tomography. Nat Med. 4:1334-6.

Sugiyama, M., Sakahara, H., Sato, K.*, et al.* (2004). "Evaluation of 3'-deoxy-3'-18F-fluorothymidine for monitoring tumor response to radiotherapy and photodynamic therapy in mice." J Nucl Med 45(10): 1754-8.

Valente, G., Orecchia, R., Gandolfo, S.*, et al.* (1994). "Can Ki67 immunostaining predict response to radiotherapy in oral squamous cell carcinoma?" J Clin Pathol 47(2): 109-12.

van Waarde, A., Cobben, D. C., Suurmeijer, A. J.*, et al.* (2004). "Selectivity of 18F-FLT and 18F-FDG for differentiating tumor from inflammation in a rodent model." J Nucl Med 45(4): 695-700.

Vesselle, H., Grierson, J., Muzi, M.*, et al.* (2002). "In vivo validation of 3'deoxy-3'-[(18)F]fluorothymidine ([(18)F]FLT) as a proliferation imaging tracer in humans: correlation of [(18)F]FLT uptake by positron emission tomography with Ki-67 immunohistochemistry and flow cytometry in human lung tumors." Clin Cancer Res 8(11): 3315-23.

Wilson, G. D., Paschoud, N., Pavy, J. J.*, et al.* (1999). "Reproducibility of measurements of potential doubling time of tumour cells in the multicentre National Cancer Institute protocol T92-0045." Br J Cancer 79(2): 323-32.

Wong, R. J., Lin, D. T., Schoder, H.*, et al.* (2002). "Diagnostic and prognostic value of [(18)F]fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma." J Clin Oncol 20(20): 4199-208.

Yao, M., Graham, M. M., Hoffman, H. T.*, et al.* (2004). "The role of post-radiation therapy FDG PET in prediction of necessity for post-radiation therapy neck dissection in locally advanced head-and-neck squamous cell carcinoma." Int J Radiat Oncol Biol Phys 59(4): 1001-10.

Yao, M., Smith, R. B., Graham, M. M.*, et al.* (2005). "The role of FDG PET in management of neck metastasis from head-and-neck cancer after definitive radiation treatment." Int J Radiat Oncol Biol Phys 63(4): 991-9.

Yao, M., Dornfeld, K. J., Buatti, J. M.*, et al.* (2005). "Intensity-modulated radiation treatment for head-and-neck squamous cell carcinoma--the University of Iowa experience." Int J Radiat Oncol Biol Phys 63(2): 410-21.

Zackrisson, B., Flygare, P., Gustafsson, H., Sjostrom, B. and Wilson, G. D. (2002). "Cell kinetic changes in human squamous cell carcinomas during radiotherapy studied using the in vivo administration of two halogenated pyrimidines." Eur J Cancer 38(8): 1100-6.

INFORMED CONSENT DOCUMENT

Evaluation of Response to Chemoradiation Therapy in Patients with Locally Advanced Head and Neck Cancer using F-18 Fluorothymidine Positron Emission Tomography

Yusuf Menda, MD et al

What Is The Purpose Of This Study?

This is a research study. We are inviting you to participate in this research study because you have cancer of the head and neck and it has been recommended you receive radiation therapy combined with chemotherapy.

The main purpose of this research study is to learn if a new imaging study, Positron Emission Tomography (PET) scan using F-18 Flurothymidine (FLT), can be used to see how well your cancer treatment is working. FLT is an imaging drug, which is imaged with a PET scanner. We want to study the concentration of FLT in the tumors before treatment and how it changes with treatment. FLT is considered investigational. This means it has not been approved by the U.S. Food and Drug Administration (FDA).

How Many People Will Participate?

Approximately 48 people will take part in this study at the University of Iowa.

How Long Will I Be In This Study?

If you agree to take part in this study, you will be in it for about 3-5 weeks. We will first see you for a screening visit. You will have 3 FLT PET scans altogether. Your first FLT PET scan will be within 14 days before you start your cancer treatment. You will have a second FLT PET scan after 3-5 days of radiation treatment and a third and final FLT PET scan 19-21 days after you started your cancer treatment. We will follow your progress for 2 years after completion of your treatment using your clinical chart at the University of Iowa.

What Will Happen During This Study?

1. You will have an FLT PET scan in Nuclear Medicine. You will be there for about 3 to 4 hours.
   a. The FLT PET scan will be arranged for you by the department of Radiation Oncology.
   b. If you are a woman who is capable of becoming pregnant, you will have a urine pregnancy test done in Nuclear Medicine, and you will need to sign a form stating that you could not have become pregnant within the past 14 days. Pregnant women may not participate in this study because there may be long term effects of this study that could increase the risk to an unborn child.

c. We will place an intravenous (IV) catheter in your arm. A catheter is a small flexible tube that can be used to put fluids or medicines into your vein. We will use this to inject the FLT and collect some blood samples. The amount of blood samples will total to about 60 ml (about 4 tablespoons).
e. We will place an arterial catheter at your wrist to take blood samples. This is different than the IV catheter. This small tube will be placed in an artery. We will use a local anesthesia to numb the area to minimize discomfort.
f. A nuclear medicine technologist will help you lay down on the PET scanner and help you get comfortable. An initial image will be obtained for 5-10 min.
g. The FLT will be administered through the IV tube.
h. The next series of images will start. This will last for about 2 hours. You may fall asleep if you would like. If there is a break in the scans, the technologist will tell you so you may get up and stretch.
i. At the end of the scans, the IV and arterial lines will be removed.
j. We will monitor you for 30 minutes after removing the arterial line to make sure everything is okay. We will tell you how to take care of the site where the arterial line was placed. You will then be able to go home.

2. You will start your chemotherapy and radiation therapy that your doctor has prescribed for you.
3. Between 3rd and 6th radiation treatment day, you will have another FLT PET scan. This scan will be similar to the first scan except that no arterial line will be placed and no blood samples will be collected.
4. Between 19-21 days after you start your cancer treatment, you will have the 3rd and final FLT PET scan. This scan will be exactly like your first FLT PET scan.

The PET scan results are research only and will not be used in making any decisions about your cancer treatment. For this reason, the results will be kept in a research chart, separate from your UIHC medical chart. This study will not add any information to your personal medical record.

What Are The Risks Of This Study?

There may be some risks from being in this study.

From the arterial line, you will experience some pain, and may experience bleeding, clotting, or bruising at the line site.

From the PET scan, you may feel uncomfortable lying still on your back for an extended period of time. Also, because the PET scanner is like a tube, you may feel "confined." In order to minimize these discomforts, we will try to make you as comfortable as possible before the scanning begins. You may sleep during the scanning time.

You may develop a discoloration (bruise) underneath your skin at the place where we take your blood and administer the FLT. You may feel lightheaded after we take your blood. If you do, tell a nurse right away. The place of the needle-stick may also get infected, as any cut would. You may also have a risk of clotting or

continued bleeding. A physician will be available at all times if you have any questions or problems during the procedure or after it.

The amount of radiation that you will receive from this study is equivalent to approximately 30% of the annual allowable radiation exposure for a medical worker involved within nuclear medicine or for X-ray procedures. Although there are no proven harmful effects from the radiation you will receive during this study, long-term effects of this radiation on your health cannot be excluded with certainty.

If you feel you are experiencing a side effect contact the study coordinator at (319) 356-7601 during weekday daytime hours or, after hours, call (319) 356-1616 and ask for the radiologist on call and tell them that you are a participant in Dr. Menda's study.

There is also a risk of loss of confidentiality of your medical information. We will not place your name on any of the research forms, but will use a number to identify the form and samples. If a paper is published using data from this study, your name and any identifying information will not be mentioned in the publication. If you believe confidential information about you has not been handled correctly, you can contact the study coordinator at (319) 356-7601.

Are There Any Unforeseen Risks?

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

What Are The Benefits Of This Study?

You will not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study, if FLT PET imaging proves to be a useful method for evaluating the efficacy of the treatment.

Will It Cost Me Anything To Be In This Study?

You will not have costs for being in this research study. You will not be billed for the FLT PET scans specifically done for this study.

You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses, including your chemotherapy and radiation therapy, and any hospital or clinic stays, as these are not part of this research study.

Will I Be Paid For Participating?

You will not be paid for being in this research study.

Who Is Funding This Study?

What If I Am Injured As A Result Of This Study?

If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.

No compensation for treatment of research-related illness or injury is available from the University of Iowa unless it is proven to be the direct result of negligence by a University employee.

If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

What About Confidentiality?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people may become aware of your participation in this study. For example, federal government regulatory agencies and the University of Iowa Institutional Review Board (a committee that reviews and approves research studies) may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

To help protect your confidentiality, we will identify you only by a coding system on any data, forms, or samples, including your biopsy sample and blood samples. The information is kept is in locked filing cabinets and storage areas, and the computers are password protected. To help any physicians in your treatment, and to make them aware you are on a study, a copy of this informed consent document will be placed in your UIHC medical record/chart. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The Informed Consent Document will be placed in your medical record.

Will My Health Information Be Used During This Study?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study. Once University of Iowa Health Care has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff and The Holden Comprehensive Cancer Center's Data and Safety Monitoring Board. You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes **University of Iowa Health Care** to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to:

Dr. Yusuf Menda
Department of Radiology
3858 JPP
University of Iowa Hospitals and Clinics
Iowa City, Iowa 52242

However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

Is Being In This Study Voluntary?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to drop out of the study?

If you decide to leave the study early, we may call and ask you how you are doing and how you feel.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?

Under certain circumstances, the researchers or the study sponsor might decide to end your participation in this research study earlier than planned. This might happen because you became pregnant or because funding for the research study has ended.

What if I have questions?

We encourage you to ask questions. If you have any questions about the research study itself, please contact:

Dr. Yusuf Menda
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3858 JPP
University of Iowa Hospitals and Clinics
Iowa City, Iowa 52242

If you feel you are experiencing a side effect contact the study coordinator at (319) 356-7601 during weekday daytime hours or, after hours, call (319) 356-1616 and ask for the radiologist on call and tell them that you are a participant in Dr. Menda's study.

If you have questions about the rights of research subjects or research related injury, please contact:

The Human Subjects Office
300 College of Medicine Administration Building
The University of Iowa
Iowa City, IA 52242
(319) 335-6564
or e-mail **irb@uiowa.edu**

General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://research.uiowa.edu/hso