A Study Using Fluorine-18-Labeled Fluoro-Misonidazole Positron Emission Tomography to Detect Hypoxia in Head and Neck Cancer Patients

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.0 PROTOCOL SUMMARY AND SCHEMA

This is a study utilizing the hypoxia tracer fluorine-18-labeled fluoro-misonidazole (^{18}F-FMISO) to evaluate the presence and bio-distribution of tumor hypoxia in head and neck cancer patients. Two cohorts of patients will be accrued to this protocol:

- Cohort 1 will consist of 150 head and neck cancer patients over a 5-year accrual period who are not expected to undergo surgical resection of their cancer. This cohort will consist of 100 patients with Human Papilloma Virus positive (HPV+) tumors and 50 patients with Human Papilloma Virus negative (HPV-) tumors.

- Cohort 2 will consist of 19 head and neck cancer patients who will undergo surgery for their cancer per standard of care.

When possible, we will also obtain multi-parametric magnetic resonance (MR) scans consisting of conventional anatomical MR imaging (e.g. T1- and T2-weighted), diffusion-weighted MR imaging (DW-MRI), and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI). These MR scans will be utilized to assess changes in MR intensities and the perfusion and diffusion of water molecules in tumor and irradiated normal structures during and after the course of fractionated external beam radiation therapy (RT). The DCE-MRI data will provide insight into the tumor pathophysiology. With proper compartmental modeling, the DCE-MRI data will yield results on tumor-vessel permeability, tumor perfusion, and extracellular-extravascular volume fraction, i.e. data relating to the tumor microenvironment. These results will determine the potential of DCE-MRI data as a priori or early markers of tumor response to chemoradiation as well as long term disease-free survival after treatment.

This study will further entail the first human study of ^{18}F-FMISO PET image-guided core biopsy of neck node(s) in both HPV+ and HPV- head and neck squamous cell carcinoma (HNSCC; for Cohort 1 patients that consent to this optional biopsy). Additional tissue will be collected from patients who will undergo surgical resection of their cancer per standard of care (Cohort 2). We will correlate the intensity of the ^{18}F-FMISO PET signal with the degree of immunohistochemical staining of the following hypoxia biomarkers, among others: HIF-1α, Lysyl Oxidase, and Ki67 (an independent marker of tumor aggressiveness).

Lastly, this study will evaluate a number of treatment approaches to HPV-related head and neck cancer. The approaches applicable to Cohort 1 of this study are outlined below:

1. Definitive chemoradiation without pretreatment surgical resection in which both the primary tumor site and the neck nodes receive 70Gy. In patients who exhibit a complete nodal response with this treatment, no further treatment is necessary.
2. Definitive chemoradiation without pretreatment surgical resection in which the primary site receives 70Gy while the neck nodes receive a lower dose of radiation at 60Gy instead of 70Gy. This definitive chemoradiation is followed by a FDG PET/CT scan at 3 months (+/- 4 weeks) post-treatment. In patients who exhibit a

complete nodal response with this method of treatment (as determined by the 3-month post-treatment FDG PET/CT scan), no further treatment is necessary.

Patients enrolled on to this protocol who will receive either of the treatments above (i.e. those without surgical resection of their cancer) will be included in Cohort 1, and will continue with standard institutional care in the case of incomplete or no nodal response. The information obtained from the use of ^{18}F-FMISO PET scans in Cohort 1 will be used to guide these patients' treatment on this protocol. HPV+ head and neck cancer patients in Cohort 1 that exhibit no evidence of hypoxia on their baseline ^{18}F-FMISO PET scan and HPV+ head and neck cancer patients in Cohort 1 with early resolution of hypoxia on their repeat ^{18}F-FMISO PET scan will receive 70Gy to the primary site and 60Gy to the neck nodes followed by a FDG PET/CT scan and observation.

Cohort 2 of this protocol will consist of patients who are to receive surgical resection of their tumor. Following this surgery, patients may or may not undergo adjuvant radiation with or without concurrent chemotherapy, which is dependent on the pathologic features of their disease. Within this cohort, select HPV+ tumors that demonstrate no evidence of hypoxia on a ^{18}F-FMISO PET scan will receive 30Gy to the surgical bed and neck lymph nodes concurrent with standard chemotherapy followed by a 3 to 4-month post-treatment neck dissection. In patients who exhibit a complete response with this method of treatment, no further treatment is necessary. For patients within this select group who still have pathologic nodal disease, further standard chemoradiation will be given. All other patients in this cohort (i.e. those who are not in the select HPV+ tumor group outlined above) will receive standard of care treatment following their surgery.

Please note the ^{18}F-FMISO PET imaging protocol is exactly the same for all patients on this protocol, regardless of cohort.

Schema:

1.1 Evaluation, determination of cohort, and consent.

1.2 Baseline studies (standard of care) for head and neck cancer.

1.3 Perform a pretreatment FDG PET/CT scan for Cohort 1 patients.

1.4 Perform a recommended pretreatment multiparametric MRI scan for Cohort 1 patients. This scan will be used to derive a pixel-by-pixel mapping of true diffusion (D), perfusion fraction (f), and apparent diffusion coefficient (ADC) using available software when available (unless contraindicated; for main campus only).

1.5 Prior to the injection of the ^{18}F-FMISO radiotracer, check the patient's vital signs.

1.6 Perform a pretreatment dynamic ^{18}F-FMISO PET/CT scan. This scan will be used to verify the constancy of the hypoxic regions within the gross tumor volume (GTV_h).

1.7 A safety assessment will be performed: vital signs and a toxicity assessment will be completed immediately after the scan session, and a follow-up phone call to assess for toxicities will be done on the next business day following the ^{18}F-FMISO PET/CT scan (excluding holidays and weekends).

1.8 An ^{18}F-FMISO PET image-guided core biopsy procedure of the neck nodes will be performed after the last ^{18}F-FMISO PET image acquisition for Cohort 1. This biopsy procedure will only occur if the patient consents to the procedure and if the procedure is deemed applicable by the Principal Investigator.

1.9 Surgical resection for Cohort 2 (if it has not already occurred) and collection of the resected tissue for the correlation of ^{18}F-FMISO PET/CT signal with the degree of immunohistochemical staining of hypoxia biomarkers.

1.10 Prior to the injection of the ^{18}F-FMISO radiotracer for the repeat ^{18}F-FMISO PET/CT scan for patients deemed eligible for a repeat ^{18}F-FMISO PET/CT scan, check the patient's vital signs.

1.11 Perform a repeat dynamic ^{18}F-FMISO PET/CT scan early during the course of chemoradiotherapy (5-10 treatment days after the start of radiation therapy) for patients deemed eligible for a repeat ^{18}F-FMISO PET/CT scan. This scan will be utilized to determine whether there is a reduction of the ^{18}F-FMISO-avid or GTV_h within the gross tumor volume.

1.12 A safety assessment will be performed for patients who received a repeat ^{18}F-FMISO PET/CT scan: vital signs and a toxicity assessment will be completed immediately after the scan session, and a follow-up phone call to assess for toxicities will be done on the next business day following the ^{18}F-FMISO PET/CT scan (excluding holidays and weekends).

1.13 An ^{18}F-FMISO PET image-guided core biopsy procedure of the neck nodes will be performed after the last ^{18}F-FMISO PET image acquisition for Cohort 1. This biopsy will only occur if the patient consents to the procedure and if the procedure is applicable as determined by the Principal Investigator.

1.14 Perform recommended approximately weekly MRI scans during treatment, unless contraindicated, for main campus Cohort 1 patients. A DCE-MRI is recommended between the first and second weeks of

treatment and between the third and fourth weeks of treatment, unless contraindicated, for main campus Cohort 1 patients. Subjects with a known contraindication to the standard MRI contrast agent (Gadavist; a gadolinium-based contrast agent) and/or a recent estimated glomerular filtration rate (eGFR) of 30 or less will be excluded from all recommended DCE-MRIs, and will instead receive recommended non-contrast MRIs at the DCE-MRI time points.

1.15 Recommended MRI scans, unless contraindicated, will also be repeated at 3 months, 6 months, and 1 year post-external beam RT for Cohort 1 patients. The time windows for these MRI scans will be +/- 4 weeks. Only Cohort 1 patients on main campus will receive these recommended MRIs.

1.16 Perform a FDG PET/CT scan at 3 months (window +/- 4 weeks) post-RT for Cohort 1 patients. Perform a planned neck dissection at three to four months (+/- four weeks) post-RT for Cohort 2 patients who received 30Gy.

1.17 Standard of care follow-up.

1.18 Longitudinal chart review for adverse event assessment, locoregional control rates, and disease status as assessed through standard of cares through two years post-treatment for Cohort 1 and Cohort 2.

2.0 OBJECTIVES

Primary

- To improve the accuracy of hypoxia imaging for head and neck cancers through pixel by pixel kinetic analysis of ^{18}F-FMISO tracer of dynamic PET images (Cohort 1 and Cohort 2).
- To detect on repeat ^{18}F-FMISO PET/CT scans whether there is a reduction of the ^{18}F-FMISO-avid or GTV_h 5 to 10 days into treatment with standard chemoradiotherapy for a series of locally advanced head and neck cancers (Cohort 1).
- To show that it is feasible to deliver 70Gy to primary site and 60Gy to the neck nodes in HPV+ patients who exhibit no evidence of hypoxia on their baseline ^{18}F-FMISO PET/CT scans or those who have early resolution of hypoxia on their early repeat ^{18}F-FMISO PET/CT scans (Cohort 1).
- To show that it is feasible to deliver 30Gy to the surgical bed and neck nodes in low-risk HPV+ patients who exhibit no evidence of hypoxia on their repeat ^{18}F-FMISO PET/CT (Cohort 2).
- To correlate the intensity of the ^{18}F-FMISO PET signal with the degree of immunohistochemical staining of hypoxia biomarkers for tissue obtained via biopsy (Cohort 1) and surgical resection (Cohort 2): HIF-1α, Lysyl Oxidase, and Ki67 (an independent marker of tumor aggressiveness), among others.

Secondary

- To compare tumor heterogeneity derived from pixel-by-pixel kinetic analysis of PET scan and DWI-MRI (Cohort 1).
- To assess changes in tumor heterogeneity over the course of external beam RT using serial multiparametric MR and DCE-MRI scans (Cohort 1).
- To determine the potential of DCE-MRI data as a priori or early markers of tumor response to chemoradiation as well as long term disease-free survival after treatment (Cohort 1).
- To assess normal tissue response as a function of dose for parotid, submandibular glands, muscles and bones in the head and neck region during and after EBRT using serial multiparametric MR scans (Cohort 1).
- To bank specimens for further IRB/PB approved exploration of genetic analysis (Cohort 1 and Cohort 2).

3.0 BACKGROUND AND RATIONALE

Hypoxia

Hypoxia is a characteristic feature of malignant tumors that has been well established (1, 2). Unlike healthy tissues, many tumors contain a fraction of hypoxic cells, which immunohistochemical studies suggest consist of nests of cells of up to several hundred micrometers in diameter, located at poorly perfused locations within the tumor (3). It is well known that hypoxia renders tumor cells up to three times more resistant to ionizing radiation than aerobic cells (1-3). In addition to increased radioresistance, hypoxia is associated with a more aggressive and metastatically viable malignant phenotype. It has been shown in several studies to be an important determinant of loco-regional control of head and neck tumors (4, 5). Positron Emission Tomography (PET) is a noninvasive imaging modality with the potential to identify tumor hypoxia at both global and local levels through the use of hypoxia targeting molecules. If these hypoxic regions are identified, they may be specifically targeted with additional radiation and perhaps translate into further improvement in local control.

^{18}F-FMISO PET/CT Scan

A recently developed PET imaging-based hypoxia measurement technique using ^{18}F-FMISO can detect and quantify hypoxic regions within a tumor (6). Misonidazole is a hypoxic cell radiosensitizer, which is preferentially and metabolically reduced and entrapped within hypoxic cells and not aerobic cells. An ^{18}F-FMISO PET/CT scan is a noninvasive imaging method in detecting tumor hypoxia. In a R3327-AT Dunning rat prostate tumor model at Memorial Sloan Kettering Cancer Center (MSKCC), microPET imaging of ^{18}F-FMISO has been used to detect tumor hypoxia, followed by direct pO_2 verification of the hypoxic regions by using the pO_2 Oxylite probe.

PET studies using hypoxic markers have also been performed in patients at numerous institutions (e.g. Rasey et al) (6). A phase I trial of using concurrent tirapazamine, a hypoxic cell sensitizer, cisplatin, and radiotherapy in the treatment of advanced head and

neck cancer has been done at the Peter MacCallum Cancer Institute in Australia (8). All patients underwent ^{18}F-FMISO PET to provide evidence of tumor hypoxia. All patients also had baseline FDG PET scans and the scan was co-registered with the ^{18}F-FMISO PET. ^{18}F-FMISO PET scans in this study were obtained 2 hours after radiotracer administration. All PET imaging was performed on a dedicated PET scanner with the data processed using measured attenuation correction and iterative reconstruction. Fourteen out of the 15 patients studied had detectable hypoxia on baseline ^{18}F-FMISO scan with focal abnormality corresponding to a region of increased FDG uptake in either the primary lesion or the nodal mass. In all cases, the intensity of ^{18}F-FMISO uptake was less than the corresponding FDG abnormality. On the co-registered PET images, in the necrotic lesions, evidenced by central photopenia on FDG PET, ^{18}F-FMISO was distributed only at the inner border of FDG uptake, whereas in lesions without necrosis on FDG PET, only the central part of the metabolically active lesion had ^{18}F-FMISO retention. In all but only one of the 14 cases with an initially positive ^{18}F-FMISO PET showed complete resolution of the abnormality within 4-5 weeks of treatment. The pattern of ^{18}F-FMISO uptake was consistent with the expected pattern of hypoxia in tumor tissue being adjacent to areas of tumor necrosis or in the center of non-necrotic lesions. The rapid normalization of ^{18}F-FMISO PET suggests successful treatment of the hypoxic component.

We have performed preliminary clinical studies with ^{18}F-FMISO obtaining PET images at 2.5 hours post-injection for 20 head and neck cancer patients (MSKCC 04-070). These studies focused first on determining the constancy of ^{18}F-FMISO PET image sets when repeat scans were performed 3 days apart (an essential pre-requisite for IMRT dose painting). Preliminary results demonstrated that imaging of hypoxic subvolumes (GTV_h) is feasible and that reproducible zones of hypoxic tracer uptake are observed (7). We also performed a third ^{18}F-FMISO scan on patients at four weeks into their radiotherapy treatment (MSKCC 04-070). The objective of this third scan was to determine whether tumor reoxygenation occurred, as indicated by no ^{18}F-FMISO uptake, or whether hypoxia persisted throughout treatment. Our finding from this second clinical study objective, as evidenced by 18/20 patients exhibiting no ^{18}F-FMISO uptake, was that hypoxia is no longer evident late into a course of radiotherapy. Patients in this cohort experienced at 95% nodal control rate (9). The possibility of tumor reoxygenation early during the course of fractionated radiotherapy cannot be overlooked. Therefore, in the current version of this protocol, our goal is to perform a repeat ^{18}F-FMISO PET/CT scan early in the course of standard chemotherapy and fractionated radiotherapy (5 to 10 treatment days) for a series of locally advanced head and neck cancer patients (Cohort 1). If these repeat scans also demonstrate no evidence of residual ^{18}F-FMISO uptake early in the course of fractionated radiotherapy, this information will have major implications for hypoxia-guided fractionated radiotherapy.

In summary, hypoxia is a characteristic feature of malignant tumors that can render tumor cells up to three times more resistant to ionizing radiation than aerobic cells. With the use of ^{18}F-FMISO PET, a noninvasive imaging modality, hypoxic subvolumes (GTV_h) within a tumor can be identified. If these hypoxic regions are identified and verified, they may be specifically targeted by the delivery of more ionizing radiation to that

specific region. Ultimately, by the delivery of a differential dose of radiation to the tumor, the local control rates of head and neck cancer patients may further be improved.

Multiparametric MRI

MRI is a non-invasive technique utilized to assess morphological and physiological changes in tumor and irradiated normal structures. In this study we will be taking a series of multiparametric MR images around the same time as ^{18}F-FMISO PET/CT that will enable a direct comparison between PET defined hypoxia volume and MR defined tumor volume. The excellent soft tissue contrast will aid in improved normal tissue contouring of salivary glands and lymph nodes which will ultimately help in further sparing of normal structures during external beam planning. Similar immobilization techniques employed during CT simulation and MR scan will help in co-registering MR images with CT and PET scans, when available.

Radiation of the head and neck can irreversibly damage oral mucosa, vasculature, muscle and bone resulting in xerostomia, dental caries, trismus, soft tissue necrosis and osteoradionecrosis. A change in intensity or image texture over the course of radiation obtained from these MR scans may be an indication of radiation damage to these sensitive structures. In addition, we hypothesize that perfusion and diffusion changes observed in tumor and normal structures could be dose dependent.

DW-MRI

DWI-MRI measures differences in tissue microstructures based on the random Brownian motion of water molecules in biological tissues. It quantifies the degree of restriction of water diffusion or tissue diffusivity and has the potential to differentiate benign lesions from malignant tumors. The quantitative measure of water mobility is calculated in terms of apparent diffusion coefficient (ADC) by varying the diffusion weighting or ‘b’ values. Tumors with more densely packed tumor cells and more cell membranes have a lower ADC due to greater restriction to diffusion. Non-tumoral tissue changes such as edema, inflammation, fibrosis, and necrosis typically have low cellularity and result in high ADC (28, 29). In addition to molecular diffusion of water in biological tissue, microcirculation of blood (or “perfusion”) in the capillary network can also be captured using low ‘b’ values. DWI-MRI using both low and high b values (also called intravoxel incoherent motion sequence or IVIM) gives a quantitative measure of true diffusion (D) and perfusion fraction (f) (30) without the use of an intravenous contrast agent.

DWI-MRI has been successfully applied for various disease sites. Its clinical applications in head and neck cancer have been in differentiating malignant tumors from benign lesions (31, 32), characterizing and staging of lymph nodes in the head and neck region (33) and monitoring tumor response (34, 35, 36, 37). A few studies have investigated the salivary gland response based on changes in ADC value (38, 39). Malignant tumors usually show low ADC values compared to benign tumors. A mean cut-off value of 1.2x10-3 for adult tumors and 1.25x10-3 for pediatric head and neck tumors has been shown to distinguish between malignant and benign tumors with 87% and 92.8%

accuracy, respectively (5). Dirix et al have shown superior accuracy of DW-MRI compared to conventional imaging in nodal staging where DW-MRI was shown to agree with pathology with a sensitivity of 89% and specificity of 97% per lymph node (33). Changes in ADC value have been shown to correlate significantly with 2-year local regional control based on multiple MRs taken over the course of chemotherapy (34, 35). In a chemoradiation setting, efficacy of ADC was investigated for prediction and early detection of treatment response. Changes in ADC, compared with pretreatment value, after the first week of chemoradiation therapy have shown high sensitivity and specificity in separating complete responders from partial responders (36).

Very few studies have looked at the utility of DWI for normal tissue response. Dirix et al and Zhang et al have looked at radiation induced changes in major salivary glands using DWI. ADC changes were inversely related to salivary flow measurements and may represent a sensitive marker of salivary gland dysfunction. Both these studies have shown potential to predict radiation-induced xerostomia. A more recent study from our group looked at the efficacy of pre-treatment multimodality imaging consisting of MRS, DCE-MRI and FDG PET (40) in head and neck cancer patients to predict short-term response to treatment. We are not aware of any studies that have looked at ^{18}F-FMISO and DW-MRI for tumor heterogeneity in head and neck cancer patients. In this study, when possible, we will obtain a MR scan before (Cohort 1 and Cohort 2 main campus patients), approximately weekly (Cohort 1 main campus patients only), and post-external beam RT at 3 months, 6 months, and 1 year after external beam RT (+/- 4 weeks; Cohort 1 main campus patients only), unless contraindicated. We will evaluate changes in tumor heterogeneity between PET and MR scans as markers of tumor response. Changes in perfusion and diffusion fraction for normal structures from serial MR scans over the course of radiation therapy will enable us to evaluate markers of radiation-induced acute and long term toxicities.

Treatment for Head and Neck Cancer

Currently, there are several approaches in the treatment of head and neck cancer.

1. Definitive chemoradiation where both the primary tumor site and the neck nodes receive 70Gy. In patients in whom a complete nodal response is achieved with this treatment, no further treatment such as neck dissection is needed.

2. Definitive chemoradiation where the primary site receives 70Gy while the neck nodes receive a lower dose of radiation at 60Gy instead of 70Gy. This treatment is then followed by a FDG PET/CT scan and continued observation.

3. Surgical resection of the tumor. Following this surgery, patients may or may not undergo adjuvant radiation with or without concurrent chemotherapy. The utilization of radiation and/or chemotherapy following surgical resection is dependent on the staging and pathologic features of the disease/resected tissue, among other risk factors.

Although a high loco-regional control rate of >90% is seen for oropharyngeal carcinoma treated with chemoradiation, patients still experience significant acute and late toxicities (13, 45). These toxicities are particularly concerning considering the increasing prevalence of HPV-associated head and neck carcinoma (42), particularly those of the base of tongue and tonsillar sites (both anatomical sites of the oropharynx) in individuals ages 20-44 in the United States (46). This latter statistic will ultimately coincide with longer-lasting long-term morbidities associated with OPSCC-targeted chemoradiation, which may have significant social and financial implications in the future (45) and an adverse effect on the long-term quality of life of patients who undergo this treatment.

Given the recent rise in HPV-related oropharyngeal carcinoma and the toxicities associated with the standard treatment course for this disease, an investigation into the efficacy and safety of treatment de-escalation to reduce the morbidity associated with the treatment of this disease is warranted. This is particularly true for the cohort of patients who present with HPV-related oropharyngeal carcinoma, as these patients are more likely to be younger and healthier than those presenting with non-HPV-related disease. When making the determination of which patients should undergo a less intense treatment regiment, it is important to make an evidence-guided selection. This cohort should only include patients most likely to: (1) respond efficaciously to treatment reduction, and (2) maximally benefit from a decrease in treatment-related toxicities. Otherwise, unwarranted tumor recurrences may result.

A number of investigations have established that the prognosis of patients with HPV-related oropharyngeal carcinoma is superior to that of patients with non-HPV-related oropharyngeal carcinoma (41, 44, and 47). In addition to HPV status serving as a mediator of overall prognosis and treatment response, it is well known that the presence of hypoxia renders tumor cells up to three times more resistant to ionizing radiation than aerobic cells (1-3). Hypoxia is also associated with a more aggressive and metastatically viable malignant phenotype, and has been shown in several studies to be an important determinant of loco-regional control of head and neck tumors (4, 5).

At our institution, we have an active hypoxia imaging protocol, MSKCC IRB# 04-070, for all head and neck tumors regardless of HPV status. The first 20 head and neck cancer patients that were enrolled in this protocol were all treated with 70Gy to both the primary site and the neck nodes. An exceptionally high locoregional control rate of 95% was seen with a nodal control rate of 95% as well (9). Furthermore, all but two patients had resolution of their baseline hypoxia on repeat ^{18}F-FMISO PET/CT imaging.

When considering the evidence regarding HPV status and the effects of hypoxia on tumor response, it can be inferred that oropharyngeal carcinoma patients with the most superior prognosis are those who meet the following criteria: HPV-related and no evidence of hypoxia. Therefore, given: (1) the rise in HPV-related oropharyngeal carcinoma, (2) the significance and burden of oropharyngeal carcinoma treatment-related toxicities, and (3) in-house data where hypoxia response correlated with high loco-regional control, the current version of this protocol seeks the following for select patients in Cohort 1 (patients receiving chemoradiation without surgical resection):

A. to give HPV+ oropharyngeal carcinoma patients who demonstrate no evidence of hypoxia on a ^{18}F-FMISO PET/CT scan the option of an alternative standard approach to the treatment of oropharyngeal carcinoma through delivering 60Gy to the neck nodes followed by a FDG PET/CT scan. The primary site will receive 70Gy, and these patients will undergo standard chemotherapy regimens. Delivering 60Gy to the neck nodes followed by a FDG PET/CT scan and continued observation does not deviate from one current standard of care, and allows for the ability to deliver a lower dose of radiation to the neck with the goal of minimizing radiation toxicities while ensuring that no unwarranted compromise to the already excellent loco-regional control in this population occurs. All the imaging studies will be done exactly per protocol.

Similar to oropharyngeal cancer, rates of the oncogenic HPV-16 subtype have been demonstrated to be present in as many as 79% of HPV-related anal carcinoma cases (53). In the early 1970s, investigators at Wayne State University demonstrated that anal carcinoma (Nigro Protocol) could effectively be treated preoperatively with a concurrent course of chemotherapy with 30Gy (56). Results demonstrated 84% of patients to be free of cancer following treatment per the Nigro Protocol, suggesting 30Gy could effectively treat carcinomas when administered concurrently with chemotherapy. Furthermore, a 79% five-year overall survival rate was demonstrated (48). When utilizing salvage therapy in the setting of treatment failure with the Nigro Protocol, rates of successful treatment response, as defined by no evidence of disease at a mean of 34-months follow-up, have been documented to be as high as 95% (49).

When utilizing a combination of surgery, radiation, and chemotherapy for HPV-related oropharyngeal cancers today, a number of cancer treatment centers often omit radiation to the primary disease site in low-risk patients whose surgical margin is negative. When taking this into consideration with the evidence of HPV status on tumor response, hypoxia on tumor response, and the work that has been done in anal carcinoma, it can be inferred that low-risk HPV+ oropharyngeal carcinoma patients treated initially with surgical resection of their primary disease site may optimally respond to 30Gy with concurrent standard chemotherapy. The current version of this protocol seeks the following for select patients in Cohort 2 (patients receiving surgical resection of their cancer):

B. to give a select HPV+ tumors an alternative treatment for oropharyngeal carcinoma. This select cohort will be comprised of patients who meet all of the following criteria:

    1. resection of their primary tumor site
    2. low-risk HPV-related oropharyngeal carcinoma
    3. demonstrate no evidence of hypoxia on a ^{18}F-FMISO scan obtained 5-10 treatment days into radiation therapy

These patients will undergo post-operative standard chemotherapy regimens and 30Gy to the surgical bed and neck nodes. A planned neck dissection three to four months post-treatment will be given. Should there be any evidence of residual disease at the time of this neck dissection, additional chemoradiation will be given.

Please note that initially this pilot trial was written for 35 patients and after a meeting requested by the IRB with the PI and the coPI's, and with the advice from the IRB, it was decided to close the trial at patient 19 and write a new trial for cohort B. This new trial is MSKCC IRB 17-409.

Immunohistochemistry

Several studies examined the relationship between p16 expression by IHC and HPV DNA viral load by real-time PCR and found great correlation. These studies all uniformly showed that either is a good prognostic marker for treatment outcome. RTOG 0129 was a large randomized controlled clinical trial that was recently published for head and neck cancer of which there was a large tissue sample size that examined the relative strength of HPV DNA using in situ hybridization vis-a-vis p16 IHC as a prognostic marker (13). The study also showed that there was a very strong agreement between the presence of HPV DNA and p16 expression in head and neck tumors. Results of analyses using p16 expression as a stratification factor were consistent with those based on HPV status. Given p16 expression measured by IHC is a relatively simple procedure, we will stratify patients based on p16 status. This is also convenient for the patients as we will not have the need to subject the patients to further biopsy for HPV DNA analysis.

One important characteristic of tumor development is angiogenesis. Induced by hypoxia, the tumor cells secrete a variety of cytokines and growth factors that induce proliferation (evidenced by overexpression of Ki-67), migration, and blood vessel formation (23-25). Ki-67 is one known prognostic marker in head and neck squamous cell carcinoma (HNSCC) and is inversely related to the presence of hypoxia. The rationale is that a stronger and more widespread Ki-67 staining intensity signifies a higher fraction of proliferating cells in the tumor. Since cellular proliferation either does not occur or is greatly reduced within hypoxic tissue, we expect that high Ki-67 staining should be accompanied by low or absent ^{18}F-FMISO image intensity and vice versa.

Cellular response to hypoxia is regulated primarily through the transcriptional factor, hypoxia-inducible factor (HIF-1α), which is the central mediator of the angiogenic response in hypoxia. Studies have shown that the dysregulation of HIF-1α may play a role in the malignant progression of HNSCC (24, 25). Overexpression of HIF-1α has been reported as an independent prognostic factor in HNSCC and is associated with poor prognosis as well as locally aggressive behavior of HNSCC. In one series where a cohort of 98 patients were treated with curative radiation therapy for their oropharyngeal cancer,

94% showed overexpression of HIF-1α as determined by IHC (24). The degree of HIF-1α correlated inversely with both the rate of complete remission of the primary tumor as well as the lymph node metastases; local failure-free survival, disease-free survival, and overall survival. They concluded that HIF-1α is overexpressed in the vast majority of oropharyngeal cancer and that the degree of expression has prognostic significance in individuals undergoing curative radiotherapy. In addition, studies on gene expression have shown hypoxia induces metastasis-mediated genes. The overexpression of the recently identified lysyl oxidase (LOX) as a hypoxia and HIF-1α regulated gene was strongly associated with increased metastasis, progression and OS (26, 27). LOX has been implicated as a marker for metastasis and OS for HNSCC.

This is the first human study that that uses a non-invasive imaging technique for hypoxia (^{18}F-FMISO PET/CT) for the purposes of immunohistochemistry (IHC) correlation for tissue markers of hypoxia. To date, nearly 20 biopsy specimens have been obtained on this protocol where an interventional radiologist biopsied areas that demonstrated high ^{18}F-FMISO uptake on the ^{18}F-FMISO PET/CT scan. However, initial results from these biopsies have demonstrated that nearly 50% of these specimens did not contain tumor cells, despite being obtained from both FDG avid and ^{18}F-FMISO avid regions. Only stromal, fibrous, and lymphoid tissues were able to be identified. In order to overcome the sampling error associated with small needle biopsy, we will obtain more tumor tissue without deviating from current standards of care for head and neck cancer. Given that one current standard in the treatment of loco-regionally advanced oropharyngeal cancer is surgical resection using the robotic surgery technique, we plan to utilize the surgical specimens of these patients for our IHC hypoxia studies. Furthermore, we will image these patients with an ^{18}F-FMISO PET/CT scan prior to their standard of care pretreatment surgical resection in order to correlate hypoxia on imaging with IHC performed on their surgical specimen. The surgeons performing these surgical resections will be asked to orient their surgical specimen according to the ^{18}F-FMISO PET/CT. Patients undergoing this standard of care surgical resection will make up Cohort 2 of this protocol.

In summary, we will perform the first human study of ^{18}F-FMISO PET image-guided core biopsy of neck node(s) in both HPV positive and negative HNSCC (for Cohort 1 patients that consent to this optional biopsy). Additional tissue will be collected from patients who will undergo surgical resection of their HNSCC per standard of care (Cohort 2). We will correlate the intensity of the ^{18}F-FMISO PET signal with the degree of IHC staining of the following hypoxia biomarkers, among others: HIF-1α, Lysyl Oxidase, and Ki67 (an independent marker of tumor aggressiveness).

4.0 OVERVIEW OF STUDY DESIGN AND INTERVENTION

4.1 Design

PROTOCOL SUMMARY

TIMEPOINT	COHORT 1	COHORT 2
Pretreatment	*All Patients*	*All Patients*

	1) Patient simulation. 2) FDG scan with immobilization. 3) Recommended pretreatment MR scan with immobilization when possible (unless contraindicated, for main campus only). 4) ^{18}F-FMISO scan (only 1 injection). Patient injected on the PET scanner: (a) Dynamic scan from 0-45 min (b) 10 min scan at about 90 min (c) 10 min scan at about 150-180 min 5) ^{18}F-FMISO image-guided core biopsy (optional, if consented)	1) ^{18}F-FMISO scan (only 1 injection). Patient injected on the PET scanner: (a) Dynamic scan from 0-45 min (b) 10 min scan at about 90 min (c) 10 min scan at about 150-180 min
During Treatment	*Select Patients* 1) Repeat ^{18}F-FMISO scan (only 1 injection) that occurs 5-10 treatment days after RT start*. Patient injected on the PET scanner: (a) Dynamic scan from 0-45 min (b) 10 min scan at about 90 min (c) 10 min scan at about 150-180 min 2) ^{18}F-FMISO image-guided core biopsy (optional, if consented) 3) Recommended approximately weekly MRI when possible (unless contraindicated, for main campus only). Recommended DCE-MRI between treatment weeks one and two and between treatment weeks three and four, when possible.	*Patients who Receive Radiation* 1) Repeat ^{18}F-FMISO scan (only 1 injection) that occurs 5-10 treatment days after RT start*. Patient injected on the PET scanner: (a) Dynamic scan from 0-45 min (b) 10 min scan at about 90 min (c) 10 min scan at about 150-180 min
Post-treatment	*All Patients* 1) Recommended MR Scans at 3, 6, and 12 months (+/- 4 weeks) post end of RT (unless contraindicated, for main campus only) 2) Longitudinal chart review for two years post RT for adverse event assessment and disease status	*Patients Who Receive 30Gy* 1) Neck dissection three to four months post-chemoradiation (+/- 4 weeks). (a) If no residual disease, standard of care (b) If residual disease, booster dose of chemoradiation 2) Standard of care

Please note that a window period of 5-10 treatment days was chosen to accommodate holidays, weekends, and patient scheduling issues. Also, note that the repeat dynamic ^{18}F-FMISO scan is performed early during the course of chemoradiotherapy (5-10 treatment days). For Cohort 1, this scan will be used to see whether there is a reduction of the ^{18}F-FMISO avid or GTV_h within the gross tumor volume. For patients in Cohort 2 receiving a repeat scan, this repeat scan will be used to detect tumor hypoxia.

Safety measurements of typical vital signs, such as oral body temperature, respiratory rate, heart rate, and blood pressure will be performed before the administration of ^{18}F-MISO, and at the end of each ^{18}F-MISO PET/CT scan session. The patient will also be assessed for adverse events at the end of the ^{18}F-MISO PET/CT sessions. Additionally, one business day (excluding holidays and weekends) following the completion of the ^{18}F-MISO PET/CT scans, patients will receive a follow up phone call to assess adverse events.

Rationale for Change in ^{18}F-FMISO PET/CT Imaging Protocol

The preliminary ^{18}F-FMISO PET image data acquired in patients with head and neck cancers have shown variable hypoxia tracer uptake at the fixed 2.5 hour time point used in the initial study. In order to convert the ^{18}F-FMISO images to parametric images of tumor hypoxia, a group in Tübingen, Germany has recently shown the importance of obtaining kinetic information of the tracer in the tumor (14-17) for an unambiguous interpretation of the hypoxia images.

PET/CT Scan Protocol

Dynamic scans will be acquired on one of the PET/CT scanners qualified by the Department of Radiology and the Molecular and Imaging Therapy Service at the main hospital of MSKCC. 3-D mode and with listmode option will be turned ON. The listmode option allows the patient data to be reconstructed in a cine mode (in variable time frames) so that pharmacokinetics of tumor uptake of the radiotracer can be studied. The patient will be set up in the radiotherapy treatment position with an intra-venous line for radiotracer injection. A PET/CT scan will be performed with the tumor at the field center. These images will be used for both attenuation correction and registration of the serial image set.

Approximately 5-10 mCi dose of ^{18}F-FMISO will be injected as a bolus, and the dynamic scan initiated coincident with the injection. Data will be acquired in dynamic mode for up to a maximum of 45 minutes from the time of injection, but may be shorter (e.g. if the patient is in discomfort in the immobilization device for this duration). The patient will then be removed from the scanner, and instructed to return at approximately 90-minutes for a second PET scan and again at approximately180-minutes for a third PET scan. No further activity will be injected in the patient at these times. The 2nd and 3rd PET scans will consist of a 10-minute image of the tumor. A low dose CT scan will be performed at each of these two image sessions for attenuation correction and image registration.

In up to 10 selected patients, the first segment of the scan shall be performed over the heart with the later segments still being performed over the tumor. These scans ill be used to calibrate the input function currently derived from the carotid artery.

MR Scan Protocol

Multiparametric MR scans for Cohort 1 and Cohort 2 main campus patients will be performed on the Philips 3T scanner located in the Department of Radiation Oncology according to the standard IVIM departmental protocol and utilization of the patient's immobilization device when the immobilization device is available and the patient agrees to utilize it. DWI-MR images will also be acquired according to the standard IVIM departmental protocol.

At the pretreatment MR scan for Cohort 1 and Cohort 2 main campus patients, an additional scan will be acquired based on a research sequence provided by Philips (the

manufacturer of the machine on which these MRIs occur) that will allow visualization of cortical bones in the head and neck region and potentially differentiate bone from air sinus cavity. This scan will be used to evaluate the potential of using MR alone images to differentiate and segment normal tissues used in radiotherapy treatment planning. This additional sequence will add an extra 5 minutes to the total scan time. This sequence is written, maintained, and updated by Philips. When an update to this sequence occurs, the sequence may become unavailable for a few weeks, at which time the updated version is installed and tested internally by MSK staff. Therefore, this sequence will only be run when it is available. The total pre-treatment MR scan duration will be approximately 30-60 minutes.

For Cohort 1 main campus patients, the follow-up MR scans, which will occur during concurrent chemoradiation, will last approximately 20-40 minutes. Information collected from all MR scans will not affect the standard of care, as baseline and post-treatment scans are currently a component of the standard of care. Additional scans will be acquired on our Philips 3T research scanner. Images will be sent to the research Pinnacle workstation for storage and evaluation. These images may be used for contouring of normal structures during the treatment planning process. DW-MRI images will be processed on the Philips research platform and corresponding diffusion and perfusion maps will be analyzed for therapy response assessment and treatment planning. Spatial changes during treatment will also be evaluated using functional diffusion maps or parametric response maps. No clinical decision will be made at this point based on MR findings.

PET/CT Image-guided Core Biopsy (Optional – Cohort 1 Patients Only)

The PET/CT scan will be performed in the Center for Image-Guided Intervention and Surgery at MSKCC, which houses a PET/CT scanner in an interventional radiology and operating room environment. The PET image-guided core biopsy procedure will conducted as follows:

On the day of ^{18}F-FMISO PET/CT imaging, patients will be injected with the study tracer, ^{18}F-FMISO. After the final ^{18}F-FMISO PET image acquisition at each visit session (where applicable), biopsy samples will be removed from tumor tissue exhibiting high and low ^{18}F-FMISO uptake (if both are available). These high and low ^{18}F-FMISO uptake regions correspond to putative hypoxic and normoxic regions, respectively. Parametric image maps will also be retrospectively generated from compartmental models that define the rate of ^{18}F-FMISO radiotracer entrapment. These values will be used, in addition to the percent injected dose per gram, for correlation with IHC of hypoxia specific markers.

The aforementioned biopsy samples will be obtained by an interventional radiologist according to the features of the ^{18}F-FMISO PET/CT images. 1% lidocaine will be used for local anesthesia supplemented with midazolam and fentanyl citrate for light conscious sedation. The biopsy needle will be placed in position to remove core biopsy material of the node(s), and the patient will have an additional low dose CT to visualize the biopsy

needle trajectory and location. In this way, we will obtain information of the exact location of the biopsy specimen in regard to the CT and therefore co-registered PET image. If movement should occur between biopsy localizer CT and the CT attenuation scan, then these two CT images will be co-registered using mutual information density software. Immediately following biopsy, the specimen will be properly oriented and pinned. Based upon published experience, discussion with other investigators, and our own experience of obtaining tissue prior and during treatment, we anticipate it will take approximately fifteen minutes to perform each biopsy. The specimen acquired from these tumor samples will be taken for paraffin embedding, fresh frozen (if patient consents to any of optional banking studies), and histological processing to our Pathology Department. Ten 5μm thick sections from paraffin tumor blocks or core samples will be deparaffinized and rehydrated, and stored at −80 °C until processing. IHC analyses will also be performed for the following hypoxia relevant biomarkers, among others: HIF-1α, LOX, and Ki-67.

Pretreatment Surgical Resection (Cohort 2 Patients Only)

The eligible patient will undergo a pre-surgery FDG PET scan and an ^{18}F-FMISO PET/CT scan. Following these pre-surgical scans, the patient will undergo his/her standard of care surgery. The surgeon will annotate the location of each sample resected from the lesion by a text description for documentation of relative position. The specimen will be embedded in paraffin in an orientation that will allow sectioning parallel to the imaging plane of the PET/CT image. Tissue sections will be stained with H&E, hypoxia specific, and proliferation markers using the same procedures as the described for the biopsy specimens in this protocol.

Biospecimen Samples

Biospecimen samples from Cohort 1 (obtained via biopsy) and Cohort 2 (obtained via surgical resection) will not used for diagnostic purpose. They will instead be utilized for a research purpose. They will be labeled with de-identified subject IDs, initials, date and time of specimen collection, and visit time point, which are linked to the identifiable PHI and will be kept confidential. The participant's personal identity will not be used in reports that are written about the research. The MSKCC IRB/PB will review all requests for research performed involving tissues ascertained through this protocol. With the permission of IRB/PB, research studies on cellular, genetic, immunologic, or other features of tumor or normal samples may be performed with no names attached to the samples but linked by codes to personal identifiers. The results of any research using tissues will not be placed in the medical record.

HIF-1α

IHC staining will be performed on biospecimen samples using the antibody against HIF-1α (Novus Biologicals, Littleton, Colorado, dilution 1:1600) utilizing previously reported techniques. Briefly, 4 micron formalin-fixed paraffin embedded tissue sections will be mounted on Superfrost Plus slides, deparaffinized with xylene and rehydrated. Tissue

will be then avidin/biotin blocked with blocking kit (Vector SP-2001). For HIF-1α, DakoCytomation catalyzed signal amplification system (Dako, K1500) will be used according to the manufacturer directions. Slides will be counterstained with hematoxylin, dehydrated and cover-slipped. Only the nuclear staining for HIF-1α will be considered a positive result. Expression of HIF-1a will be determined by semi-quantitatively assessing the percentage of marked tumor cells and the staining intensity to calculate an immunoreactive score (IRS). Therefore, the percentage of positive cells will be rated as 1–10% positive cells (1×), 11–50% positive (2×), 51–80% positive (3×), and > 80% positive cells (4×). The staining intensity will be scored as weak (1×), moderate (2×), and intensive (3×). Scores for expression and scores for percentage of positive cells will be multiplied to calculate an IRS ranging from 0 to 12.

Lysyl Oxidase

5µm formalin-fixed paraffin-embedded tissues will be deparaffinized in xylene, then rehydrated before antigen retrieval by microwaving in sodium citrate buffer (pH 6.0). The slides will then be incubated with a peroxidase block, followed by the primary antibody lysyl oxidase (LOX) according to the company's protocol. After hematoxylin counterstain, the slides will be cover slipped. Cytoplasmic staining will be considered as positive. The intensity and proportion of immunostaining will be scored on a semiquantitative six-point scale. Negative samples will receive a score of 0, whereas weak, moderate, and intense staining samples will receive a score of 1, 2, or 3, respectively. For the percentage tumor cell positivity the following scoring will be used: negative=0, 1–25%=1, 25–50%=2, >50%=3. Both the staining intensity and percentage positivity scores will be summed and tumors with scores ranging from 0 to 5 will be assigned to group 0=low lysyl oxidase, whereas those with a score of 6 will be assigned to group 1=high lysyl oxidase.

Ki-67

5µm formalin-fixed paraffin-embedded tissue will be subjected to IHC for Ki-67 staining using the MIB1 mouse mAb (Immunotech, Westbrook, ME) at a 1:500 dilution. Standard avidin–biotin–peroxidase complex techniques will be used. Antigen retrieval in heated citrate buffer at pH 6.0 will be applied. Slides will be counterstained with hematoxylin. Only nuclear staining of tumor cells will be considered positive. Ki67 expression will be determined by semi-quantitatively assessing the percentage of positive tumor cells.

Tissue Banking

With the patient's consent, we will bank the additional and left over tissue after the biopsy (Cohort 1) or surgical resection (Cohort 2) in Tissue Procurement Service (TPS). To further access this tissue, we will submit a plan to the Human Biospeciman Utilization Committee (HBUC). For retrospective feasibility studies, tissue use at MSKCC is governed by the HBUC. The HBUC has trans-departmental and multidisciplinary representation. As institutional policy, the HBUC will give special consideration to tissues requested for correlative analysis as part of a clinical trial, or to develop a tissue

bank at an academic institution, cooperative group or corporate entity. While the specimens for this protocol will reside in local repositories, we will nevertheless seek HBUC approval for use of the resources in this study as other investigators in the Center. We recognize that specimen resources are ultimately institutional resources, wherever they are stored and by whatever means they are ascertained. Approval by the HBUC committee will follow institutional standards. Each specific research use proposed for use of these banked specimens will be reviewed in the context of the scientific study design and human subjects' protection implications.

In a series of check boxes at the end of the consent form, patients in both Cohort 1 and Cohort 2 are asked if: 1) they permit their biospecimen to be stored and used in future research to learn about or prevent cancer or side effects of treatment, or to develop new treatments; 2) if they permit their samples to be stored and used in future research to learn about, prevent, or treat diseases other than cancer; or 3) if they permit their samples, with personal identifiers protected, to be used for research about inherited genetic factors; 4) if they permit their samples to be used for genetic analysis of the tumor and normal samples to learn about the causes of cancer; 5) if they agree to be contacted in the future as part of research studies for additional health information or to be asked to participate in future biospecimen research studies; 6) if they consent to be contacted to discuss research findings that may come from their sample; and 7) if he/she (the patient) is not available (e.g. deceased), if they wish to have their designee designated on the consent form to be contacted.

Participants will not be provided with specific results of research tests performed on their collected human biologic specimens. With their permission, the patient may be contacted in the future to ask if they are interested in joining new biospecimen research studies, if they would consent to research that would allow updates of their health status and if they consented to be contacted to discuss research findings which may come from their sample.

It will be stated that researchers at MSKCC may either keep indefinitely or dispose of any tissues, including DNA that the samples contain. Tissues will be stored with identifiers in secure tissue banks. It is stated that the samples could be lost or ruined because of mechanical failure, and that MSKCC cannot guarantee that samples will be stored indefinitely. The samples will be store for as long as deemed useful for research purposes.

The protocol consent form asks participants for permission for re-contact to discuss research findings if their samples are used in an HBUC project and an incidental research finding is made that may be critical to their preventive care. If a participant agrees to be re-contacted, he/she will not be told the specific results of the research test, but will be informed that his/her samples were used in a project and a potential risk was uncovered. If the participant is interested in further discussion of the research findings, he/she will be asked to come into MSKCC Clinical Genetics Service for counseling and specific genetic testing.

In the event an investigator's research identifies a finding that he or she believes should be communicated to the subject, the investigator shall communicate this to the Clinical Research Administration-IRB. The finding will be reviewed by a group convened by the IRB to determine whether the incidental finding should be discussed with the subject. In the event that group convened by the IRB determines that the finding should be discussed with the subject, and the subject has consented to be re-contacted, then the treating/consenting physician shall be contacted by the Clinical Research Administration-IRB representative and asked to refer the subject to the Clinical Genetics Service for further discussion of the research finding. After appropriate counseling and consent, the Clinical Genetics Service will request permission to confirm the result in a New York DOH-approved laboratory prior to communication of the specific test result. If the patient is not available (e.g. deceased), then the surrogate designated on the consent will be contacted and the above will occur.

The following information will be provided to the Clinical Research Administration-IRB representative and Clinical Genetics:

- Participant Name/MRN #
- Type of Biospecimen
- Incidental finding
- Project# (HBUC/Waiver #) that this analysis occurred under
- Collection Protocol #

Clinical Genetics Service Contact: ocrgapirb@mskcc.org

4.2 Intervention

For patients in Cohort 1, there will be no change or intervention in a patient's treatment regime using chemoradiation where both the primary and the neck nodes receive 70Gy if the tumors are not associated with HPV or if there is no resolution of hypoxia on their repeat ^{18}F-FMISO PET/CT scan. This is currently one accepted standard of care.

Patients in Cohort 1 with tumors that are positive for HPV who exhibited no evidence of hypoxia on their baseline ^{18}F-FMISO PET/CT scan or whose tumors have early resolution of hypoxia on their repeat early response ^{18}F-FMISO PET/CT scan will undergo an alternative treatment where the primary tumor site receives 70Gy while the neck nodes receive 60Gy followed by a planned FDG PET/CT scan and observation.

Select Cohort 2 HPV+ tumors that demonstrate no evidence of hypoxia on an ^{18}F-FMISO PET scan will receive 30Gy to the surgical bed and neck lymph nodes concurrent with standard chemotherapy followed by a 3 to 4-month post-treatment neck dissection. In patients who exhibit a complete response with this method of treatment, no further treatment is necessary. For patients within this select group who still have pathologic

nodal disease, further standard chemoradiation will be given. All other patients in this cohort (i.e. those who are not in the select HPV+ tumor group outlined above) will receive standard of care treatment following their surgery.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

DCE-MRI studies will be acquired using a fast multi-phase spoiled gradient echo sequence. A Gadolinium-based agent will be used for DCE-MRI studies. This is the standard contrast agent used with MRIs.

^{18}F-FMISO is prepared and tested for quality assurance in this study at MSKCC or by an equivalent qualified supplier. The radiopharmaceutical is being utilized in this protocol under a MSKCC IND.

Radionuclide dosimetry

Biodistribution data on ^{18}F-FMISO has been obtained for 60 patients at the University of Washington, School of Medicine, and dosimetry was performed. The normal organ doses absorbed following ^{18}F-FMISO administration was published by Graham et al. (15) and is summarized in the table below.

Radiation Absorbed Doses to Organs following ^{18}F-FMISO administration.

Target Organ	Median Dose (mGy/MBq)	Dose (cGy) per 10mCi (370 MBq) injection	Total Procedure Dose (cGy) Tracer + 3 attenuation CT scans
Adrenals	0.0166	0.61	3.31
Brain	0.0086	0.32	3.02
Breasts	0.0123	0.46	3.16
Gall bladder wall	0.0148	0.55	3.25
Lower Large Intestine	0.0143	0.53	3.23
Small Intestine	0.0132	0.49	3.19
Stomach	0.0126	0.47	3.17
Upper Large Intestine	0.0140	0.52	3.22
Heart Wall	0.0185	0.68	3.38
Kidney	0.0157	0.58	3.28
Liver	0.0183	0.68	3.38
Lungs	0.0099	0.37	3.07
Muscle	0.0142	0.53	3.23
Ovaries	0.0176	0.65	3.35
Pancreas	0.0179	0.66	3.36
Red Marrow	0.0109	0.40	3.10
Bone Surface	0.0077	0.28	2.98
Skin	0.0048	0.18	2.88
Spleen	0.0163	0.60	3.30
Testes	0.0146	0.54	3.24
Thymus	0.0155	0.57	3.27
Thyroid	0.0151	0.56	3.26
Urinary Bladder Wall	0.0210	0.78	3.48
Uterus	0.0183	0.68	3.38
Eye Lens	0.0154	0.57	3.27

Total Body	0.0126	0.47	3.17

The original approved protocol MSKCC 04-070 consisted of 3 injections of 370 MBq of ^{18}F-FMISO per patient. The current protocol involves up to 2 injections of 370 MBq of ^{18}F-FMISO per patient. The dose estimates derived from the University of Washington data were used to provide the dose from the single 10 mCi administration of ^{18}F-FMISO and were confirmed by our pilot study. The urinary bladder wall is subject to the largest dose of 0.78 cGy. This is an insignificant addition to the total therapeutic radiation dose that the patient will receive for his or her head and neck cancer. In addition, the patient will receive a low dose CT attenuation scan each contributing an addition of 0.9 cGy whole body dose to the patient. The dose to the eyes from the combination of an ^{18}F-FMISO and CT scan would be 0.57 + (3X0.9) cGy = 3.27 cGy. This will also not significantly add to the total radiation dose that the patient will receive from treatment for his or her head and neck cancer.

Also note that these radiation doses are overestimates, because the CT scan (and therefore dose) will only apply to a single 15cm field of view surrounding the lesion of interest. For example, for patients in which the lesion is remote from the eye, the lens will only receive a dose of 0.57 cGy resulting from the ^{18}F-FMISO administration and nothing from the CT.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria for Cohort 1 and Cohort 2

- Histologically confirmed diagnosis of head and neck carcinoma (excluding nasopharynx, paranasal sinus, salivary, and thyroid malignancies). Any unknown primary squamous cell carcinoma of head and neck with gross nodes is allowed (2002 AJCC)
- 18 years of age or older
- Must not have received prior radiation therapy or chemotherapy for this diagnosis.
- Patients who have had their primary site tumor removed by surgery but still present with grossly enlarged lymph nodes are eligible for this study.
- Karnofsky performance status $\geq$ 70.

6.2 Subject Exclusion Criteria for Cohort 1 and Cohort 2

- All nasopharyngeal, paranasal sinus, salivary cancer, and thyroid malignancies
- Prior chemotherapy or radiotherapy within the last three years
- Patients that underwent previous surgical resection for the same disease (except for biopsy or surgery removing primary site tumor but still present with grossly enlarged lymph nodes)
- Any prior radiotherapy to the head and neck region

- Pregnant (confirmed by serum b-HCG in women of reproductive age) or breast feeding

6.3 Subject Exclusion Criteria for Optional Contrast MRIs – Cohort 1 Only

- Subjects with a known contraindication to the standard MRI contrast agent (Gadavist, a gadolinium-based contrast agent) and/or a recent estimated glomerular filtration rate (eGFR) of 30 or less will be excluded from all DCE-MRIs, and will instead receive non-contrast MRIs at the DCE-MRI time points.

7.0 RECRUITMENT PLAN (WITH LIMITED WAIVER OF AUTHORIZATION)

Patients will be evaluated by an attending physician from the Department of Radiation Oncology and entered onto the study and into the appropriate cohort if they are appropriate candidates. The attending physician will obtain informed consent from the eligible patient.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at MSKCC. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

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. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients

regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.0 PRETREATMENT EVALUATION

All patients will receive the necessary scans and tests according to the standard of care for their head and neck cancer.

9.0 TREATMENT/INTERVENTION PLAN

For patients in Cohort 1, there will be no change or intervention in a patient's treatment regime using chemoradiation where both the primary and the neck nodes receive 70Gy if the tumors are not associated with HPV or if there is no resolution of hypoxia on their repeat ^{18}F-FMISO PET/CT scan.

Patients in Cohort 1 with tumors that are positive for HPV who exhibited no evidence of hypoxia on their baseline ^{18}F-FMISO PET/CT scan or whose tumors have early resolution of hypoxia on their repeat early response ^{18}F-FMISO PET/CT scan will undergo an alternative treatment where the primary tumor site receives 70Gy while the neck nodes receive 60Gy followed by a planned FDG PET/CT scan and observation.

Select Cohort 2 HPV+ tumors that demonstrate no evidence of hypoxia on an ^{18}F-FMISO PET scan will receive 30Gy to the surgical bed and neck lymph nodes concurrent with standard chemotherapy followed by a 3 to 4month post-treatment neck dissection. In patients who exhibit a complete response with this method of treatment, no further treatment is necessary. For patients within this select group who still have pathologic nodal disease, further standard chemoradiation will be given. All other patients in this cohort (i.e. those who are not in the select HPV+ tumor group outlined above) will receive standard of care treatment following their surgery.

Please note that for patients who receive a repeat ^{18}F-FMISO PET/CT scan, the repeat ^{18}F-FMISO PET/CT scan will only be performed 5-10 days into chemoradiotherapy treatment. For Cohort 1 patients, a repeat ^{18}F-FMISO PET/CT scan will only be performed if the pretreatment baseline ^{18}F-FMISO PET scan is positive for hypoxia.

Chemotherapy will be administered in two doses. Chemotherapy will begin +/- 3 days from the first day of radiation therapy. The second cycle of chemotherapy will begin 3 weeks later (+/- 5 days), although delays for safety (e.g., low white blood count, elevated creatinine) are allowed. Standard chemotherapy with either Cisplatin or Carboplatin/5-Fluorouracil is strongly recommended. Any other schedule (e.g., weekly chemotherapy) is discouraged and requires approval of the principal investigator.

- Patients should receive standard high dose Cisplatin chemotherapy at 100 mg/m^2. If the patient is unfit or cannot tolerate Cisplatin, the treating physician must discuss with study medical oncologist, Dr. Eric Sherman, to jointly confirm what chemotherapy should be given in place of Cisplatin.

- If a patient is not tolerating Cisplatin well, dose modification(s) must be discussed with study investigator, Dr. Eric Sherman, prior to making any changes.

Patients on main campus, unless contraindicated, will have a recommended MRI at pre-treatment (Cohort 1), recommended MRIs approximately weekly (Cohort 1), and a recommended MRI post-treatment at 3 months, 6 months, and 1-year post-treatment (+/-4 weeks) when possible (Cohort 1). Cohort 2 patients will not receive approximately weekly MRIs, and will not receive a post-treatment MRI at 3 months, 6 months, and 1 year post-treatment.

Central review of all radiation treatment plans must be reviewed by study PI Dr. Nancy Lee and/or investigator Dr. Nadeem Riaz prior to initiating radiation treatment.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

All patients will be evaluated according to the standard of care for their head and neck cancer.

11.0 TOXICITIES/SIDE EFFECTS

No side effects are expected as a result of this study. However, in the unlikely event that an adverse reaction to either radiopharmaceutical occurs, these toxicities will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The results will be documented and reported by the Principal Investigator to both the Institutional Review Board and the IND Committee chairmen.

Cohort 1 patients who will have optional ^{18}F-FMISO PET image-guided core biopsies might experience the following:

Likely
- Discomfort when the needle enters into your neck
- Minimal if any bleeding from your neck

Less Likely
- Infection
- Neck pains

Cohort 2 patients who undergo neck dissection might experience the following:

Likely
- Temporary postoperative discomfort
- Numbness of the skin
- Visible healed scar line

Less Likely
- Scar tissue (fibrosis) of the neck leading to tightness

- Infection

Rare but serious

- Fluid collection in the neck requiring drainage(seroma)
- Bleeding (hematoma) requiring a second surgery
- Loss of function of a nerve (lower lip asymmetry, shoulder dysfunction, hoarseness, others)
- Chyle leak (prolonged fluid drainage from the neck)

Patients who partake in the optional storage and analysis of tissue samples will not have additional risks or toxicities other than the unauthorized and inadvertent release of PHI.

Gadavist, a gadolinium-based contrast agent, is the standard contrast agent utilized in contrast MRIs. However, adverse reactions to gadolinium-based contrast agents have been documented, which may include headaches, rash, and itching. Furthermore, gadolinium-based contrast agents are associated with a risk for Nephrogenic Systemic Fibrosis (NSF) and renal failure. Due to these associated risks, subjects enrolled on this protocol with a known contraindication to the standard MRI contrast agent (Gadavist, a gadolinium-based contrast agent) and/or a recent estimated glomerular filtration rate (eGFR) of 30 or less will be excluded from all DCE-MRIs, and will instead receive non-contrast MRIs at the DCE-MRI time points.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Not applicable.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease he/she will be taken off study and referred for alternative therapy. If at any time the patient develops unacceptable toxicity he/she will be removed from study.

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

If at any time a patient wishes to participate in the optional sub-study regarding additional banking and analysis of tissue via the optional biopsy (Cohort 1) or via the standard of care surgical resection (Cohort 2), the patient has a right to withdraw participation and prohibit any future use of their biologic specimen that has not already been undertaken. If the specimen has already been sent out from the archive for research purposes, it cannot be excluded from the research, nor would any results derived from the research activity be excluded.

14.0 BIOSTATISTICS

Cohort 1 will accrue a cohort of 150 head and neck cancer patients over 5 years, of which 100 will be HPV+ tumors and 50 will be HPV- tumors. Due to biomarker screening and to accommodate a 20% exclusion rate, in order to reach 28 eligible patients, Cohort 2 will accrue 19 patients who are expected to undergo surgical resection for their cancer per standard of care.

This is a feasibility study of using ^{18}F-FMISO PET to detect tumor hypoxia in HPV negative head and neck cancer of which patients will undergo standard chemoradiation. Information obtained from the imaging studies will not alter from the standard of care. We will image 50 non-HPV positive patients to evaluate the ability of dynamic ^{18}F-FMISO PET scanning to accurately determine the location hypoxia sub-regions within the tumor volume. For those HPV negative patients whose ^{18}F-FMISO PET exhibits hypoxia, we will also perform a repeat ^{18}F-FMISO PET/CT scan 5-10 days into treatment with chemoradiotherapy. This will provide us the volume of hypoxic region at the 5-10 days time-point. The changes in the volume of the hypoxic regions after 5-10 days of therapy will be summarized. We estimate that 40 HPV negative patients will require repeat ^{18}F-FMISO PET. Among these patients, we anticipate Wilcoxon rank sum tests will be used when the imaging results are measured continuously and Fisher's exact tests will be applied when the imaging results are dichotomized. We will also search for the best cut-off value for SUV and/or k_3 to predict "response". To this end, we will examine all possible cut-off values and the corresponding sensitivity and specificity.

The Youden index, defined as sensitivity+specificity-1, will be used to determine the best cut-off value for SUV. For long-term treatment outcomes, Kaplan-Meier estimates will be calculated for each stratum and compared using the log-rank tests. When competing risks are present (death without distant metastasis), Gray's test will be used. Due to the moderate sample size, we may not have enough power for declaring statistical significance for our tests, in which cases we will report all summary and test statistics and point out future research directions.

As ^{18}F-FDG PET scans are routinely obtained before and after chemoradiation for head and neck cancer, we will include a prospective MTV (metabolic tumor volume) calculation in addition to the already calculated standard uptake value (SUV) for the routine ^{18}F-FDG PET scans. We will not alter any patient management based on the calculated MTV. The MTV, defined as tumor volume with 42% or greater of the maximum ^{18}Fluorine-fluoro-deoxyglucose (^{18}F-FDG) signal intensity on positron emission tomography (PET), has been demonstrated to correlate with loco-regional control, freedom from distant metastases, and overall survival in oropharyngeal cancer patients treated with definitive chemoradiation therapy at MSKCC (21). These findings corroborate those of previously published retrospective studies from Stanford Medical Center (22, 23).

Biostatistics for HPV+ tumors with no evidence of hypoxia on their baseline ^{18}F-FMISO PET/CT or that exhibited hypoxia resolution on their early repeat ^{18}F-FMISO PET/CT.

100 HPV+ patients with negative baseline scan or early resolution of tumor hypoxia of their node(s) at 5-10 treatment days into chemoradiation, defined by an absence or disappearance of ^{18}F-FMISO uptake on PET/CT, will achieve an equivalent nodal control with nodal radiation dose at 60Gy in the setting of chemotherapy with concomitant reduction in treatment-related complications. To test if patients receiving 60Gy to the node(s) followed by an FDG PET and observation similar treatment outcomes when compared to the radiation of 70Gy to the nodes both in the setting of concurrent chemotherapy, we will apply a one-sided one sample proportion test. Our past experience is that the nodal control rate at 3 months for such patient with 70Gy to the nodes is 94%. We will reject our hypothesis of equivalent control whether patients receive 70Gy to the nodes or 60Gy to the nodes followed by an FDG PET and observation if ≤57 patients out of the 66 in total who received 60Gy to the nodes achieve the same 3-month nodal control after chemoradiation. With this rule, we have a power of 0.93 for detecting that 60Gy will result in 3-month regional control lower than 80% with the type I error rate lower than 0.05. To test if patients receiving 60Gy to the nodes followed by an FDG PET and observation show superior toxicity outcomes when compared to the historical results from similar patients receiving 70Gy, we will apply a one-sided one sample proportion test. Grade 2 or higher toxicities that occurred within 3 months from the completion of IMRT will be counted in this analysis. Our past experience is that this toxicity rate for patients receiving 70Gy is around 75%.
Using the total of 66 patients that undergo 60Gy to the nodes, we will reject our hypothesis of equivalent or higher toxicity rate when the nodes receive 10Gy less radiation from 70Gy when ≤43 patients have at least one ≥ grade 2 toxicities. With this rule, we have a power of 0.84 for detecting the probability of 60% of patients will have at least one ≥grade 2 toxicity with the type I error rate lower than 0.05. Effort will be made to monitor all toxicities occurring beyond 3 months from chemotherapy and IMRT for all patients. However, censoring can be an issue so we will not apply the proportion test for toxicities after 3 months from chemoradiation. Instead, we will summarize the data descriptively and when applicable, we will use survival analysis tools such as Kaplan-Meier estimation and log-rank tests to determine whether 60Gy results in lower toxicity. To examine the potential correlations between various evaluation methods for nodal control status, we will apply a series of Fisher's exact tests.

The spatial extent of ^{18}F-FMISO PET imaging within the neck node(s) determines the underlying hypoxia tumor phenotype for both HPV positive and negative HNSCC. To determine whether baseline ^{18}F-FMISO PET/CT and/or early-response ^{18}F-FMISO PET/CT at 5-10 treatment days after chemotherapy and IMRT correlate with selected proliferative/hypoxia molecular markers, Wilcoxon rank sum tests will be used for each marker. Multiple testing adjustments such as Bonferroni procedures will be used. To investigate whether the extent of ^{18}F-FMISO PET/CT measured hypoxia at baseline and/or 5-10 treatment days into chemoradiation for both HPV positive and negative tumors correlates with the development of distant metastasis, Kaplan-Meier estimates will be calculated for each stratum and compared using the log-rank tests. When competing risks are present, Gray's test will be used to examine the correlation between the extent of ^{18}F-FMISO PET/CT measured hypoxia with the development of distant metastasis. To examine the potential correlations between the baseline and early

response ^{18}F-FMISO PET imaging and tumor's underlying HPV status, we will apply Fisher's exact tests.

Multiparametric scans will also be obtained. We will attempt comparisons to ^{18}F-FMISO PET results and immunohistochemistry hypoxia results, but due to the small pilot size of this exploratory aim, we may not produce significant results. In that case, we will present summary statistics and suggest directions for future study.

> For this study cohort, 14 eligible patients will be needed for the analysis. Assuming approximately 25% of the patients enrolled will not be eligible, we will plan to recruit 19 patients upfront. For evaluation on the efficacy of the regimen in this cohort, a simple decision rule will be implemented, which is as follows: If, among the total 14 eligible patients, we have at least 10 patients who are alive, followed and have a pathologic CR at 4 months from the end of the treatment, then we will declare the treatment modality using 30 Gy is feasible and worthy of further investigation. Any patient who died or is lost to follow up within 4 months from the end of radiotherapy will be regarded as a failure, i.e., without pathologic CR. Feasibility for the primary objective in cohort 2 will be defined according to aforementioned decision rule. This decision rule has the following probabilities of declaring success.

True Locoregional Control Rate								
0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90
Probability of Declaring Success								
0.090	0.167	0.279	0.423	0.584	0.742	0.870	0.953	0.991

15.0 SUBJECT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. 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 eligible 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).

15.2 Randomization

Not applicable.

16.0 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 coordinate 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. All research material from this study will be handled with the same confidentiality as patient's other medical data.

16.1 Quality Assurance

Eligibility of patients will be verified with the Principal Investigator. Only the designated investigators can obtain informed consent.

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 QA) 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 committees: *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 Institutional Review Board (see section 16.2).

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

16.2 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://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: https://one.mskcc.org/sites/pub/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 QA) 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 committees: 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 Institutional Review Board.

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.

17.0 PROTECTION OF HUMAN SUBJECTS

Risks of Study Participation: Patients who will undergo a treatment that deviates from the current standard of care for their disease will be those patients in Cohort 2 who receive a dose of radiation of 30Gy to the surgical bed and lymph nodes, a neck dissection at three to four months post-chemoradiation, and a possible booster dose of chemoradiation following neck dissection (this booster dose is dependent on the result of the planned neck dissection). The risks involved include those entailed by giving a decreased dose of radiation and a neck dissection at three to four months post-chemoradiation. However, the risk associated with the decreased dose of radiation is mediated by the neck dissection three to four months post-chemoradiation. Should any residual disease be discovered at the time of this neck dissection, the patient will be treated with a chemoradiation boost per standard of care. These patients will be closely monitored throughout their treatment on this protocol, and will receive standard of care treatment should any complications occur.

Financial Costs to Patients: All diagnostic and therapeutic interventions except for the ^{18}F-FMISO PET/CT scans and the neck dissection three to four months post-chemoradiation for select Cohort 2 patients are part of the current routine care of patients/subjects eligible for this study. A research grant will cover the cost of the ^{18}F-FMISO -PET scans and the tracer, the optional ^{18}F-FMISO PET image-guided core biopsies, and the neck dissections. In addition, the multiparametric scans on the Phillips MR machine will not generate a charge. There are no additional financial costs or burden to the patient beyond the charges routinely incurred as part of standard medical care.

Patient Confidentiality: Patient/subject privacy and confidentiality will be maintained according to MSKCC guidelines and all data derived from this study will be kept in a secure database. All data and results will be anonymously reported with regard to individual subjects.

Voluntary nature of the study: Subjects will be made aware of the voluntary nature of the study as part of the informed consent process. They will be allowed to withdraw participation at any time without the risk of alteration in the quality of their medical care.

17.1 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.

For the biospecimen banking and analysis study, it will be explained that future research may also be done to identify changes in genes that predict risk for cancer or other diseases; if such germline genetic research is performed, then to be in compliance with New York State Law (New York State Civil Rights Law §79-1(30(a)), it will not be possible to provide results of research tests not performed in a New York State Department of Health approved clinical laboratory.

The consent indicates that samples and genetic information collected may be shared with other qualified researchers. Such information will not include identifying information such as name. It is also stated in the consent and Research Authorization that research data (e.g. genomic sequence) may be placed into databases monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government.

The requirements for submission of genotype/phenotype data into the NIH GWAS Repository (or any other public database) will be outlined in the biopsecimen analysis application, i.e., IRB Biospecimen Correlative Protocol/HBUC Application/Application of Exemption for Existing data.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. SAE reporting is required for 30 days after the last ^{18}F-FMISO PET/CT scan. Any SAEs that occur after the 30 day period and that are at least possibly related to the ^{18}F-FMISO isotope must be reported. The IRB/PB requires a Clinical Research Database (CRDB) SAE report is submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form

The Principal Investigator's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.3 Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

18.0 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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20.0 APPENDICES

Not applicable.