Title: To evaluate the utility of NETSPOT Imaging in Head and Neck Cancer Patients

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Investigator Initiated Study Proposal

Proposed Study Title	
Study Title:	To evaluate the utility of NETSPOT Imaging in Head and Neck Cancer Patients
Request Date:	12/28/2017
Principal Investigator Contact Information	
Name:	Rusha Patel
Title:	MD
Address	1 Medical Center Drive
City, State, Zip	Morgantown, WV 26506 - 9200
Phone:	304-293-3457
E-mail:	Rusha.patel@hsc.wvu.edu
Contracting Information (if applicable)	
Name:	
Phone/Fax:	
E-mail:	
Study Information	
Indication:	Enrollment criteria include all patients with head and neck cancer undergoing ^{18}F FDG PET/CT at time of primary diagnosis or after completion of therapy.
Line of treatment:	
Phase:	Preliminary
Number of Subjects:	30

Background and Rationale:

Provide background (including references) on unanswered question(s) the study is attempting to answer

Head and neck squamous cell carcinoma (HNSCC) makes up 90% of head and neck cancers. The incidence is increasing, in part due to the human papilloma virus (HPV), a well-established factor in the development of HNSCC. Unfortunately, tumor-specific imaging for HNSCC and HPV-related HNSCC are non-existent, making detection and follow-up reliant on surrogate markers for metabolic activity. ^{18}F FDG Positron Emission Tomography (PET), combined with computerized tomography (PET/CT), is the current standard for imaging in HNSCC. Specifically, ^{18}F FDG PET/CT is used for patients with advanced stage disease, those with unknown primary site, and as part of the post-treatment imaging. ^{18}F FDG PET/CT has a high sensitivity, but the specificity can be limited in pateints with underlying inflammation, infection, or after radiation therapy. As such, tumor-specific imaging has the potential to improve detection of de novo and/or recurrent tumors in this high risk population.

Interestingly, HNSCCs have been found to express somatostatin receptors (SSTRs). SSTRs have also been found in laryngeal cancer specimens and cancers of the oral cavity and oropharynx, but not in control tissue[1,2]. Recent studies have found that HPV causes mutations in the same pathways that activate SSTR expression on tumor cells[3]. These studies suggest a correlation with HPV-positive HNSCC and SSTR expression. This latter group of patients often have non-detectable primary tumors that arise from the oropharynx, an area that normally exhibits ^{18}F FDG PET/CT uptake thus making tumor localization difficult. Schartinger et al studied SSTR PET/CT in a small series of HNSCC patients and found that all patients showed radionucleotide uptake on imaging[4]. Multiple case reports have been published showing similar uptake for head and neck squamous cell carcinomas by ^{68}Ga[5,6.] An unpublished trial was performed comparing SSTR PET/CT with ^{18}F FDG PET/CT for 35 patients with HNSCC; the study concluded that SSTR PET/CT had the potential to be more specific for HNSCC than ^{18}F FDG PET/CT[7]. Unfortunately the study was small, HPV status was not correlated, and recurrent/post-treatment patients were not studied. These studies show that SSTR-specific imaging, such as NETSPOT, has the potential to be equal to and possibly more specific than ^{18}F FDG PET/CT for HNSCC patients, especially in the setting of HPV positivity, unknown primary site tumors, and post-treatment follow-up. More importantly, a therapeutic target for SSTRs is widely available; as such, HNSCC patients who show clinical updake on NETSPOT imaging may be candidates for future studies using targeted therapeutics.

Objectives and study aims:

List the primary/secondary objectives to correspond directly with the listed hypotheses; define the role of AAA compounds

Study Aim:

Evaluate utility of NETSPOT imaging for disease detection in HNSCC, as well as the potential for targeted receptor-specific therapeutics.

Primary Objectives:

To determine the utility of NETSPOT imaging, as compared to ^{18}F FDG PET/CT, in detection and staging of HNSCC.

To evaluate the potential of NETSPOT imaging in guiding the use of targeted radiopeptides for HNSCC treatment.

Secondary Objectives:

To determine if NETSPOT imaging and ^{18}F FDG PET/CT, when used together, can lead to improved tumor delineation and detection of metastatic disease.

To determine the imaging charactersistics of NETSPOT versus ^{18}F FDG PET/CT in the setting of inflammation.

To determine if NETSPOT imaging uptake correlates with tumor HPV-positivity.

To determine if patients with tumor uptake on NETSPOT imaging exhibit different disease outcomes than patients without uptake.

Hypothesis:

List the clinical hypotheses in order of priority

NETSPOT imaging will be at least equivalent to ^{18}F FDG PET/CT in the detection and staging of HNSCC.

The combination of NETSPOT imaging and ^{18}F FDG PET/CT, will have increased specificity for detecting the primary site for HNSCC of unknown primary than ^{18}F FDG PET/CT alone.

The combination of NETSPOT imaging and ^{18}F FDG PET/CT, will have increased specificity for detecting disease recurrence and metastasis following treatment than ^{18}F FDG PET/CT alone.

Is a study protocol already available (Yes/No)? If yes, please attach to the IIS form

No.

Study Design/Clinical Plan:

Provide a concise overview stating the type of experimental design (for ex, randomized/non-randomized, condensed eligibility criteria etc)

Design: This study will be designed as a “proof-of-concept” trial to compare NETSPOT with ^{18}F FDG PET/CT for HNSCC.

Inclusion Criteria:

HNSCC patients undergoing planned ^{18}F FDG PET/CT at time of primary diagnosis.

HNSCC patients undergoing planned ^{18}F FDG PET/CT for unknown primary site.

HNSCC patients undergoing planned ^{18}F FDG PET/CT after completion of adjuvant treatment.

Exclusion Criteria:

Inability to undergo ^{18}F FDG PET/CT imaging due to medical comorbidities.

Enrollment:

Patients meeting inclusion criteria will be enrolled on evaluation. Based on our current clinical volume, we plan to enroll 30 patients over a 6 month time frame.

Preliminary analysis (outlined below) will be done after the first 30 patients to assess the utility of NETSPOT imaging in HNSCC.

Treatment:

List the clinical dosage/dosage form, route, and dose regimen

Brief Overview:

Patients meeting inclusion criteria will be consented at the time of scheduling.

All patients will undergo ^{18}F FDG PET/CT per established protocol.

Following ^{18}F FDG PET/CT, the patient will undergo NETSPOT imaging with the AAA-provided dose. These scans will be performed no less than 24 hours, no more than 7 days apart.

Analysis:

Both ^{18}F FDG PET/CT and NETSPOT images will be reviewed by the senior radiatiologist and the primary surgeon for concordance between images. SUV will be measured for both images and recorded.

Patients will undergo clinical follow-up based on ^{18}F FDG PET/CT results as per protocol.

True positive results will be recorded for both ^{18}F FDG PET/CT and NETSPOT images and analyzed for sensitivity and specificity.

For patients undergoing surgical treatment, pathology results including routinely reported HPV markers will be recorded and compared to NETSPOT imaging characteristics.

Follow-up

All enrolled patients will be followed for 1 year after imaging.

Expected Results/Outcomes:

We expect that ^{18}F FDG PET/CT and NETSPOT will have similar uptake and specificity for primary tumor. We hypothesize that NETSPOT will have increased specificity for unknown primary site tumor and recurrent or metastatic disease. Finally, we hope that NETSPOT positivity in HNSCC will allow for future study of targeted radionuclide therapies for HNSCC.

Applicability of Results:

Any other information regarding the medical need and/or the strategic importance of the research which may help the committee's evaluation

A proof-of-concept trial to compare SSTR/ PET/CT with ^{18}F FDG PET/CT in the head and neck cancer population would be a novel use of the NETSPOT technology. The study is warranted based on past data and the potential for success, especially in patients with oropharyngeal tumors, previous radiation or inflammatory disease; all of whom ^{18}F FDG PET/CT is difficult to interpret. If the hypothesis is supported, Advanced Accelerator will have a new application for the NETSPOT technology and a new area for business development and revenue.

Additional Research (if applicable):

Histology, biomarkers, PK etc.

Statistical Plan:

Include justification for clinical sample size and primary hypothesis testing

Statistical Considerations:

The primary objective of this study is to evaluate SSTR receptor expression in the head and neck cancer population. The secondary objective is to assess the concordance based on SSTR PET/CT with and without FDG PET/CT outcomes.

A Student t-test will be used to assess the difference of SSTR expression between the diagnostic results (positive vs negative) and Fisher's exact test will be used to assess the association between dichotomized expression (high vs low) and a binary outcome (positive vs negative). The sensitivity will be estimated by a proportion of true positives that are correctly identified by the new method. The specificity will be estimated by a proportion of true negative that are correctly identified by the new method. The corresponding 95% confidence intervals will be estimated based on binomial distributions.

Sample Size: Based on the two-sided t-test, a sample size of 30 will have 81% power to detect 0.95 standard deviations of the SSTR expression between positive and negative outcomes (15 per group) at a 0.10 significance level. In addition, based on the historical data and current literatures, head and neck squamous cell carcinoma (HNSCC) makes up 90% of head and neck cancers. For primary tumor detection, 18F FDG PET/CT is about 96% sensitive (oral cavity only) and anywhere from 91%-98% accurate at detecting lymph node metastasis, with sensitivity of 67%-79%, and specificity of 82-95%. For detecting recurrent disease, 18F FDG PET/CT is ranged from 83%-100% sensitive and 90-98% specific. Based on one-sided non-inferiority test for two correlated proportions with a concordance of 0.90, when the maximum allowable difference between these proportions that still results in non-inferiority (the range of non-inferiority) is 0.15, a sample size of 30 subjects achieves 81% power at a significance level of 0.10.