**Note: Sample uses older template format

**RSNA CLINICAL TRIALS METHODOLOGY WORKSHOP**
(Protocol template)
Revised 10-06-2011

Color-coded Timetable

**Orange Font: Draft due Sunday**

**Green Font: Draft due Tuesday**

**Blue Font: Draft due Wednesday**

**Purple Font: Final draft due Friday**
[NOTE: As each section is completed, change font color to black.]

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***Dual tracer F18-FDG-PET and 68GA-Dotatoc PET/MRI as a biomarker of biological behavior in patients with metastatic neuroendocrine tumors***


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**Original Date:** *Insert date of final and approved protocol (blank during this workshop)*
**Version Date:** *Insert version number and date of each amendment of the protocol (Each version during the workshop should have a new version number and date)*
**Activation Date:** *On activated protocols only (blank during this workshop)*

## Table of Contents

***Note: The Protocol Overview also serves as the basis for Poster that will be displayed on Thursday evening.***

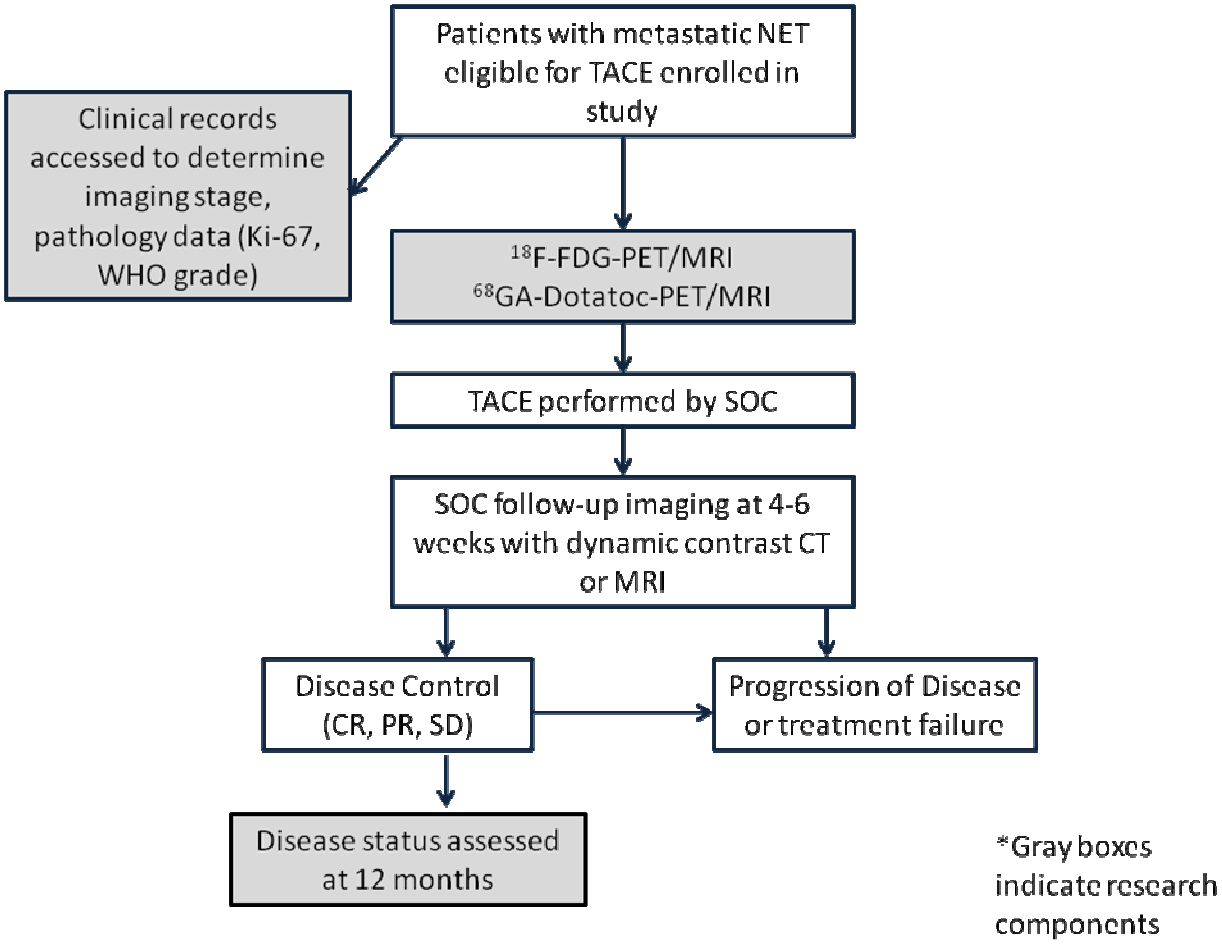
## 1.0 PROTOCOL ABSTRACT/OVERVIEW

Background: Neuroendocrine tumors (NET) comprise a heterogeneous group of tumors with variable biological behavior. The main factor in progression profiles of these tumors appears to be histological grade, determined primarily by Ki-67 expression as well as mitotic counts. While tumor grade can guide therapy decisions, the biological behavior of these tumors can be unpredictable and often patients present with metastatic disease despite low or intermediate tumor grade. Further adding to the prognostic dilemma is the intraindividual heterogeneity of tumor histology and Ki-67 expression, with small core biopsies likely undersampling and potentially misrespresenting the true phenotype of the tumor. In recent years, focus has been on imaging biomarkers of tumor differentiation. Expression of somatostatin receptors allows for somatostatin analogue imaging with 68Ga-Dotatoc-PET; and positivity on somatostatin imaging has been linked to higher histologic differentiation. On the contrary, 18F-FDG-PET uptake in NET tumors has been linked to poorly differentiated tumors and worse prognosis. MRI functional imaging parameters have also shown promise in correlating with outcome in NET. New PET/MRI simultaneous systems allow the integration of molecular/receptor imaging data with functional MRI data to produce a comprehensive evaluation of both tumor burden and potentially insight into tumor biology thus informing therapeutic decisions.

One population with complicated therapeutic options is patients with liver dominant metastatic disease. Treatment options vary from systemic therapy alone to combination of systemic and hepatic directed, to surgery if possible. Often the triage of patients between these treatment arms depends largely on the biological grade of tumor. A diagnostic test that would allow a global assessment of tumor biology and tumor burden in these patients would provide useful prognostic information to help inform clinical decisions and select the most appropriate therapies.

1. Primary objective:
   Determine the accuracy of dual tracer DOTATOC/FDG-PET/MRI for predicting biological aggressiveness (as measured by progression of disease) of metastatic neuroendocrine tumors in patients presenting for hepatic directed therapy.

2. Secondary objectives:
   a. Determine the heterogeneity of tumor PET signature (relative percentage of Dotatoc positive and FDG positive lesions) as predictor of response.
   b. Compare the PET/MRI results to tumor grade and markers of proliferation (WHO grade, Ki-67 expression) to determine which is a better predictor of time to progression.




## 2.0 Background:

The clinical behavior of neuroendocrine tumors (NET) is variable and assessing the biological aggressiveness presents a major clinical challenge in determining appropriate management. Prognosis is closely linked to tumor grade: low (G1), intermediate (G2), and high (G3), which is based upon either the mitotic index on microscopy or the Ki-67 labeling index (Edge S, AJCC Cancer Staging Manual 2009; Bosman FT, IARC Press 2010; Rindi G, Virchows Arch 2006). The Ki-67 labeling index tends to be a more powerful driver of grade than mitotic index (Adsay V, Am J Surg Pathol 2012; Dhall D, Hum Pathol 2012). While these tumors tend to be slow growing, about 50% of patients present with liver metastases, which is an adverse prognostic event reducing the 5-year survival rate to 20-40% (Edge 2009). Liver metastases are present in both patients with low and high grade tumors and studies have shown heterogeneity of Ki-67 labeling within individual patients. Zen et al found that in 30 patients with liver metastases from NET, that in one third of patients the Ki-67 index was > 3% higher than in the primary. The authors also demonstrated significantly lower tumor-specific survival in patients with elevated Ki-67 in the metastatic foci irrelevant of the primary tumor's labeling index (Zen, Pathology International 2013). In many instances, the diagnosis and grading of patients is established by fine needle aspiration or core biopsy of the primary site;

however, it is unclear if this captures the total biology of the tumor which can be heterogeneous within the same patient.

Given the importance of tumor grade and differentiation, several small studies have focused on imaging markers of differentiation. The vast majority of NETs over express somatostatin receptors (SSTR). The presence of SSTR in NET has been exploited by imaging for several decades, from $^{111}$In SPECT to recently developed $^{68}$Ga PET imaging. The degree of uptake of somatostatin analogue has been correlated with lower grade more well-differentiated tumors and linked to better prognosis (Giesel F, Exp Oncol 2013; Pape U, Ann N Y Acad Sci 2004, Modlin Cancer, 2003, Ghevariya South Med J 2009, Roche A, Eur Radiol 2003, Pitt S, J Gastointest Surg 2008). 18F-FDG-PET has also been evaluated as a diagnostic tool and marker of tumor differentiation, with a few studies indicating that FDG uptake correlates with poorly differentiated tumors and a poor prognosis (Bahri JNM 2014; Ghevariya South Med J 2009, Pitt SC 2008, Vogl Eur J Radiol 2009). The sensitivity for both somatostatin anologue PET imaging and FDG PET imaging varies in the literature and likely reflects different biology of different tumors within the small single center patient series.

In addition to molecular imaging, magnetic resonance imaging has evolved as a useful diagnostic and potential prognostic imaging tool. Studies have shown that enhancement patterns may correlate with early progression in patients with NET liver metastases (Denecke Eur J Radiol 2013; Armbruster Investigative Radiology 2013). Diffusion weighted imaging, which is a surrogate for cellular density, has also been shown to be a predictor of objective response in patients treated with hepatic directed therapy (Wulfert S, Mol Imaging Biol 2014). Several authors have shown an inverse correlation between ADC values (measure of diffusion restriction) and FDG uptake (Rakheja AJR 2013…). Recently, PET/MRI simultaneous imaging platforms have become available to allow combining state-of-the-art MRI with PET in a single imaging session. The advantage of simultaneous PET/MRI over traditional PET/CT platforms is the superior soft tissue contrast and liver lesion sensitivity and specificity of MRI over CT as well as the potential advantage of improved registration of simultaneous acquisition.

Whole-body imaging with somatostatin receptor analogues and FDG may provide a comprehensive assessment of tumor biology in individual patients. In a pilot study of 68GA-Dotatoc PET/MRI compared to the PET/CT, PET/MRI performed better with the MRI providing identification of additional lesions (Beiderwellen K, investigative radiology 2012). In a small series of patients undergoing intra-arterial $^{90}$Y/177Lu-DOTATOC therapy, both DWI and DOTATOC-PET demonstrated utility as early response indicators. [16] A study of 42 patients with liver metastases from NET suggested that DCE-MRI and PET imaging may provide complementary information about the biology of the tumors.[17] Performing these studies on a simultaneous PET/MRI system will provide the highest lesion conspicuity for anatomic localization of PET signal as well as functional MRI information related to lesion enhancement and diffusion restriction. The combination of MR and PET data may be complimentary in understanding the overall tumor biology.

Treatment of NET varies by grade and biological aggressiveness. Accurate depiction of tumor biology can be challenging when basing it on a very small sampling of tumor, especially when intrapatient tumor biology heterogeneity seems to exist. In patients with liver metastases, hepatic directed therapies are a mainstay. Hepatic directed therapy such as transarterial chemo-embolization (TACE) has been included in recent guidelines and shown to provide symptomatic improvement in 50-100% and objective response in 25-86% of patients. [7-13] Hepatic directed therapy may be more appropriate for patients with Grade 1 or 2 tumors as opposed to those with higher grade. Chemotherapy may be administered in patients with aggressive tumors or those inadequately managed by hepatic therapy. Whether to administer concomitant chemotherapy can be a challenging decision and response assessment measures by conventional imaging may lag behind or inadequately capture response leading to delays in treatment decisions. Imaging prognostic and predictive markers are valuable for triaging patients to appropriate therapies. In a study by Bahri et al, 18F-FDG-PET imaging was found to be a prognostic indicator, with FDG positivity portending a poor prognosis. In the same study, the investigators found that even in patients with some somatostatin receptor positive tumors, if they also had FDG positive lesions, they did worse. In another study by Has Simsek et al, the use of combined FDG-PET and 68GA-Dotatate-PET/CT provided added value in the therapeutic decision making process.

The goal of this study is to evaluate the accuracy of simultaneous 68Ga-Dotatoc-PET/MRI and 18F-FDG-PET/MRI in depicting biological aggressiveness/tumor heterogeneity as a prognostic tool for predicting treatment outcomes in patients undergoing hepatic directed therapy.

## 3.0 **Objectives**

1. Primary objective:
   Determine the accuracy of dual tracer DOTATOC/FDG-PET/MRI for predicting biological aggressiveness (as measured by progression of disease) of metastatic neuroendocrine tumors in patients presenting for hepatic directed therapy.

2. Secondary objectives:
   a. Determine the heterogeneity of tumor PET signature (relative percentage of Dotatoc positive and FDG positive lesions) as predictor of response.
   b. Compare the PET/MRI results to tumor grade and markers of proliferation (WHO grade, Ki-67 expression) to determine which is a better predictor of time to progression.

*This section describes the overall objectives, including the **primary** objective and any **secondary objectives**. (Each Primary and Secondary Objective should have its own Endpoint and an associated statistical analysis plan in Section 6.)*

## 4.0 **Eligibility Criteria**

### 4.1 Inclusion Criteria

1. Adult patients > 18 years of age with biopsy proven metastatic neuroendocrine tumors (from any primary) presenting for transarterial chemoembolization therapy.
2. Measurable disease in the liver.
3. Liver dominant disease.

### 4.2 Exclusion Criteria

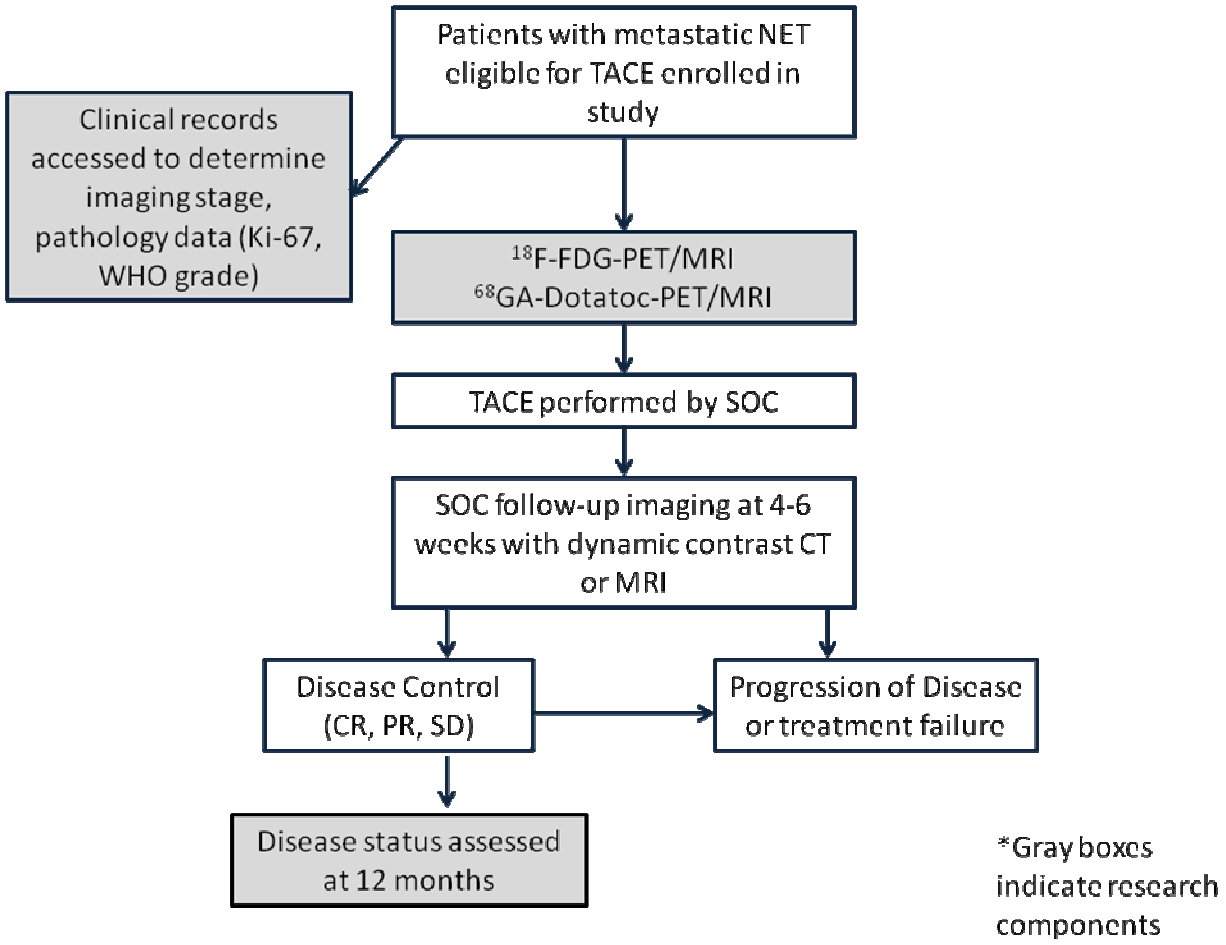
1. Pregnancy or breastfeeding
2. Contraindications to PET/MRI
3. Contraindications to TACE
4. Known other liver malignancy
5. Prior transarterial therapy to the existing liver lesions.

## 5. 0 Research Design and Methods

### 5.1 Study Design

*Provide an overview of the general study design and the primary and secondary endpoints*

All patients eligible for standard of care transarterial chemoembolization for metastatic NET tumors will be potentially eligible to undergo PET/MRI with dual tracer Dotatoc and FDG imaging.




PET/MRI: Dual tracer (Dotatoc and FDG)-PET will be performed on Siemens Biograph mMR simultaneous system at baseline (pre-therapy). Images will be interpreted by a nuclear medicine and diagnostic radiologist in consensus, as is the traditional read-out pattern for PET/MRI studies. Assessment of liver involvement with tumor by dynamic MRI with the addition of the fused dual tracer PET data will be performed on a MimVista workstation.

1. 68Ga-Dotatoc-PET/MRI –Fused data will be analyzed. The SUVmax of all lesions within the intended to treat portion of liver (lobar, segmental or total) will be measured. A background region of interest at least 3 cm in diameter will be obtained from normal liver in the same region from which the SUV mean will be obtained. The ratio of SUVmax/background will be measured (Tumor:non-tumor). Additional analysis of % of lesions seen on MRI with clear uptake will be performed. Subjective analysis of lesion uptake relative to background liver will be performed.
2. MRI-ADCmean/max of tumors will be measured. Enhancement patterns of tumors will be determined (arterially enhancing, delayed enhancing, hypoenhancing), sum total of viable tumor (mRECIST).
3. FDG-PET/MRI - The SUVmax of all lesions within the intended to treat portion of liver (lobar, segmental or total) will be measured. A background region of interest at least 3 cm in diameter will be obtained from normal liver in the same region from which the SUV mean will be obtained. The ratio of SUVmax/background will be measured (Tumor:non-tumor). Additional analysis of % of lesions seen on MRI with clear uptake will be performed. Subjective analysis of lesion uptake relative to background liver will be performed.

TACE: Treatment will be performed per standard of care by the interventional radiology division. Eligibility for TACE will be determined by the treating physician and is a requirement for enrollment.

Follow-up Imaging: Per standard of care, follow-up imaging will be performed according to clinical routine (typically q 4-12 weeks following each TACE treatment) and will consist of dynamic contrast enhanced MRI or CT. In the event that a patient cannot receive contrast, the best possible imaging option will be selected for follow-up as deemed by the treating physicians.

Pathologic data evaluation: WHO tumor grade, ki-67 staining and other markers of proliferation, tumor heterogeneity on histology and density of IHC staining.

Follow-up assessment: At 12 months following TACE all patients not meeting the event of progression will be analyzed for disease status according to mRECIST as determined by their most current imaging/clinical assessment.

## 5.2 Reference standard, as applicable (i.e., "Gold standard")

1. Follow-up imaging with dynamic contrast enhanced MRI or CT will be performed to assess disease control (CR, PR, SD) and progression (mRECIST).
2. Pathology records will be used to determine the clinical grade of the tumors

## 5.3 Registration Procedures

**Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.**

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

## 5.4 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

## 5.5 Patient Registration in the Siteman Cancer Center Database

All patients must be registered through the Siteman Cancer Center database.

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

## 5.6 Study Calendar / Schedule

| | Screening/ enrollment | Pre-TACE | TACE Per SOC | Follow-up after TACE | 12 months after TACE |
|---|---|---|---|---|---|
| Informed consent | X | | | | |
| MRI screening form | X | | | | |
| 68Ga-Dotatoc PET/MRI | | X[a] | | | |
| 18F-FDG-PET/MRI | | X[a] | | | |
| SOC CT or MRI scan | | X[b] | | X[b] | X[b] |
| Tumor biopsy | | X[c] | | | |

A-Pre-therapy PET/MRI should be performed within 8 weeks of the TACE procedure.
B-SOC Imaging will be prescribed by the treating physician and typically takes place 4-6 weeks following TACE and at regular intervals. Final assessment will be performed at 12 months using the patients most recent imaging study to assess disease status (PR, SD, PR, CR).
C-Tissue documenting diagnosis of NET is required for enrollment. If Ki-67 and grade of tumor was not performed, a repeat biopsy will be done prior to therapy. This may be done as standard of care.

## 5.7 Intervention (Imaging and/or Therapy) Visit(s)

Enrolled patients will be scheduled for PET/MRI examinations in the Center for Clinical Imaging Research (CCIR) on the Biograph mMR scanner. The investigational imaging will be performed within 8 weeks of the TACE procedure. The 68Ga-PET/MRI exam and 18F-FDG-PET/MRI exams will be scheduled no sooner than within 24 hours of one another. Screening for MRI safety and renal disease that may prohibit performance of the PET/MRI examination will be performed as part of the routine CCIR screening/eligibility process (appendix A). In instances where a creatinine value is not available within the last 90 days, point of care creatinine will be drawn in the CCIR. Patients will have an IV placed for injection of radiopharmaceutical and gadolinium contrast administration. The MRI with contrast will be performed with the FDG-PET/MRI examination and a non-contrast MRI will be performed with the Dotatoc-PET/MRI examination. The examinations each will require approximately 2-3 hours of uptake and imaging time.

## 5.6 General Concomitant Medication and Supportive Care Guidelines

**Dotatoc-PET/MRI**: Patients will not be required to withdraw SST analogue therapy before PET scanning. It has been recommended by some authors to temporarily withdraw SST analogue therapy (when possible) to avoid possible SST receptor blockade, however, for some patients the withdrawal of therapy might not be tolerated. This issue is still not definitely clarified and many centers do not require octreotide withdrawal before PET scanning. (Virgolini, Ambrosini et al. 2010).

Fasting is not needed before injection.

Patients should void before scanning. This will reduce the background activity in the pelvis as well as the radiation dose to the kidneys and bladder. All patients will have IV access established prior to entering the scanning room.

18F-FDG-PET/MRI: A minimum fasting interval of 4 hours is recommended before the study (consult a Radiologist or Nuclear Medicine physician if patient is diabetic). The patient's last meal prior to the PET study (which is typically the day before the study) should have a high protein and low carbohydrate content. In patients with well-controlled diabetes, the PET study will be scheduled to be performed in the morning as the first case of the day; the patient should fast for at least 4 hours and insulin or other diabetic medications (particularly sulfonylureas—chlorpropamide, glimepiride, glipizide, glyburide, tolazamide and tolbutamide—and rapid insulin releasers—nateglinide and repaglinide—which increase insulin secretion) should be withheld. Metformin should also be withheld, if possible since it increases gastrointestinal tract uptake of FDG. In patients with poorly controlled diabetes, whose fasting blood glucose is greater than 200 mg/dL, the following regimen should be discussed with the patient's physician and, after approval, should be followed by the patient. The patient will eat a normal breakfast, which will be followed by subcutaneous injection of approximately 10 units of regular insulin (or other short-acting insulin). FDG will be injected 4-5 hours later. The patient should not eat between the time of insulin injection and the time of FDG injection. Infusions of glucose-containing intravenous fluids or of parenteral ali-mentation (TPN) solutions should be discontinued for at least 4 hours before the study.
In diabetic patients treated with a continuous insulin infusion pump, the insulin infusion should not be interrupted for FDG-PET imaging. The protocol may need to be modified in patients with cardiac disease, renal disease, or other conditions in which fluid intake is (or may need to be) restricted (consult the responsible Radiologist or Nuclear Medicine physician before initiation of study).

### 5.7 Post-Therapy Visits

Post-therapy/imaging study visits will be conducted at routine SOC intervals as prescribed by the patient's physician. A final response assessment will be performed at 12 months for patients who did not previously progress. The final assessment will utilize the most recent imaging available.

### 5.8 Criteria for Removal from Study

Patients may be removed from study at any time if they withdraw consent. If a patient develops a contraindication to PET/MRI during the study period, they may be converted from FDG-PET/MRI examination to FDG-PET/CT.

### 5.9 Image Acquisition, Archiving, and Interpretation

**68Ga-Dotatoc-PET/MRI:** Combined whole-body PET/MRI acquisition will begin approximately 45-90 minutes after injection of $^{68}$Ga-DOTATOC and will consist of MR

sequences with simultaneous PET acquisition for 2-5 minutes per bed position adjusted as needed based on subject height, weight, and injected dose. The patient will be placed supine on the imaging table with arms resting comfortably by the side of the body. First, a localizer MRI scan will be performed to define the number of bed positions to be imaged. The whole-body acquisition will proceed from the skull base to the middle of the leg. PET emission data will be corrected for randoms, dead time, scatter and attenuation. A 3D-OSEM (ordered-subset expectation maximization) iterative reconstruction algorithm will be applied with 3 iterations and 21 subsets, 4 mm full-width at half-maximum Gaussian smoothing and zoom 1. For attenuation correction of the PET data from the PET/MRI, attenuation maps generated on the basis of the 2-point Dixon MRAC sequences obtained for every bed position will be applied. This procedure has been implemented in the post-processing software of the scanner and operates automatically. The MR sequences for whole body images will consist of dual echo DIXON sequences for attenuation correction and T2 single-shot fast spin echo sequences. Dedicated liver sequences will consist of pre-contrast 3D volumetric interpolated breath held examination (VIBE).

All patients will have IV access established prior to entering the scanning room. $^{68}$Ga-DOTATOC will be administered intravenously in conjunction with the PET/CT scan. The one-time nominal injected dose will be 3-5 mCi containing <50 µg $^{68}$Ga-DOTATOC (estimated, allowing for adherence of peptide to glassware or syringes, a portion of the 50 µg original quantity used for QC, etc). The dosage will be adjusted for body size such that the administered activity will be approximately 0.043 mCi/kg with a minimum dose of 3 mCi.

| | |
|---|---|
| ≤ 80 kg | 3.0 mCi |
| 80 – 94 kg | 3.5 mCi |
| 95 – 104 kg | 4.0 mCi |
| 105 – 114 kg | 4.5 mCi |
| ≥ 115 kg | 5.0 mCi |

The radiopharmaceutical will not be injected into intravenous lines together with parenteral nutrition solutions (Virgolini, Ambrosini et al. 2010)

**18F-FDG-PET/MRI (baseline and follow-up):** Combined PET/MRI imaging will begin 50-70 minutes following injection. Standard dosing of FDG per SOC regimen will be administered. A 3D-OSEM (ordered-subset expectation maximization) iterative reconstruction algorithm will be applied with 3 iterations and 21 subsets, 4 mm full-width at half-maximum Gaussian smoothing and zoom 1. For attenuation correction of the PET data from the PET/MRI, attenuation maps generated on the basis of the 2-point Dixon MRAC sequences obtained for every bed position will be applied. This procedure has been implemented in the post-processing software of the scanner and operates automatically. MRI stations will be assigned to cover from skull base to upper thighs (usually 4-5 stations). The sequences for whole body images will consist of dual echo DIXON sequences for attenuation correction and T2 single-shot fast spin echo sequences. Dedicated liver sequences will consist of 3D volumetric interpolated breath held examination

(VIBE) pre- and dynamic post-contrast, T2 with and without fat suppression, diffusion weighted imaging (b values-50, 400, 800) with scanner generated ADC maps, dual echo chemical shift T1 imaging.

Adult dose will range from 10-20 mCi according to patient weight.

| Weight (pounds) | Dosage (mCi) | NRC Range: ± 20% (mCi) |
|---|---|---|
| < 100 | 10 | 8 - 12 |
| 100 – 150 | 12.5 | 10 - 15 |
| 150.1 – 200 | 15 | 12 - 18 |
| 200.1 – 250 | 17.5 | 14 - 21 |
| > 250 | 20 | 16 - 24 |

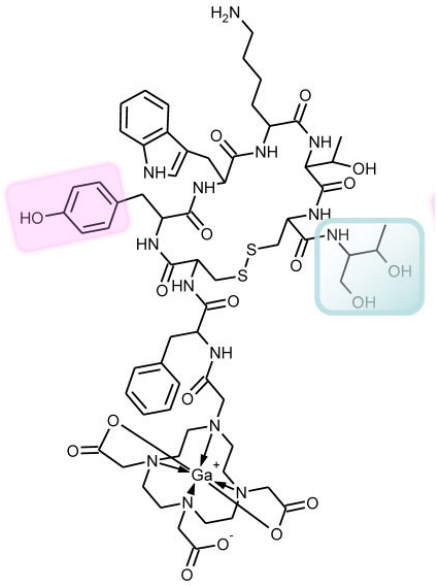
**Radiation Dosimetry:** FDG Radiation Dose:
Adult (15-mCi dose). Critical organ (urinary bladder wall): 3.3 rem with a 1-hour voiding interval and 6.2 rem with a 2-hour voiding interval. Effective dose: 1.1 rem with a 1-hour voiding interval and 1.3 rem with a 2-hour voiding interval.
Infant (1-year; 2.5-mCi dose) Critical organ (urinary bladder wall): 5.5 rem. Effective dose: 0.9 rem.

**Image Storage/Interpretation:** MR and PET data will be archived in the CNDA database and sent to MimVista workstation for fusion and evaluation. Images will be reviewed in consensus by a nuclear medicine and diagnostic radiologist. Post-contrast images from the FDG-PET/MRI will be used for fusion with the Dotatoc-PET/MRI examination. Subjective analysis of the liver MRI images will be conducted to identify all lesions within the liver and extrahepatic tissues (radiologists will identify lesions that are metastases by using anatomic MR sequences). PET images will be analyzed for regions of abnormal uptake within the liver and extrahepatic tissues. PET contours will be applied to the liver lesions to determine the SUV max. Anatomic imaging will guide localization of PET signal via fusion imaging and relative uptake of Dotatoc and FDG will be assessed for each lesion. Each patient will be categorized as being FDG + or -, Somatostatin + or -, neither, or both. A region of interest will be assigned to non-tumoral background liver to assess a non-tumor SUVmean.

**SOC Imaging:** Standard of care imaging will be performed per routine clinical practice and typically consist of contrast enhanced dynamic MR or CT. Images will be accessed and mRECIST assessment will be performed to determine time of progression by imaging. Clinical progression may also be deemed by the clinical oncologist.

## 6. Pharmaceutical Information.

Dotatatoc-PET is available at Washington University through an Expanded Access Investigational New Drug (EA-IND) Application.



(27) [$^{68}$Ga]Ga-DOTA-TOC

**$^{68}$Ga-DOTATOC PET/CT related radiation**

$^{68}$Ga-labeled radiopharmaceuticals general have lower level of effective dose compared to analogous compounds labeled with $^{18}$F, $^{99m}$Tc, and $^{111}$In as shown in Table 1 (Eberlein and Lassmann 2013). For example, the effective dose from $^{68}$Ga-DOTATOC is approximately 4-5 fold less than $^{111}$In-DTPA-octreotide. The reported effective whole body dose (less than 2.3 mSv) for one time dose to the patient which represents approximately less than half maximum annual permissible whole body radiation to radiation worker (50 mSv).

The recommended activity to obtain diagnostic images is at least 100 MBq; the organ that receives the largest radiation dose is the spleen, followed by the kidneys and urinary bladder (Virgolini, Ambrosini et al. 2010). The associated mass of unlabeled peptide injected in this protocol is less than 50 μg; this amount would be expected not to have any clinically significant pharmacological effect (Virgolini, Ambrosini et al. 2010). Considering the risk from either delay in diagnosis or inaccurate staging of known malignancies, the small risk of additional radiation to the patient is much less than the potential benefits in patients with a clinical indication for SRS.

Table 1 Effective dose for some PET and SPECT imaging agent

| **Agent** | **Examination Time** | **Effective dose (mSv)** |
|---|---|---|
| [$^{111}$In]In-DTPA-octreotide/SPECT | 24-48 h | 10.8 |
| [$^{68}$Ga]Ga-DOTATOC/PET | 30-60 min | 2.3 |
| [$^{18}$F]FDG/PET | 60-120 min | 5.6 |

**Toxicities Related $^{68}$Ga-DOTATOC-PET Imaging**

**Likely:**

Mild discomfort from the placement of the IV in the patient's arm.

**Less Likely:**

Discomfort from lying still on the imaging table
Claustrophobia from lying inside the PET scanner
Bruising at sites of venipuncture

**Rare:**

There is a remote risk of infection and an even smaller risk of thrombosis at the site of the IV placement.

There is a rare possibility of an allergic-type or other adverse reaction to $^{68}$Ga-DOTATOC choline or the gadolinium contrast agent (when MRI contrast is given).

There is a theoretical risk of nephrogenic systemic fibrosis (NSF), which has been linked to gadolinium contrast agents administered in patients undergoing MRI scanning who have severe renal dysfunction. This risk is mitigated by screening for renal dysfunction.

## 6.0 Statistical Considerations

### 6.1 Study Design and Endpoints

Patients will undergo a baseline dual tracer PET/MRI to determine tumor signature and relative SUV values of tumors for both tracers. MRI data will include ADC values and enhancement pattern. The main endpoint will be the time to tumor progression. Final assessment of response will be determined at one year following TACE for all patients who have not progressed prior to that time point. Data will be censored at death or for patients who are lost to follow-up prior to reaching an endpoint.

Lesion-level variables: the primary predictors SUVmax and SUVmaxTumor:Non-tumor ratio will be collected as continuous variables for FDG and Dotatoc. Each lesion will also be classified into one of four categories as FDG +, Dotatoc +, both FDT and Dotatoc +, or neither (+ defined as tumor:non-tumor ratio> 1). The ADC max/mean and

enhancement pattern (categorical-hyperenhancing, hypoenhancing, delayed enhancing) will be collected from the MRI

Patient-level variables: mRECIST sum of all tumor diameter and peak SUVmax for each tracer will be collected as continuous variables. The patients will each be categorized as having any FDG + lesions, any Dotatoc + lesions, at least one FDG+ lesion and at least one Dotatoc lesion, or all lesions not FDG or Dotatoc + (+ defined as tumor:non-tumor ratio> 1).

The agreement between PET relative SUV values for each tracer and SUVmax for each tracer and clinical tumor grade (WHO grade and Ki-67 rates) will be conducted with Bland-Altman analysis.

### 6.2 Objectives and Analysis Plans

1. Primary objective:

Determine the accuracy of dual tracer DOTATOC/FDG-PET/MRI for predicting biological aggressiveness (as measured by progression of disease) of metastatic neuroendocrine tumors in patients presenting for hepatic directed therapy.

2. Secondary objectives:
    a. Determine the heterogeneity of tumor PET signature (relative percentage of Dotatoc positive and FDG positive lesions) as predictor of response.
    b. Compare the PET/MRI results to tumor grade and markers of proliferation (WHO grade, Ki-67 expression) to determine which is a better predictor of time to progression.

The primary endpoint is the time to progression. We will fit separate Cox proportional hazards regression models to estimate the effects of each of our individual primary predictor variables (dual tracer SUVmax, SUV ratio, and ADC values on the time to progression. It is not known which variable may have the greatest impact. If significant hazard ratio is identified, step-wise adjustment for confounders will be performed as part of a secondary analysis. Given our small sample size, we will only be able to adjust for one confounder at a time, to ensure at least 10 events per covariate. Patient follow-up will begin following TACE treatment. Patients without an event will be censored at 1 year of follow-up from the date of their TACE procedure or at date of drop-out or lost-to-follow-up. We will assess the proportional hazards using -log-log plots. The estimated linear predictor given the observed covariate values will serve as the prognostic score. The discriminatory accuracy of this prognostic score with and without the PET/MRI measures will be summarized using the area under the time-dependent receiver operating characteristic curve (AUC).(1)

As a secondary analysis, we will estimate the Kaplan-Meier curves subgrouped by the categorical PET signature (+SSRT, +FDG, +both, neither).[J Am Stat Assoc. 1958; 53:457-481] The log-rank test will be used to compare time to progression for these four groups of patients. [J R Stat Soc. 1972; (A) 135-185]

For secondary endpoint analysis, the intraindividual variance of SUVmax tumor:non-tumor for multiple lesions will be assessed to provide a site-by-site information about tumor heterogeneity within each patient. The within patient variation in uptake of the two tracers for patients with multiple lesions will be assessed by looking at the range in SUVmax tumor:non-tumor ratios for each patient with multiple lesions to determine the site-to-site variation (Kurland JNM 2011). This will provide information regarding the variance of uptake that may reflect underlying tumor biology.

### 6.3 Sample Size Considerations

We expect 20-40% of patents will progress within 1 year. If we recruit 45 patients and 18 (40%) progress, we will have 80% power to detect an AUC of 0.75 under a null hypothesis that the AUC is 0.50 using a one-sided z-test with a type I error of 0.05. We will have 80% power to detect a hazards ratio (associated with a one-SD change of the PET/MRI measure) of 1.94 using a two-sided test with type I error of 0.05. If 9 (20%) progress, we will have 80% power to detect an AUC of 0.77 and a hazard ratio 2.54. We estimate that it would take about 24 months to accrue the 45 patients for this study given that we are currently following approximately 90 patients with this disease and have performed approximately 50 TACE procedures on patients with this condition in the last three years.

### 6.5 Study monitoring, interim analyses, and early stopping rules

## 7.0 Adverse Events; Safety Issues

*Adverse events (AEs) are a routine part of every clinical trial. There is language available that you may copy and paste into this overview and the following sections. However, it is critical to determine how AEs are managed at your institution and to utilize institution-specific language.*

### 7.1 Definition of Adverse Events and Potential Risks (1. Comprehensive Adverse Events and Potential Risks List and 2. Agent Specific Adverse Events List)

### 7.2 Definition of Serious Adverse Events (Serious Adverse Events List)

A Serious Adverse Event (SAE) is an injury or illness that:

Causes death

Is life threatening, even if temporary in nature

Results in permanent impairment of a bodily function or permanent damage to a body structure

Necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure

An increased level of care (e.g., unscheduled admission, transfer from a routine inpatient bed to an intensive care unit, etc.).

Events meeting the criteria for an SAE require notification of the sponsor and the reviewing IRB within the specified timeframe identified in section 8.4.1.1.

## 7.3 Adverse Events Characteristics

### 7.3.1 Grading of Adverse Events

### 7.3.2 Definition of Expected / Unexpected (Anticipated / Unanticipated) Adverse Events

### 7.3.3 Attribution of Adverse Events

**Attribution** of the AE:

Definite – The AE *is clearly related* to the study intervention.
Probable – The AE *is likely related* to the study intervention.
Possible – The AE *may be related* to the study intervention.
Unlikely – The AE *is doubtfully related* to the study intervention.
Unrelated – The AE *is clearly NOT related* to the study intervention.

## 7.4 Adverse Event Reporting

### 7.4.1 When and How to Report Adverse Events

It is the responsibility of the investigator to document all Adverse Events (AEs) which occur during the course of the study.

#### 7.4.1.1 Expedited Adverse Event Reporting

***Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.***

#### 7.4.1.2 Protocol-specific Expedited Adverse Event Reporting Exclusions

#### 7.4.1.3 Routine Adverse Event Reporting

## 8.0 Ethical Considerations (Including Informed Consent)

**[Note to CTMW Participants: In addition to the relevant sections below (8.1 to 8.5), fill out the 2-page "Template for Basic Elements of Informed Consent" at the end of this Word document.]**

### 8.1 Protection of Patient Rights

*You may also reference the Informed Consent form in this area.*

*If the device or therapy under investigation is one in which the PI, co-investigator, site, or sponsor has a vested financial interest please include text outlining how subjects will be protected from any real or potential conflict of interest.*

### 8.2 Confidentiality

### 8.3 Inclusion of Women and Minorities

All eligible patients will be screened for consent.

### 8.4 Audit and Monitoring

### 8.5 IND-

Dotatoc-PET will be available at Washington University through an expanded IND.

## 9.0 Data Management; Administrative Issues

Data will be stored on the CNDA database and analyzed on Mimvista and PACS.

## 10.0 REFERENCES

References for ROC calculations:
Hanley, J. A. and McNeil, B. J. 1983. 'A Method of Comparing the Areas under Receiver Operating Characteristic
Curves Derived from the Same Cases.' Radiology, 148, 839-843. September, 1983.
Obuchowski, N. and McClish, D. 1997. 'Sample Size Determination for Diagnostic Accuracy Studies Involving
Binormal ROC Curve Indices.' Statistics in Medicine, 16, pages 1529-1542.

References for hazard ratio calculations:
References
Hsieh, F.Y. and Lavori, P.W. 2000. 'Sample-Size Calculations for the Cox Proportional Hazards Regression Model
with Nonbinary Covariates', Controlled Clinical Trials, Volume 21, pages 552-560.
Schoenfeld, David A. 1983. 'Sample-Size Formula for the Proportional-Hazards Regression Model', Biometrics,
Volume 39, pages 499-503.

## 11.0 APPENDICES

**Appendix A-MRI screening form**

**Appendix B-SOC PET/MRI protocol**

**RSNA Clinical Trials Methodology Workshop**

**Template For**
**Basic Elements of Informed Consent**
**45 CFR Part 46.116 (A)**

Your Informed Consent document must address the 8 basic elements listed in Section a below. The first 4 elements will be specific to your protocol. Text approved by your local IRB for the last 4 elements should be available from your institution.

Your Informed Consent document should also address the 6 additional elements listed in Section b below, if they are relevant to your clinical trial.

**For purposes of the RSNA CTMW, please write a few sentences for each of the 8 basic elements, and any of the 6 additional elements that are relevant, in language understandable by the potential subjects for your clinical trial.**

"§46.116 General requirements for informed consent.

No investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Section (a):

1. Statement that study involves research; explanation of purpose(s) and expected duration of participation; description of procedures and identification of experimental procedures.

2. Description of risks or discomforts to subject. For studies involving research-related radiation exposure, information regarding radiation dose and risks should be included.

3. Description of benefits to subject or to others.

4. Disclosure of alternative procedures, if appropriate.

5. Description of the extent to which confidentiality will be maintained.

6. For research involving more than minimal risk, explanation as to whether compensation and medical treatments are available if injury occurs.

7. Explanation of whom to contact if questions arise about the research or the subjects' rights or whom to contact if research-related injury occurs.

8. Statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits, and that subject may discontinue at any time.

Section (b):

Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects to be involved in the study."

***Note: The Protocol Abstract/Overview should be completed after the protocol is nearly final, and then be moved to the front of the finished document. The Abstract/Overview also serves as the basis for Poster that will be displayed on Thursday evening.***

*__TITLE__ OF PROTOCOL*

## 1.0 PROTOCOL ABSTRACT/OVERVIEW

### BACKGROUND AND RATIONALE

*In one or two short paragraphs this section should telegraphically present:*

*Information about the target disease*
*Descriptions of and information about the investigational agent, device, or modality*
*The hypothesis being tested and why it is an important question*
*Rationale for the protocol/trial development*
*Why the risks are reasonable in relation to the anticipated benefits*
*What will be different after the study is completed as compared to the present status.*

### OBJECTIVES

*Study Objectives (also include a brief statement of primary endpoint(s) taken from section 6 of the protocol)*

### ELIGIBILITY

*Main clinical disease*
*Key inclusion criteria (the entire list of inclusion and exclusion criteria will appear later in section 4 of the protocol)*

### STUDY DESIGN

*Stratification criteria (if applicable)*
*Arm(s) descriptions (if applicable)*
*Procedure or treatment description*
*(Very brief description of the main elements and the primary endpoint, extracted from section 5)*

### REQUIRED SAMPLE SIZE

*Total number of subjects projected for the entire study, as extracted from section 6.*