Moving ^{68}Ga-labeled DOTA PET Imaging Agents Towards Approval

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Gallium-68-labeled somatostatin analogs ([^{68}Ga]DOTATOC, DOTATATE and DOTANOC) have been identified as important imaging agents to detect and manage neuroendocrine tumors (NETs) and have been shown to be superior to the approved product ^{111}In-octreotide. In April 2012, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) established a formal ^{68}Ga Users Group under their Clinical Trials Network (CTN) to advance the use of these ^{68}Ga-labeled analogs for the imaging of neuroendocrine tumors (NETs) in the US.

TIMELINE OF ^{68}GA-USERS GROUP ACTIVITY

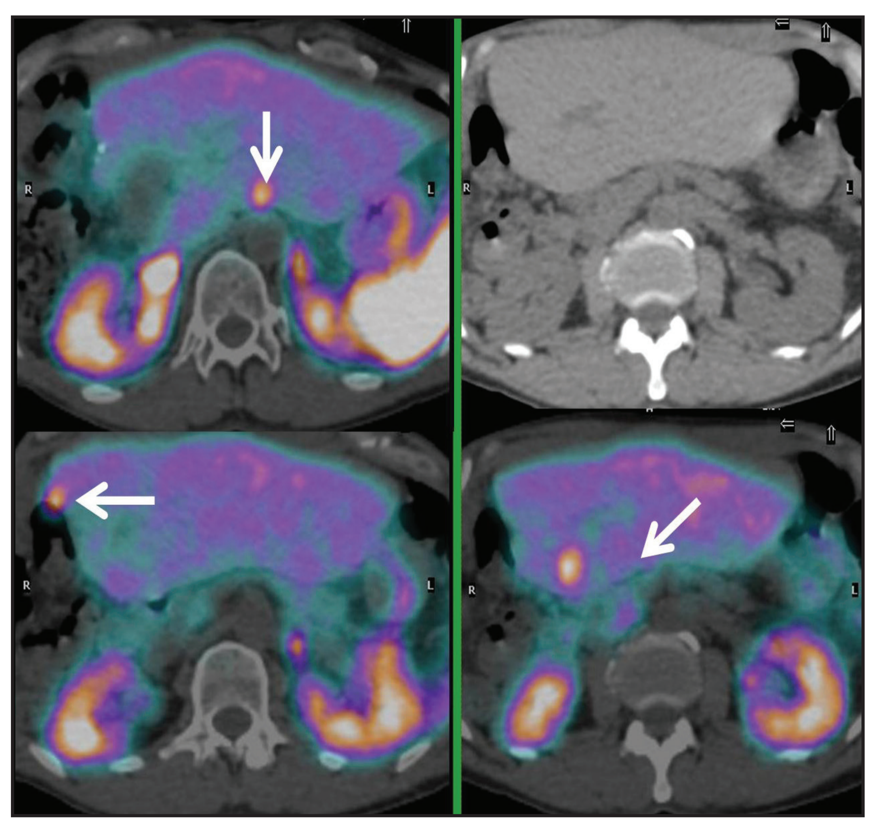
- SNMMI sets up formal ^{68}Ga-Users Group - CTN to head — **April 2012**
- **June 2012** — Working Groups formed to create IND template sections
- CTN attends FDA meeting on Orphan Drug Designation applications — **October 2012**
- **January 2013** — Decision approved to submit DOTA agent for Orphan Drug Designation
- DOE considers ending their ^{68}Ge production & distribution; Group submits comments — **March 2013**
- **April 2013** — Contact initiated with precursor producers on drug availability
- AAA (Advanced Accelerator Applications) announces plans to work on producing diagnostic 'kits' for DOTATATE and DOTATOC — **June 2013**
- **August 2013** — CTN submits application for Orphan Drug designation for DOTATOC; Slides from June 2013 Gallium Information session posted on CTN website
- Poster on the Group's activity to date submitted for the NANETS 2013 meeting — **September 2013**

Prospectively defining and harmonizing chemistry and imaging study parameters from a select group of qualified study sites allows multiple sites to combine their respective clinical trial data thereby simulating a multicenter trial that allows for pooling of data for an NDA submission. The FDA would be asked to review the data as a single multicenter study.

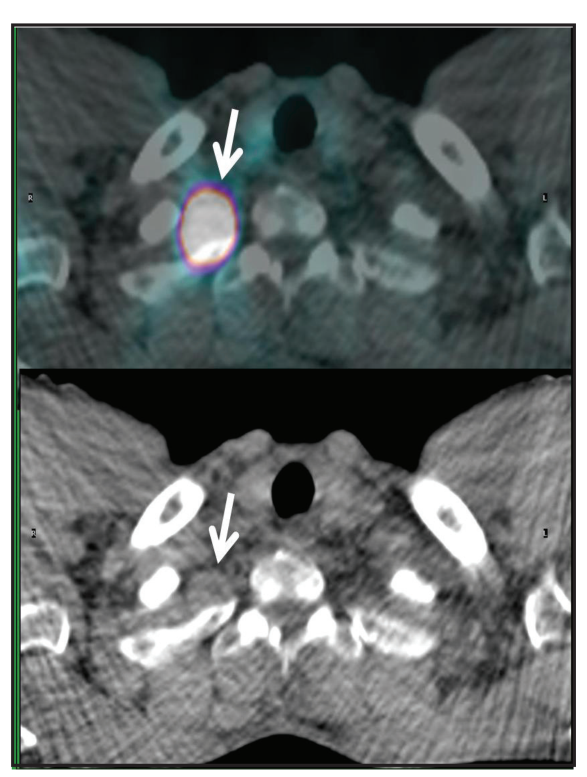
Radiopharmaceutical of Interest at US Sites:

- Indiana/Purdue University at Indianapolis: DOTANOC
- NIH Clinical Center: DOTATATE
- Radio-Isotope Therapy of America: DOTATATE
- Stanford University: DOTATATE
- University of California Los Angeles: DOTATATE
- University of Iowa: DOTATOC
- Vanderbilt University: DOTATATE

Vanderbilt University: ^{68}Ga-DOTATATE PET/CT



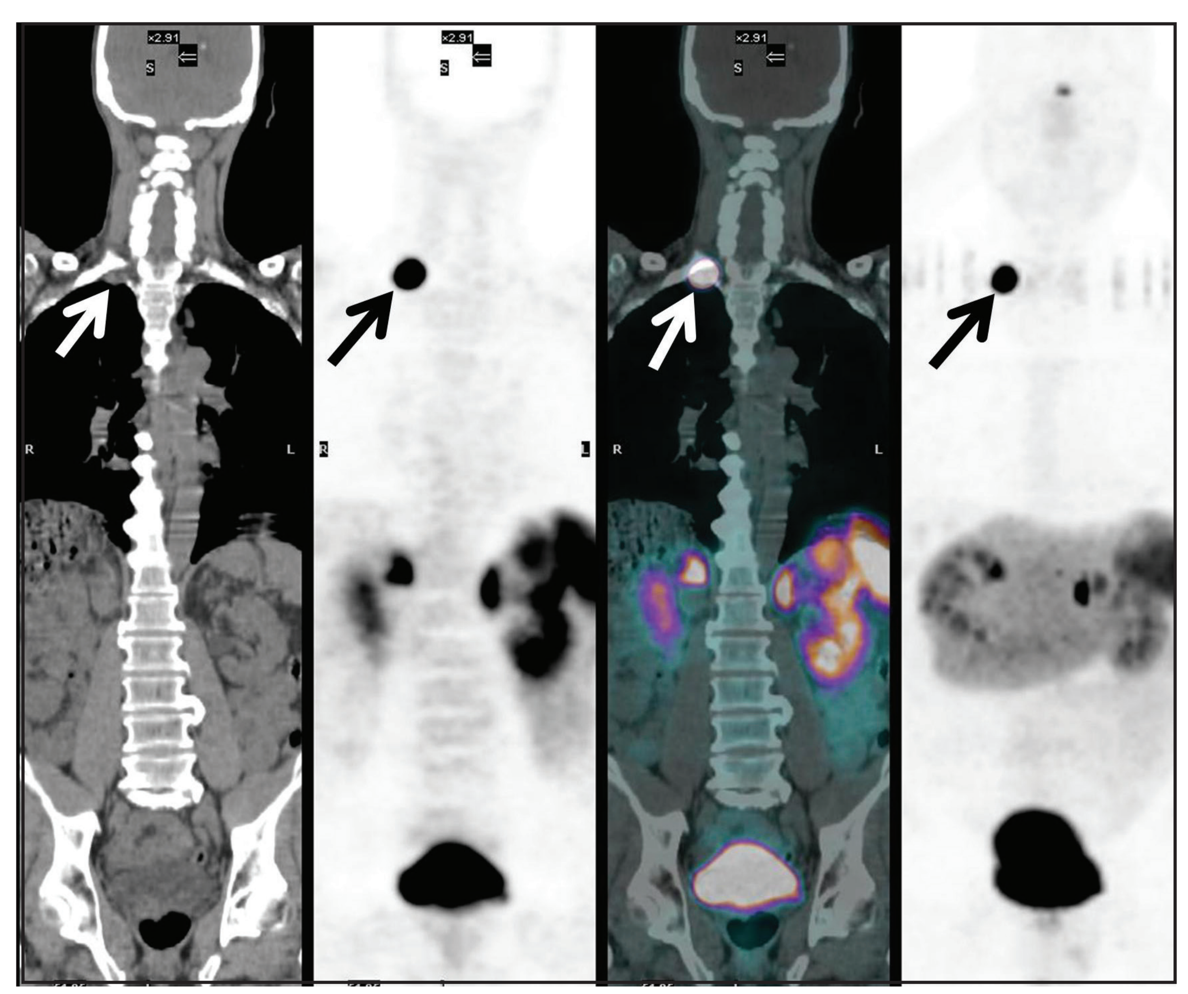
Middle aged male with prior small bowel carcinoid with extensive metastases to residual liver. The primary tumor was resected years ago, with a right lobe hepatectomy also performed. The patient presents with no symptoms and negative tumor markers for restaging with ^{68}Ga-DOTATATE PET/CT. No other imaging was available at the time of imaging. The ^{68}Ga-DOTATATE PET/CT scan demonstrated not only extensive disease in the liver but metastatic disease in the chest, establishing that the patient was not a candidate for a major surgical procedure to attempt to cure his disease. This resulted in a major impact on care (no surgery vs. futile surgery).



TOP: Multiple liver metastases, only three of which are shown on these "fused" images.

LEFT: Unexpected 2 cm metastatic lesion between right posterior ribs 1 & 2 (arrow).

RIGHT: Unexpected 2 cm metastasis in the base of the neck and multiple metastases in the remaining liver (right lobe removed years ago).



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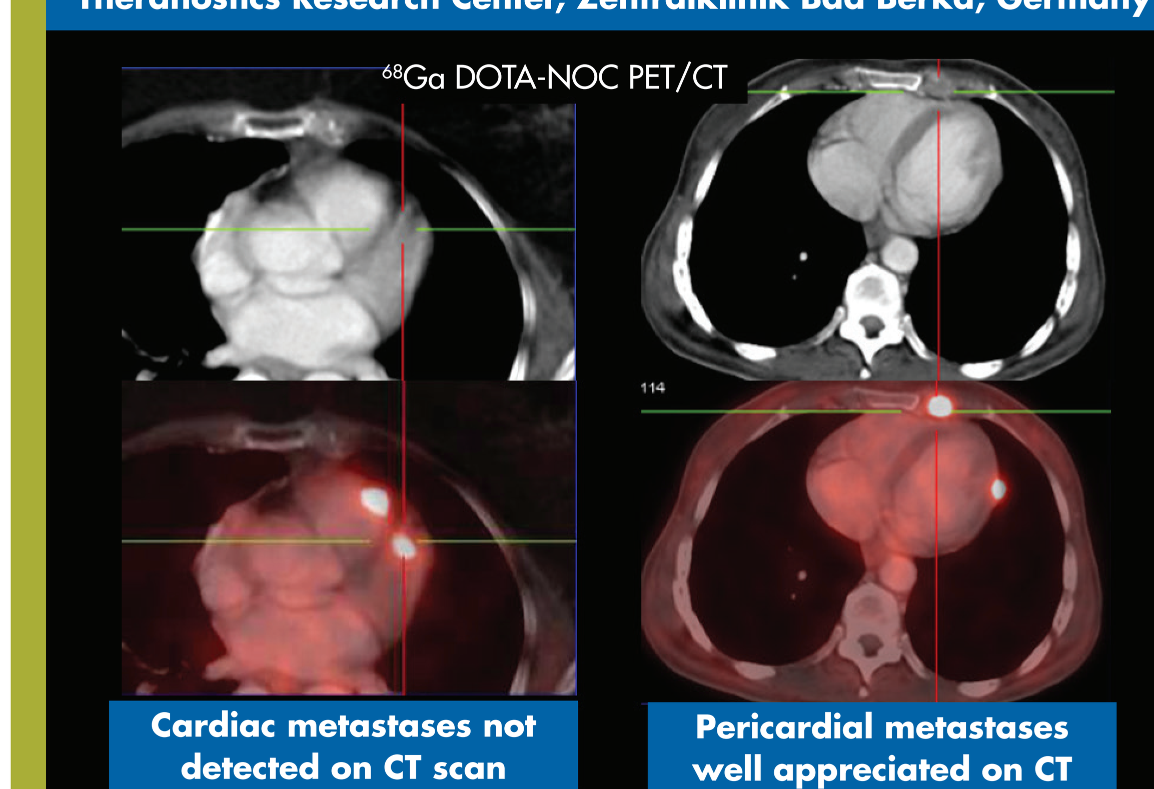
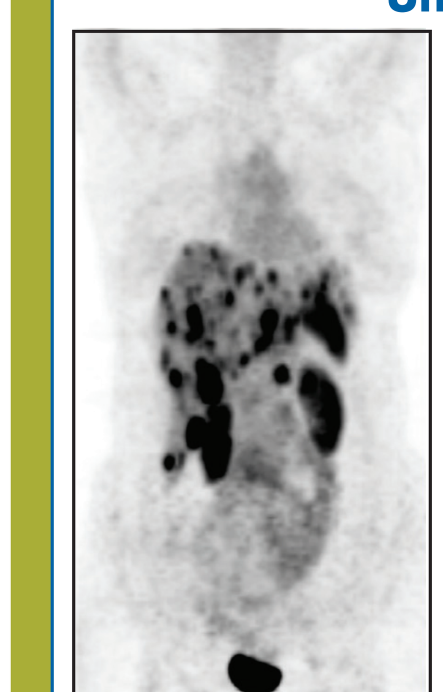
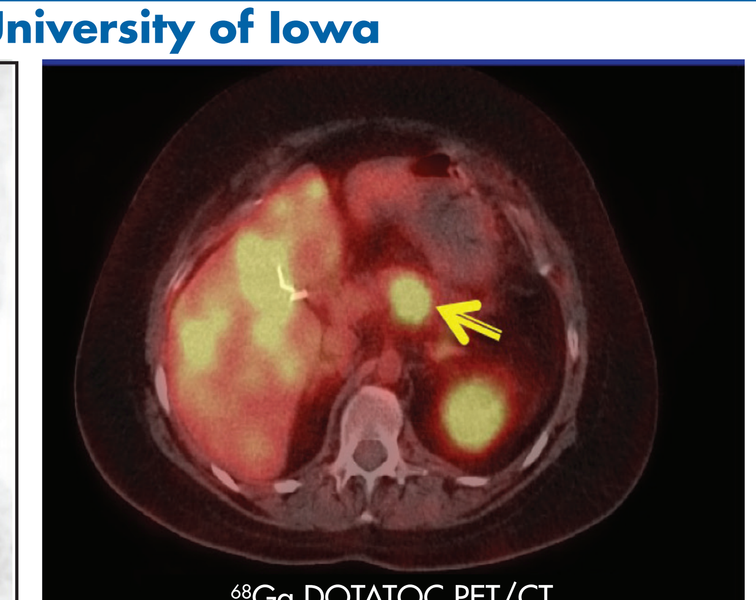


University of Iowa



MIP Image



^{68}Ga DOTATOC PET whole body and fused PET/CT images of a patient with liver metastasis of NET with unknown primary. Primary tumor identified in the pancreatic head (arrow) on ^{68}Ga DOTATOC PET/CT.

The ^{68}Ga Users Group is developing an Investigational New Drug (IND) template for the ^{68}Ga-DOTA agents that qualified sites could then utilize to file their own IND. Template Sections include:

- Basic inclusion/exclusion criteria
- Dosing information
- Safety procedures
- Adverse event reporting
- Detailed imaging acquisition guidelines
- Chemistry manufacturing section with harmonized end-product specifications to incorporate into an IND
- Generic data collection forms
- Draft informed consent form adaptable to fit a site's regulatory requirements