68Ga-DOTATATE PET/CT imaging – Initial Vanderbilt experience

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Disclosures:

- No financial disclosures or conflicts of interest to report.
- $^{68}$GaDOTATATE PET/CT is investigational and not US FDA approved in the US.
- Accordingly, all use of $^{68}$GaDOTATATE PET/CT should be in the context of a properly approved clinical trial with informed consent and local IRB approval.
- If $^{68}$GaDOTATATE PET/CT imaging is used for clinical management in the US, a US FDA IND must be obtained first.

$^{68}$GaDOTATATE PET/CT for NET
Incidence of neuroendocrine tumors

Anterior 3D Maximum Intensity Projection image of a $^{68}$Ga DOTATOC PET scan (left) compared to an $^{111}$In-Octreotide anterior planar imaging (right).

KM Analysis of survival of NET patients (time in years).

**p < 0.001**

Survival of patients with and without primary tumor resected.

Basic information theory: better information leads to better decisions

Patients do better with:
- Resection of primary than without
- As much extirpation of tumor as possible (debulking surgery)
- Better information regarding treatment response

Thus, improved imaging may improve patient management – but does it?

Outcome measured: Outcome on PFS, OS
Survival of patients with metastatic carcinoid

- 1988-99 n=892 SEER data base. Median survival 37 mo
- 1973-87 n=787 SEER data base. Median survival 17 mo
- Midgut carcinoid, n=284 Uppsala. Median survival 115 mo (5yr survival 77%)
- 1974-2004 SEER. Median survival 33 mo

Slide courtesy of Prof. Kjell Oberg
Accordingly, our NET study group at VUMC has applied for, and received, an IND from the US FDA (#111972) for the use of $^{68}$GaDOTATATE PET/CT in evaluation of patients with advanced NET.

Advanced NET:
- Metastatic disease, with or without u/k primary
- Signs and symptoms of NET without evidence of disease with conventional testing

"Investigator initiated" – 3 year process

Rate limiting step: Funding
• Applied to the US FDA for permission to charge for direct costs of the $^{68}\text{GaDOTATATATE}$ (almost $2,000/dose)
• Cost for research PET/CT about $3,000
• Initial 50 patients for safety/efficacy: additional costs for:
  ◦ Blood tests
  ◦ ECG
  ◦ Vital sign monitoring
• Estimated total cost: $7,000 - $8,000
• Research study – insurance ?? pay

$^{68}\text{GaDOTATATATE}$ PET/CT for NET
- Standard imaging must be done (CT and/or MRI, $^{111}$In-Octreotide SPECT/CT and $^{18}$F-FDG PET/CT)
- Two imaging physicians must read $^{68}$Ga-DOTATATE PET/CT blinded to standard imaging and to each other’s interpretation of $^{68}$Ga-DOTATATE PET/CT
- Case review of each study with clinical care givers to determine impact on Tx
- STARD reporting
Vanderbilt experience:
- Two patients scanned with compassionate use INDs from the US FDA
- First patient: Not previously scanned with ⁶⁸GaDOTATATE PET/CT
- After initial two, we obtained an IND for the use of ⁶⁸Ga-DOTATATE for imaging patients with somatostatin receptor expressing tumors
- We obtained IRB approval for scanning adults for staging and for search for U/K primary
- [ClinicalTrials.gov](https://clinicaltrials.gov): NCT01396382
Vanderbilt experience:
- 61 yo WF with carcinoid of small bowel resected years ago
- $^{111}$Octreotide SPECT/CT scan demonstrated focal lesions thought to be limited to right lobe of the liver
- Conventional imaging (CT, $^{18}$F-FDG PET/CT and MRI) revealed these lesions to be cystic, with other cystic lesions throughout the liver
- Prior to attempted surgical cure, evaluation of the other cystic lesions was desired by the patient

$^{68}$GaDOTATATE PET/CT for NET
Anterior view of standard of care imaging with $^{111}\text{In}$-labeled octreotide.
SPECT/CT of standard of care imaging with $^{111}$In-labeled octreotide.
Imaging of somatostatin receptor expressing tumors:

A: Anterior view of standard of care imaging with $^{111}$In-labeled octreotide.

B: Anterior view of investigational PET/CT imaging with $^{68}$Ga-DOTATATE. Arrows indicate some of the 9 sites of tumor in the liver seen with the $^{68}$Ga-DOTATATE imaging that are not seen with the standard of care imaging in the US.
Imaging of somatostatin receptor expressing tumors:

A: Anterior view of standard of care imaging with $^{111}$In-labeled octreotide.

B: Anterior view of investigational PET/CT imaging with $^{68}$Ga-DOTATATE. Arrows indicate some of the 9 sites of tumor in the liver seen with the $^{68}$Ga-DOTATATE imaging that are not seen with the standard of care imaging in the US.
Axial STIR-wt MRI

Axial CT

Axial \textsuperscript{18}F-FDG Fused PET/CT

Axial \textsuperscript{68}Ga-DOTATATE Fused PET/CT
Imaging of somatostatin receptor expressing tumors:

One coronal slice of the investigational PET/CT imaging with $^{68}$Ga-DOTATATE.

Arrows indicate some of the 9 sites of surgically verified tumor in the liver seen with the $^{68}$Ga-DOTATATE imaging that are not seen with the $^{111}$In-labeled octreotide.
The patient returned to referring provider, a world authority in NE surgery at a world-famous medical center. All 9 lesions verified by I/O U/S, 8/9 resected. One lesion could not be resected. Follow-up CT one year later, the single remaining lesion was growing. The patient returned for a repeat ⁶⁸Ga-DOTATATE PET/CT prior to planned attempt at surgical extirpation.

Follow-up:
Follow-up:

- Surgical extirpation not feasible – too much liver to be removed.
- Patient referred to Uppsala for PRRT (Peptide Receptor Radionuclide Therapy)

Next patient:
- Middle-aged female - known NET of the S. B.
- Primary resected years ago
- Presents as a possible candidate for surgical extirpation of abdominal disease
- Neg Octreotide x two large liver lesions
• Carcinoid of SB resected years ago, no nodal resection.
• FU Octreotide scans – uptake only in **uncinate process of pancreas**, biopsy negative for tumor
• Known enlarged mesenteric LNs, no uptake on Octreotide scans

Next case: Middle-aged male with hx known small bowel NET, incomplete resection
Multiple intensely avid LNs of the mesentery.
Probably normal uncinate process uptake of $^{68}$Ga-DOTATATE.

Multiphase CT of the pancreas was normal. Prior biopsy was negative for tumor.

Patient scheduled for **surgical extirpation** of residual tumor.
Survival of patients with metastatic carcinoid

Survival time (months)

Survival probability

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• How much value added by a better scan?
  ◦ Two blinded readers initially.
  ◦ Patient conference: Did the better scan change management and/or outcome; if so, how?

• Difficult to quantify: 2 hour test vs. 2-3 day test – how much is this worth?

**STARD reporting (standards for reporting of diagnostic accuracy)**
• Difficult environment to bring a new, presumed better diagnostic test to the US.
  ◦ Regulatory issues (US FDA, IRB)
  ◦ Financial issues
    • No Big Pharma
    • Third party payers
    • Difficult funding environment for research
• So far, this has been a three year process
• 3/7 patients scanned so far, major change in management.
Vanderbilt plans:

- Perform first 50 patients with:
  - Detailed toxicity testing for safety/efficacy reporting to US FDA
  - If no issues found, request subsequent studies to be done without detailed toxicity
- Request permission for ~ 800 patients to receive baseline and follow-up scans for evaluation of impact on PFS and OS
- Study to be done in accordance with STARD criteria for impact on patient management and outcome compared to conventional care
Vanderbilt NET Group