Imaging Advancements in Nuclear Medicine: Pancreatic Neuroendocrine Tumor Localization and Treatment

Chelsea Palmer Stephens, MHS, R.T.(R)(N), CNMT
Asher Street Beam, DHA, R.T.(R)(MR), MRSO
Zack Gray, MS, R.T.(R)(MR)(CT)
Julia Mansfield, MSNMT, R.T.(R)(N)
Lexie Reves, MSNMT, R.T.(R)(N)
Jennie Gray, MSNMT, R.T.(R)(N)
Alexa Stamey, MSNMT, R.T.(R)(N)
Matthew Collum, MSNMT, R.T.(R)(N)
Vani Vijayakumar, MD

Background This case report details a 57-year-old African American man with pancreatic neuroendocrine tumors (NETs). The patient underwent positron emission tomography (PET) imaging using gallium Ga 68 dotatate, which localized the tumors. Selected tumors were treated with 4 doses of 200 mCi of lutetium Lu 177 dotatate during a period of 8 months. At the conclusion of treatment, the patient demonstrated improvement, progressing from bedbound and confused to ambulatory and coherent. In addition, the patient stated he felt no adverse effects.

Discussion Pancreatic NETs are rare tumors affecting 0.001% of the population. These tumors are associated with various symptoms and are classified as functional or nonfunctional. Imaging modalities, such as computed tomography (CT), magnetic resonance (MR) imaging, and gallium Ga 68–labeled PET, are essential in detecting and evaluating pancreatic NETs. For patients with localized NETs, the primary treatment is surgery; however, the radiopharmaceuticals yttrium Y 90 microspheres and lutetium Lu 177 dotatate are used as therapy to treat nonresectable tumors.

Conclusion Lutetium Lu 177 dotatate is used in NET cases that are deemed inoperable and for patients who are not responding to treatment. This case study demonstrates the effectiveness of combining imaging with Ga 68–labeled PET and treatment with lutetium Lu 177 dotatate. This treatment is not a cure but has been shown to improve a patient's quality of life.

Keywords *neuroendocrine tumors, Lutathera treatment, positron emission tomography-computed tomography, gallium Ga 68 dotatate, lutetium Lu 177 dotatate*

Metastatic pancreatic neuroendocrine tumors (NETs) arise from the islet cells of the pancreas and are rare, accounting for approximately 2% of pancreatic cancers. Various modes of diagnostic imaging are used to help localize and treat these pancreatic NETs, including computed tomography (CT), magnetic resonance (MR) imaging, and nuclear medicine (NM). In NM, positron emission tomography (PET) combined with CT and MR can help clinicians further understand the nature of these tumors and how to treat them.

Literature Review

Pancreatic NETs are rare neoplasms that arise specifically from the endocrine tissues of the pancreas. Although rare, there are a few case studies published on this condition. For example, a 62-year-old man at the Gastroenterology and Hepatology Department at the Fundeni Clinical Institute presented with aggressive pancreatic NETs that metastasized to the liver, spleen, and bone. Imaging included contrast-enhanced CT, sonography, NM bone scans, and MR. The patient underwent palliative chemotherapy and radiation therapy; the patient died less than 1 month later.[1]

Another case study involved an incidental finding of pancreatic NETs in a 37-year-old asymptomatic man during a laparotomy after abdominal trauma. The only imaging reported was a CT, which was the standard at the time for detecting NETs. The patient underwent an endoscopy, biopsies, and exploratory laparotomies, along with chemotherapy for treatment. He was reported to have no complications other than chemotherapy toxicity, which was then discontinued, and the patient continued to improve.[2]

Although the literature includes similar cases of pancreatic NETs and treatment, there is limited information regarding imaging by gallium Ga 68 dotatate and treatment by lutetium Lu 177 dotatate. This case provides information on how this imaging technique and treatment have become successful tools for patients with pancreatic NETs.

Case Description

This case report details an individual with a pancreatic NET. Because the case study contains 3 or fewer patients, it is exempt from Institutional Review Board approval.

In August of 2017, a 57-year-old African American man was admitted to the hospital to evaluate prostate problems. He had a history of smoking, high cholesterol, and hypertension. A CT scan was performed in which doctors incidentally found tumors in his liver, and a diagnosis of metastatic high-grade malignant pancreatic neuroendocrine cancer was given (see **Figure 1**). The largest tumor was 12 cm and located in the right lobe of the liver. In addition, 2 smaller lesions were found in the right lobe, and 2 small lesions were found in the left lobe. A follow-up PET-CT scan was performed, which also showed multiple lesions on the right lobe of the liver and a hyperenhancing mass on the pancreatic tail. After completing 3 cycles of systemic therapy in January 2017, MR imaging of the liver was performed, which showed that the therapy was successful enough for him to be a candidate for surgical resection.

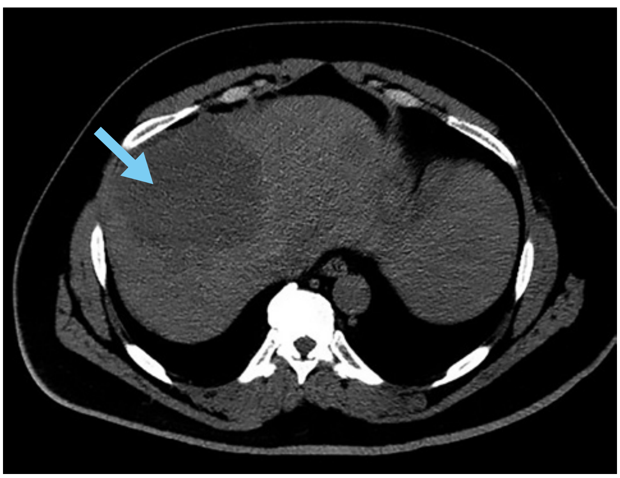

Figure 1. *Computed tomography (CT) image showing a transverse slice, indicating a 12-cm liver tumor in the right lobe (arrow). Image courtesy of the authors.*

In February 2018, he was admitted to the hospital and underwent several surgical procedures including a radical antegrade modular pancreatosplenectomy, superior mesenteric vein resection with bovine pericardial patch repair, left adrenalectomy, 15 liver ablations, and 8 microwave ablations of the liver masses. After all surgical procedures, he went into acute renal failure but was given fluids to help correct this issue. After these procedures, a CT of the chest, abdomen, and pelvis without contrast was performed, and the patient was discharged.

The patient was readmitted in March 2018, because of an abdominal abscess from the extensive surgical procedures. To treat the abscess, 3 percutaneous drains were placed. Three days after drain placement, an infection presented in the right upper quadrant of the patient's abdomen. The drain was removed, and antibiotics were given to treat the infection. A month later, the patient underwent a CT scan, which confirmed that his condition had improved, and he was discharged.

In August 2018, the patient underwent a visceral arteriogram in interventional radiology. This procedure was used to insert technetium Tc 99m macroaggregated albumin particles directly into the hepatic artery via catheter placed in the femoral artery. This procedure also ensured the placement and patency of the catheter. After the arteriogram, the patient was transported to the NM department for a hepatic arterial perfusion scintigraphy scan. His chest and liver were imaged to collect accurate counts of the amount of particles that were delivered to the lungs and the liver. It was determined that less than 20% of the tracer localized in the lungs; therefore, he was a candidate for yttrium Y 90 treatment. In September 2019, the patient received yttrium Y 90 microspheres (TheraSpheres) treatment to radioembolize his liver tumors. Two weeks later, a limited PET-CT scan confirmed a successful

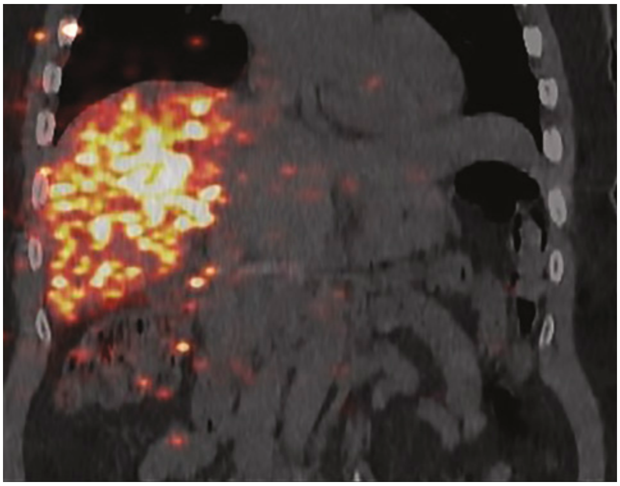

Figure 2. *Nuclear medicine scan indicating successful radioembolization of liver tumor in the right lobe. Image courtesy of the authors.*

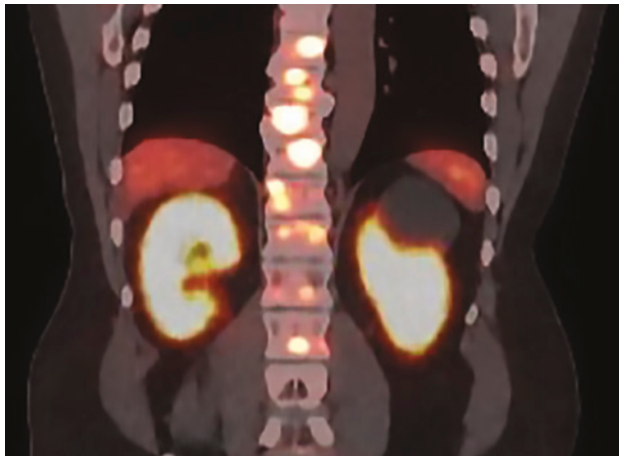

Figure 3. *Nuclear medicine positron emission tomography-CT scan with gallium Ga 68 dotatate showing osseous metastases. Image courtesy of the authors.*

transarterial radioembolization of the right hepatic lobe (see **Figure 2**).

In February 2020, the patient had an abdominal CT with and without contrast that showed continuation of metastatic NET in the liver. The CT also showed that he had progressive extrahepatic disease with the addition of new osseous metastases. A few months later, a follow-up CT of the abdomen was performed with and without contrast that revealed new bone metastases. Physicians began designing a new treatment plan to improve the patient's condition.

In June 2020, the patient had a gallium Ga 68 dotatate PET scan that showed the NETs that overexpress somatostatin receptors and precisely located the tumors in the patient's body. For this study, the patient was injected with 5.4 mCi of gallium Ga 68. The scan was delayed for 1 hour to allow the tracer adequate time to circulate throughout the body. Once started, the scan lasted about 45 minutes, and the patient was imaged from vertex to thigh. This scan suggested that the patient might respond favorably to lutetium Lu 177 dotatate treatment (see **Figure 3**).

In July 2020, the patient began receiving lutetium Lu 177 dotatate (Lutathera) treatment for NETs. For this treatment, the patient had two 20 G peripheral IVs. He was premedicated with antiemetics 15 minutes before being given an amino acids solution. Amino acids were given, and a lutetium Lu 177 dotatate infusion was started 30 minutes later (see **Figure 4**). A dose of 200 mCi of lutetium Lu 177 was infused for approximately 30 minutes total, starting with a rate of 50 mL/h for 5 minutes and then 100 mL/h for 5 minutes. Most of the dose was delivered during this time. The rate was then changed to 300 mL/h because he did not have extreme symptoms in the first 10 minutes. A pancake probe was placed over the dose during the

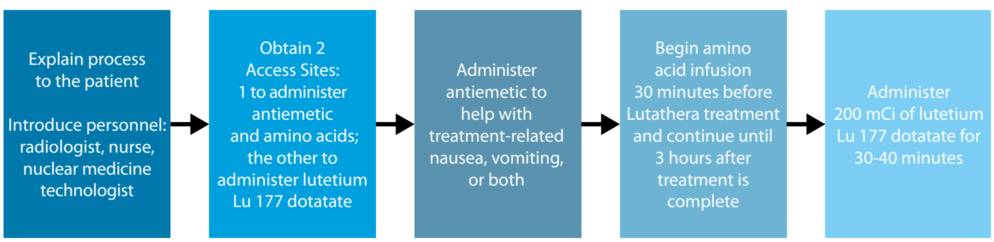

Figure 4. *Lutetium Lu 177 dotatate administration process. Flowchart courtesy of the authors.*

last part of infusion to monitor activity. The activity began decreasing quickly and started to level after about 30 minutes. When the activity had steadied, a final 5-minute countdown was started to complete the infusion. After the first treatment of lutetium Lu 177 dotatate, the patient's condition improved tremendously. He went from being bedbound and confused to ambulatory and coherent. Three more doses oflutetium Lu 177 dotatate were administered to this patient in 8-week intervals. The patient received his final treatment of lutetium Lu 177 dotatate in March 2021. After treatment was completed, the patient stated that he had not experienced adverse effects regarding treatments and was feeling better than he had in years.

Discussion

NETs are rare, occurring in 1 in 100 000 people; however, they can affect any age group. Signs and symptoms vary in each case and are classified as functional or nonfunctional. Functional cases include gastrinomas, insulinomas, and glucagonomas. Gastrinomas are associated with the hormone gastrin, which aids in the digestion of food by causing the release of stomach acid. Insulinomas arise from insulin-forming cells and can form in any part of the pancreas. In most cases, these tumors are benign and slow growing. Like insulinomas are glucagonomas that cause the liver to break down glycogen, which is necessary to control blood sugar levels. In contrast to insulinomas, glucagonomas manifest in the tail of the pancreas and usually are malignant.[3]

Nonfunctional NETs, the second classification group, are the most common. They usually are found incidentally with symptoms presenting in the later stages.[4] Overall, NETs present themselves aggressively in comparison with other tumors and often are found to be metastatic.[4,5] In this case study, the tumors were found incidentally with the disease already metastasizing to the liver on detection.

Symptoms

Depending on the functionality of the tumor, the patient might exhibit symptoms. In most cases, these tumors are nonfunctional and demonstrate no clinical indications of NETs. If functional, these tumors might present with digestive tract symptoms such as stomach ulcers, indigestion, constipation, or diarrhea. Other common indications are abdominal and back pain, weakness, fatigue, and muscle cramps. Aggressive tumors might produce more noticeable changes, including sudden weight loss, skin rash, hypoglycemia, diabetes, or yellowing of the skin and eyes. These symptoms depend on the location of the tumor, if it is functional or not, and the type of hormone secreted.[5-8] In this case, the patient's tumor was nonfunctional and resulted in no symptoms until the tumor reached its later stages.

Imaging

Medical imaging is essential to properly diagnose and treat NETs. The most common imaging modalities used to image NETs are CT, MR, and PET. CT uses ionizing radiation to form cross-sectional images of the anatomy of interest. The computer system can then reconstruct the slices by stacking them on top of each other and creating a 3-D image free of superimposition, which is not possible with conventional radiography. These scans also have better contrast resolution than do radiographs, which leads to an increased ability to distinguish differences in tissue.[9] In this case, CT was the critical imaging modality, serving as the basis of tumor diagnosis, disease management, and treatment efficacy.

MR imaging uses a magnet and radio waves to form cross-sectional images free of superimposition; however, unlike CT, this is accomplished without the use of ionizing radiation. For this reason, it might be preferred to CT because of the decreased amount of exposure to the patient. Because of its ability to distinguish the smallest differences in contrast, MR imaging is extremely useful in diagnosis.[10] These small differences in contrast in MR imaging were useful in this case in discovering the success of the initial surgical resection.

PET scans using gallium Ga 68 dotatate are becoming 1 of the main tools used to diagnose pancreatic NETs. Fusion scans, incorporating PET with CT, use a combination of the 2 technologies to form 1 fused image. The fused scans allow for attenuation correction as well as anatomic localization of such tumors. The gallium Ga 68 dotatate used in PET-CT procedures serves to enhance the sensitivity further.[3,11] Somatostatin receptors are present on the cells of NETs, which allows targeted receptor imaging. Gallium Ga 68 dotatate is chelated to these somatostatin receptors of the tumors and is shown to have a higher affinity than previously used indium In 111 pentetreotide.[12,13]

Another modality that incorporates fusion technology and is beneficial to the detection of NETs is PET-MR. This type of scanning was not available for the patient in this case report because this innovative technique that is making strides in the localization of tumors was not available at the facility. Because of the high soft tissue contrast used in MR imaging, lesions not previously detected by PET-CT might be found using the fusion of PET and MR imaging. However, in some scenarios, such as those in patients with lung metastases, PET-CT remained superior regarding sensitivity. Although PET-MR might lead to additional pancreatic NET findings, PET-CT is the most widely used because of its shorter duration, lower cost, and availability.[11]

Treatments

Treatment for pancreatic NETs depends on the stage of the cancer. For patients with localized NETs, the primary choice is surgery. Prognosis usually is favorable when the tumors are completely resected.[14] Surgical resection of hepatic metastases or hepatic artery embolization also might be beneficial in patients with hepatic-predominant metastatic disease.[15] The patient in this case did have surgical resection as the first attempt to control the disease.

Radioembolization has been shown to provide a better prognosis for patients in addition to surgery.[15] Yttrium Y 90 is a particulate radioisotope used for patients with metastatic liver cancer and is used as a radioembolization treatment after surgery of the primary tumor. The radioembolization is performed in 2 different sessions. The first session is to map out the arteries in the liver circulation to prevent radiation damage to healthy organs or tissues. The second session is the internal radiation delivery to the liver tumors.[16,17] This treatment was used twice for the patient in this case, and both occurrences yielded positive results.

Lutetium Lu 177 dotatate is a peptide receptor radionuclide therapy for the treatment of somatostatin receptor-positive pancreatic NETs. This method is used for cases that are deemed inoperable or are not responding to other treatment options. Lutetium Lu 177 dotatate binds to the surface of somatostatin receptors and then is internalized.[14] This treatment is a pure beta emitter which forms free radicals, causing damage in the cell it binds to and in neighboring cells. Patients are given 4 doses of 7.4 GBq, or 200 mCi, intravenously every 8 weeks. Standard protocol recommends that the patient receives antiemetics before administration of amino acids, which are given before, during, and after treatment to prevent renal damage and toxicity.[18] This standardized protocol was used on the patient in this case. Lutetium Lu 177 dotatate treatment is not a cure but has been shown to improve a patient's quality of life by limiting their symptoms as demonstrated in this case.[19]

Conclusion

There are new localization and treatment techniques for patients who present with NETs. NETs are rare tumors that primarily affect a person's gastrin, insulin, and glycogen levels. Symptoms of pancreatic NETs depend on the classification of the tumor; however, common symptoms include diarrhea, weakness, fatigue, and yellowing of the eyes and skin. The use of CT, MR, and gallium Ga 68 dotatate PET imaging is vital in the detection and localization of pancreatic NETs.

Surgical resection and radioembolization are 2 typical choices used for NET treatment. Prognosis is largely dependent on the stage in which the pancreatic NETs are detected with the survival rate for localized disease being approximately 70% higher than for distant disease. Gallium Ga 68 dotatate coupled with lutetium Lu 177 dotatate treatment has proven to be an effective combination for enhancing patients' quality of life. This imaging technique and treatment combination is becoming more common as its effectiveness is demonstrated in patients.

Chelsea Palmer Stephens, MHS, R.T.(R)(N), CNMT, is director of the Master of Science in Nuclear Medicine Technology program and assistant professor for the Department of Clinical and Diagnostic Sciences at the University of Mississippi Medical Center, School of Health Related Professions in Jackson.

Asher Street Beam, DHA, R.T.(R)(MR), MRSO, is director of the Master of Science in Magnetic Resonance Imaging program and associate professor for the Department of Clinical and Diagnostic Sciences at the University of Mississippi Medical Center, School of Health Related Professions.

Zack Gray, MS, R.T.(R)(MR)(CT), is assistant professor for the Department of Clinical and Diagnostic Sciences at the University of Mississippi Medical Center, School of Health Related Professions.

Julia Mansfield, MSNMT, R.T.(R)(N); Lexie Reves, MSNMT, R.T.(R)(N); Jennie Gray, MSNMT, R.T.(R)(N); Alexa Stamey, MSNMT, R.T.(R)(N); and Matthew Collum, MSNMT, R.T.(R)(N), are graduates of the Master of Science in Nuclear Medicine Technology program at the University of Mississippi Medical Center, School of Health Related Professions.

Vani Vijayakumar, MD, is chief of the division of nuclear medicine and professor in the Department of Radiology at the University of Mississippi Medical Center.

Received June 25, 2021; accepted after revision October 12, 2021.

Reprint requests may be mailed to the American Society of Radiologic Technologists, Publications Department, 15000 Central Ave SE, Albuquerque, NM 87123-3909, or emailed to publications@asrt.org.

References

1. Radu EC, Saizu AI, Grigorescu RR, Croitoru AE, Gheorghe C. Metastatic neuroendocrine pancreatic tumor - case report. *J Med Life*. 2018;11(1):57-61.
2. Amador Cano A, García F, Espinoza A, Bezies N, Herrera E, De Leija Portilla J. Nonfunctional neuroendocrine tumor of the pancreas: case report and review of the literature. *Int J Surg Case Rep*. 2013;4(2):225-228. doi:10.1016/j.ijscr.2012.10.018
3. Ro C, Chai W, Yu VE, Yu R. Pancreatic neuroendocrine tumors: biology, diagnosis,and treatment. *Chin J Cancer*. 2013;32(6):312-324. doi:10.5732/cjc.012.10295
4. Reid MD, Balci S, Saka B, Adsay NV. Neuroendocrine tumors of the pancreas: current concepts and controversies. *Endocr Pathol*. 2014;25(1):65-79. doi:10.1007/s12022-013-9295-2
5. Milan SA, Yeo CJ. Neuroendocrine tumors of the pancreas. *Curr Opin Oncol*. 2012;24(1):46-55. doi:10.1097/CCO.0b013e32834c554d
6. National Cancer Institute. PDQ Pancreatic Neuroendocrine Tumors (Islet Cell Tumors) Treatment. Accessed October 20, 2020. https://www.cancer.gov/types/pancreatic/patient/pnet-treatment-pdq
7. Muniraj T, Vignesh S, Shetty S, Thiruvengadam S, Aslanian HR. Pancreatic neuroendocrine tumors. *Dis Mon*. 2013;59(1):5-19. doi:10.1016/j.disamonth.2012.10.002
8. Pancreatic neuroendocrine tumors. Mayo Clinic. Published September 11, 2020. Accessed September 10, 2020. https://www.mayoclinic.org/diseases-conditions/pancreatic-neuroendocrine-tumors/symptoms-causes/syc-20352489
9. Kartalis N, Mucelli RMP, Sundin A. Recent developments in imaging of pancreatic neuroendocrine tumors. *Ann Gastroenterol*. 2015;28(2):193-202.
10. Beam AS, Moore KG, Stephens CP, et al. Rare orbital metastasis originating from a neuroendocrine tumor. *Radiol Technol*. 2019;91(2):112-119.
11. Pirasteh A, Riedl C, Mayerhoefer ME, Giancipoli RG, Larson SM, Bodei L. PET/MRI for neuroendocrine tumors: a match made in heaven or just another hype? *Clin Transl Imaging*. 2019;7(6):405-413. doi:10.1007/s40336-019-00344-1
12. Hofman MS, Lau WFE, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. *Radiographics*. 2015;35(2):500-516. doi:10.1148/rg.352140164
13. Khan MU, Khan S, El-Refaie S, Win Z, Rubello D, Al-Nahhas A. Clinical indications for Gallium-68 positron emission tomography imaging. *Eur J Surg Oncol*. 2009;35(6):561-567. doi:10.1016/j.ejso.2009.01.007
14. Ito T, Igarashi H, Jensen RT. Therapy of metastatic pancreatic neuroendocrine tumors (pNETs): recent insights and advances. *J Gastroenterol*. 2012;47(9):941-960. doi:10.1007/s00535-012-0642-8
15. Chan JA, Kulke MH. New treatment options for patients with advanced neuroendocrine tumors. *Curr Treat Options Oncol*. 2011;12(2):136-148. doi:10.1007/s11864-011-0148-2
16. Kim H-C. Radioembolization for the treatment of hepatocellular carcinoma. *Clin Mol Hepatol*. 2017;23(2):109-114. doi:10.3350/cmh.2017.0004
17. UCLA Health. Radioembolization (Y90). Treatments & Procedures. Accessed October 20, 2020. https://www.uclahealth.org/radiology/ir/radioembolization-y90
18. About LUTATHERA. LUTATHERA® (lutetium Lu 177 dotatate). LUTATHERA. Published March 2, 2021. Accessed September 10, 2020. https://hcp.lutathera.com/about-lutathera/?gclid=CjwKCAjw0On8BRAgEiwAincsHKz3dMIyHD3yrcpe6Ce207XME7gqQnoBppmMhoiRv0yrGIt-HMHTvhoC7wAQAvD_BwE&gclsrc=aw.ds#description
19. UC San Diego Health. Neuroendocrine Cancer. Cancer Services. Accessed October 20, 2020. https://health.ucsd.edu/specialties/cancer/programs/gastrointestinal/Pages/lutathera.aspx