

Evidence Discussion (ONC 15.1-15.8)

Gastrointestinal/Pancreatic Neuroendocrine Cancers:

General Considerations (15.1): This guideline includes low-grade or well-differentiated (Grade 1, 2 or 3; Ki-67 > 20% and < 55%) carcinoid and endocrine tumors of the lung, thymus, pancreas, gastrointestinal tract or unknown primary site; including insulinoma, glucagonoma, VIPoma, gastrinoma, somatostatinoma and others as well as catecholamine-secreting tumors of the adrenal gland such as pheochromocytoma, paraganglioma, adrenocortical carcinoma, and others. These tumors are particularly sensitive and specific to somatostatin receptor (SSR) based imaging (nearly 80% express SSR on the cell surface) while poorly differentiated or high grade tumors typically are not with imaging recommendations being addressed in separate guidelines. 1, 2

Gastrointestinal/Pancreatic Neuroendocrine Cancers-Suspected/Diagnosis (ONC 15.2): Neuroendocrine tumors (NETs) arise from cells of the endocrine system that can be found throughout the body. They can occur sporadically or arise in the context of an inherited genetic syndrome. Presentation is usually attributable to hormonal hypersecretion (functional tumors) that can include flushing/diarrhea/wheezing (Carcinoid syndrome), hypertension and hypoglycemia versus being found incidentally on various imaging studies. If these symptoms/signs are suspicious for a NET, appropriate serologic/urinary workup may include chromogranin A, 5HIAA, insulin, VIP, glucagon, gastrin, substance P, serotonin and somatostatin. If these markers are elevated, CT chest with or without contrast as well as CT or MRI of abdomen/pelvis/any other symptomatic body area is indicated. CT is best for detection of primary small bowel lesions and lymphadenopathy while MRI is preferred for pancreatic NETs and detecting hepatic metastases. If these imaging studies are negative/inconclusive, SSR based imaging with either Octreotide scan or Dotatate/Dotatoc (Gallium-68, Copper-64) may be indicated (SSR PET/CT). All three of these functional imaging modalities are FDA approved and can be performed in individuals on somatostatin analog therapy and are considered to be superior to Octreotide scan. FDG-based PET/CT has limited use as the majority of NETs are metabolically inactive and fail to take up the tracer well. 1,2,3,4

Initial work-up/Staging (15.3): See section ONC 15.2 above. In the setting where markers fail to normalize after surgery AND CT/MRI and SSR based study are negative OR there is biopsy proven NET of unknown origin AND CT/MRI and SSR based study are negative, FDG-based PET/CT is indicated for the concern of a higher grade NET being present. 3, 4

Restaging/Recurrence (15.4): For individuals with unresectable/metastatic disease, CT imaging of involved body area is recommended every 3 months if on somatostatin therapy versus every 2 cycles (6-8 weeks) if on chemotherapy. CT chest and CT/MRI abdomen/pelvis is indicated for progression of

symptoms or elevation of tumor markers while Octreotide scan or SSR PET/CT if conventional imaging is negative/inconclusive. 3, 4 To assess for candidacy for peptide receptor radionuclide therapy (PRRT) with Lutetium Lu-177 dotatate (Lutathera), any of the 3 SSR PET/CT options are supported. 2,5

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Surveillance/Follow-up (15.5): In the absence of signs/symptoms of recurrence, advanced imaging is not routinely indicated for completely resected appendiceal carcinoid ≤ 2 cm, completely resected rectal carcinoid < 1 cm, and gastric carcinoid treated with complete endoscopic resection due to their excellent prognosis and low risk of recurrence. 6,7,8 For completely resected rectal carcinoid 1-2 cm, MRI pelvis with and without contrast at 6 and 12 months post-resection and if clear, no further imaging. Due to the indolent nature of NETs, long term follow-up is recommended. For all other GI NETs, CT abdomen/pelvis with contrast once 3-12 months postoperatively and annually for 3 years then every 2 years up to year 10. Unresected GI NETs on observation should undergo CT abdomen with contrast once at 3-12 months from initial diagnosis then annually up to year 10. Resected pancreatic NETs should undergo CT abdomen with contrast once at 3-12 months postoperatively then annually up to year 10. Unresected pancreatic NETs should undergo CT abdomen with contrast once at 3-12 months from initial diagnosis then annually up to year 10. For individuals with measurable metastatic disease on maintenance or off therapy, CT of involved body area no more frequently than every 3 months. After 10 years, surveillance should be as clinically indicated. 2

Bronchopulmonary or Thymic Carcinoid:

Initial Staging (ONC-15.6): More than 80% of lung carcinoids are diagnosed at Stage I or II with the most common sites of metastases being liver, bone and lung. Most thymic carcinoids are diagnosed at Stage III or IV with the most common sites of metastases being pleura, pericardium, bone, lung and liver. 9 Recommended initial imaging includes CT chest with contrast and CT abdomen with or with/without contrast. If the latter imaging is inconclusive, MRI abdomen with and without contrast is indicated. Imaging of the brain, pelvis or osseous structures is based on signs/symptoms of disease. If the CT/MRI is inconclusive, Octreotide scan or SSR-based PET/CT can be completed. In the setting where markers fail to normalize after surgery AND CT/MRI and SSR based study are negative OR there is biopsy proven NET of unknown origin AND CT/MRI and SSR based study are negative, FDG-based PET/CT is indicated for the concern of a higher grade NET being present. 3, 4

Restaging/Recurrence (ONC 15-7): For individuals with unresectable/metastatic disease, CT imaging of involved body area is recommended every 3 months if on somatostatin therapy versus every 2 cycles (6-8 weeks) if on chemotherapy. CT chest and CT/MRI abdomen/pelvis is indicated for progression of symptoms or elevation of tumor markers while Octreotide scan or SSR PET/CT if conventional imaging is negative/inconclusive. 3, 4

Surveillance (ONC 15.8): For carcinoid tumors of the lung or thymus, prognosis varies. In typical lung carcinoid, 5-year and 10-year overall survival (OS) is approximately 81-96% and 74-91% respectively for both node negative or node positive disease. With atypical histology, 5-year OS is 82-90% in node negative disease and 58-71% in node positive disease. Thymic carcinoid 5-year OS is < 50%. Due to lack of long-term follow-up imaging studies, it is recommended to minimize risk of radiation exposure using CT or MRI. 9 In individuals with resected disease, CT chest 3-12 months post resection and then annually for up to 3 years then every 2 years up to year 10. Unresected primary tumors on observation follow a similar schedule with CT chest 3-12 months from initial diagnosis and then annually for up to 3 years then every 2 years up to year 10. Measurable metastatic disease on maintenance therapy or observation undergo CT of involved body area no more frequently than every 3 months. After 10 years, surveillance should be as clinically indicated. 2

References:

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5. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of Lu-177 Dotatate for Midgut Neuroendocrine Tumors. New England Journal of Medicine January 2017, 376(2): 125-135.
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8. Sjoblom S. Clinical presentation and prognosis of gastrointestinal carcinoid tumors. Scand J Gastroenterol September 1988, 23(7): 779-87.
9. Baudin E, Caplin M, Garcia-Carbonero R, et al. Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology April 2021, 32(4): 439-451.