

Evidence Discussion (ONC 15.9-15.13)

Neuroendocrine Cancers and Adrenal Tumors

ONC 15.9-15.13

Evidence Discussion for **Adrenal tumors-Suspected/Diagnosis ONC 15.9.**

For the evaluation of indeterminate adrenal masses, the imaging recommendations are outlined in Asymptomatic Adrenal Cortical Lesions (AB-16.1)

ONC 15.9 –ONC 15.13 outline the imaging of primary adrenal tumors. Primary adrenal tumors are a family of tumors that derive from the adrenal gland or from neural crest tissue outside of the adrenal gland. Tumors arising from the adrenal medulla or neural crest tissue outside of the adrenal gland include pheochromocytoma, paraganglioma and paraganglioma. Pheochromocytoma and paraganglioma are catecholamine –secreting tumors that are derived from the adrenal medulla and sympathetic ganglia, respectively. Paraganglioma is composed of differentiated cells of the neural crest tissue outside of the adrenal medulla and are asymptomatic. This group of tumors is imaged according to sections **ONC 15.10 through ONC- 15.12.** Adrenocortical carcinoma is derived from the adrenal cortex and is imaged according to **Adrenocortical Carcinoma ONC 15.13.** Surveillance imaging guidelines in individuals with an adrenal tumor and a cancer predisposition syndrome are outlined in **Screening Imaging and Cancer Predisposition Syndromes (PEDONC-2).**

Evidence Discussion for **Adrenal Tumors – Initial Work-up/Staging (ONC-15.10)**

Evicore imaging guidelines align with NCCN guidelines.

Radiologic evaluation of adrenal tumors should follow biochemical confirmation of the diagnosis of pheochromocytoma and paraganglioma. Ninety –five percent of this group of tumors occur in the abdomen and pelvis. Paragangliomas account for 15% of this group of tumors. The initial work-up/staging of this group of tumors includes CT chest (with contrast or without contrast) as approximately 10 % of paragangliomas are found in the chest and pheochromocytoma has a potential to metastasize to chest. CT imaging with or without and with contrast or MRI imaging without and with contrast of the abdomen, pelvis and any other symptomatic body areas are indicated for initial staging.

Functional imaging is a valuable problem-solving tool when there is continued suspicion for this group of tumors with inconclusive or negative findings on CT/MRI. ¹²³I/¹³¹I-MIBG sensitivity is higher for detecting pheochromocytoma than for detecting paraganglioma,

at 88% and 67%, respectively. Another approach to functional imaging utilizes ^{68}Ga -DOTA-somatostatin analogs including DOTATOC, DOTANOC, and DOTATATE (SSR-PET/CT). In meta-analyses, the sensitivity of ^{68}Ga -DOTA-somatostatin analogs (93%) is superior to ^{18}F -FDG (74%), and $^{123}\text{I}/^{131}\text{I}$ -MIBG (38%). Imaging with ^{111}In -pentetreotide (octreotide) (24%) is less sensitive than imaging with ^{68}Ga -DOTA-somatostatin analogs. Of note, functional imaging using ^{18}F -FDG PET/CT can be useful for evaluation in the scenario that CT/MRI and other functional imaging studies are negative/inconclusive.

Evidence Discussion for **Adrenal Tumors-Restaging/Recurrence ONC 15.11**

Evicore imaging guidelines align with NCCN guidelines.

In individuals who underwent surgery for resection of localized disease, CT abdomen with contrast is supported within the first year post resection. Follow-up imaging is based on surveillance recommendations noted in **Adrenal Tumors – Surveillance (ONC 15.12)**. In individuals who develop recurrence, progression of symptoms or elevation of tumor markers, the extent of disease must be determined with CT/MRI imaging. CT chest (with contrast or without contrast), CT imaging with or without and with contrast or MRI imaging without and with contrast of the abdomen, pelvis and any other symptomatic body areas are indicated. Functional imaging with ^{111}In -pentetreotide (octreotide scan) or ^{68}Ga -DOTA-somatostatin analogs (SSR-PET)/CT are valuable problem solving tools when there is continued suspicion of recurrence with inconclusive or negative findings on CT/MRI. Further evaluation using ^{18}F -FDG PET/CT can be useful for evaluation in the scenario that CT/MRI and other functional imaging studies are negative/inconclusive.

Evidence discussion for **Adrenal Tumors – Surveillance (ONC 15.12)**

Evicore imaging guidelines align with NCCN guidelines.

In individuals who had resectable disease. CT chest (with contrast or without contrast), CT imaging with or without and with contrast or MRI imaging without and with contrast of the abdomen, pelvis and any other previously involved body areas are indicated once within 3-12 months post resection then annually for 10 years. In individuals with measurable metastatic disease being observed off therapy or on maintenance therapy are at greater risk for recurrence. In addition to the imaging schedule noted above, imaging of the involved body is indicated with greater frequency (3 months) for up to 5 years followed by annual imaging.

References (ONC 15.9-ONC 15.12)

Carrasquillo JA, Chen CC et al. Imaging of Pheochromocytoma and Paraganglioma. J Nucl Med. 2021 Aug 1; 62(8): 1033–1042.

Fishbein L, Del Rivero J et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Management of Metastatic and/or Unresectable **Pheochromocytoma and Paraganglioma**. *Pancreas* 2021 Apr 1;50(4):469-493. doi: 10.1097/MPA.0000000000001792.

Georger B, Hero B et al. Metabolic activity and clinical features of primary ganglioneuromas. *Cancer* 2001 May 15;91(10):1905-13.

Goldner WS, Bergsland E. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine and adrenal tumors. Version 1.2024- June 20, 2024. All rights reserved. Accessed [June 26, 2024]. To view the most recent and complete version of the guideline, go online to NCCN.org.

Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of ⁶⁸Ga-DOTA-conjugated somatostatin receptor-targeting peptide PET in detection of pheochromocytoma and paraganglioma: a systematic review and metaanalysis. *J Nucl Med*. 2019; 60:369–376.

Leung K, Stamm M et al. Pheochromocytoma: The Range of Appearances on Ultrasound, CT, MRI, and Functional Imaging. *AJR* Volume 200, Issue 2. <https://doi.org/10.2214/AJR.12.9126>

Whalen, RK, Althausen AF, Daniels GH. Extra-adrenal pheochromocytoma. *J Urol*. 1992;147(1):1.

Evidence Discussion for **Adrenocortical Carcinoma ONC 15.13**

Adrenocortical Carcinoma (ACC) is a rare, aggressive tumor arising from the adrenal cortex. Most cases of ACC are sporadic; however, ACC has been described as a component of hereditary cancer syndromes that include Li-Fraumeni syndrome, Beckwith Weidemann syndrome and multiple endocrine neoplasia type 1 (MEN1). Recommended imaging guidelines for screening of individuals with these syndromes are summarized in **Screening Imaging in Cancer Predisposition Syndromes (PEDONC-2)**. ACCs that secrete excess adrenal hormones are classified as functional tumors and occur in 15-30% of cases in adults. Those patients with functional tumors present with Cushing's syndrome and/or virilization. The majority of adults with non-functioning ACCs present symptomatically with abdominal pain or flank pain; however, these tumors may present asymptotically as a large palpable intra-abdominal mass or incidentally as a small adrenal mass. Approximately 30 % of ACCs present with metastatic disease in lymph nodes, lung, liver and bone. ACCs may also present with invasion of adjacent structures and with venous extension.

Evicore HC guidelines are aligned with NCCN guidelines. CT and MRI cross-sectional imaging are the standard imaging modalities used for the evaluation of ACC. Due to the measurable risk for widely metastatic disease at initial presentation, cross-section imaging of the chest and abdomen/pelvis is indicated. CT chest (with contrast or

without contrast) is indicated to evaluate for lung metastases. Cross-sectional imaging of the abdomen/pelvis using CT abdomen/pelvis (with or with and without contrast) or MRI abdomen as well as MRI pelvis (with and without contrast) are indicated for characterization of the primary tumor and evaluation for metastatic disease. If recurrence is suspected, the same imaging studies should be completed as was done for initial staging. Additional imaging may be needed to assess other suspicious sites of disease based on clinical signs/symptoms.

FDG PET/CT scan is a valuable problem-solving tool. FDG PET/CT is supported to characterize inconclusive findings CT/MRI. Additionally, in an individual who presents with solitary mass > 4 cm on CT/MRI and there is a plan for aggressive surgical resection, FDG PET/CT is indicated to confirm that there is no metastatic disease nor disease invasion to adjacent structures.

CT imaging is the standard approach in surveillance. In individuals who had complete response to definitive therapy, the recommendation of CT imaging is annual imaging for 5 years after completion of treatment (CT chest with contrast, CT abdomen with contrast and CT of other involved body areas) as the rate of recurrence is < 25% and overall survival rate approaches 74-95 % at 5 years. In individuals with metastatic disease on maintenance therapy or being monitored off treatment, the frequency of CT imaging is shortened and repeated at 3 month intervals for up to 5 years (CT chest with contrast, CT abdomen with contrast and CT of other involved body areas).

References (ONC 15.13)

Bharwani N, Rockall AG et al. Adrenocortical Carcinoma: The Range of Appearances on CT and MRI. AJR (2011) 196: 6, w706-714. <https://doi.org/10.2214/AJR.10.5540>

Goldner WS, Bergsland E. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine and adrenal tumors. Version 1.2024- June 20, 2024. All rights reserved. Accessed [June 26, 2024]. To view the most recent and complete version of the guideline, go online to NCCN.org.

Fassnacht M, Dekkers O, et al. European Society of Endocrinology Clinical Practice Guidelines on the Management of Adrenocortical Carcinoma in Adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2018;

Fassnacht M, Johanssen S, et al. Improved survival in patients with stage II adrenocortical carcinoma followed up prospectively by specialized centers. J Clin Endocrinol Metab. 2010; 95(11):4925. Epub 2010 Jul 28.

Sidhu S, Sywak M, et al. Adrenocortical cancer: recent clinical and molecular advances. Curr Opin Oncol. 2004; 16(1):13