

ACR Appropriateness Criteria[®] Staging and Follow-Up of Adrenal Cancer

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Abstract

Primary adrenal gland malignancies include adrenocortical carcinoma (ACC) and pheochromocytoma. For initial staging and restaging or surveillance of known or suspected ACC, MRI of the abdomen and pelvis without and with contrast, CT of the abdomen and pelvis with contrast, CT of the chest with contrast, and fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT, or FDG-PET/MRI are recommended to assess for local extent and distant metastases or to evaluate for recurrence. For initial staging and restaging or surveillance of known or suspected pheochromocytoma, MRI of the abdomen and pelvis without and with contrast, CT of the abdomen

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Disclaimer: The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

and pelvis with contrast, CT of the chest with contrast, DOTATATE PET/CT, or DOTATATE PET/MRI are recommended to assess local extent and distant metastases or to evaluate for recurrence. Meta-iodobenzylguanidine (MIBG) scan whole body with single-photon emission CT (SPECT) or SPECT/CT area of interest is an acceptable alternative for initial staging of known or suspected pheochromocytoma, in particular to determine eligibility for I-131 MIBG therapy.

The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision process support the systematic analysis of the medical literature from peer reviewed journals. Established methodology principles such as Grading of Recommendations Assessment, Development, and Evaluation or GRADE are adapted to evaluate the evidence. The RAND/UCLA Appropriateness Method User Manual provides the methodology to determine the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where peer reviewed literature is lacking or equivocal, experts may be the primary evidentiary source available to formulate a recommendation.

Key Words: Appropriateness Criteria, appropriate use criteria, AUC, adrenocortical carcinoma, ACC, CT, DOTATATE PET, FDG-PET, MRI, pheochromocytoma

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ACR Appropriateness Criteria® Staging and Follow-Up of Adrenal Cancer. [Variants 1 to 4](#) and [Tables 1 and 2](#).

Variant 1. Adult. Known or suspected adrenocortical carcinoma. Initial staging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen and pelvis without and with IV contrast	Usually Appropriate	0
CT abdomen and pelvis with IV contrast	Usually Appropriate	⦿⦿⦿
CT chest with IV contrast	Usually Appropriate	⦿⦿⦿
FDG-PET/MRI skull base to mid-thigh	Usually Appropriate	⦿⦿⦿
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	⦿⦿⦿⦿
Radiography chest	Usually Not Appropriate	⦿
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	0
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	⦿⦿⦿
CT chest without and with IV contrast	Usually Not Appropriate	⦿⦿⦿
CT chest without IV contrast	Usually Not Appropriate	⦿⦿⦿
DOTATATE PET/CT skull base to mid-thigh	Usually Not Appropriate	⦿⦿⦿
DOTATATE PET/MRI skull base to mid-thigh	Usually Not Appropriate	⦿⦿⦿
MIBG scan whole body	Usually Not Appropriate	⦿⦿⦿
MIBG scan whole body with SPECT or SPECT/CT area of interest	Usually Not Appropriate	⦿⦿⦿
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	⦿⦿⦿⦿

Variant 2. Adult. Known or suspected adrenocortical carcinoma. Restaging or surveillance.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen and pelvis without and with IV contrast	Usually Appropriate	0
CT abdomen and pelvis with IV contrast	Usually Appropriate	⚠⚠⚠
CT chest with IV contrast	Usually Appropriate	⚠⚠⚠
FDG-PET/MRI skull base to mid-thigh	Usually Appropriate	⚠⚠⚠
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	⚠⚠⚠⚠
CT chest without IV contrast	May Be Appropriate	⚠⚠⚠
Radiography chest	Usually Not Appropriate	⚠
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	0
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	⚠⚠⚠
CT chest without and with IV contrast	Usually Not Appropriate	⚠⚠⚠
DOTATATE PET/CT skull base to mid-thigh	Usually Not Appropriate	⚠⚠⚠
DOTATATE PET/MRI skull base to mid-thigh	Usually Not Appropriate	⚠⚠⚠
MIBG scan whole body	Usually Not Appropriate	⚠⚠⚠
MIBG scan whole body with SPECT or SPECT/CT area of interest	Usually Not Appropriate	⚠⚠⚠
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	⚠⚠⚠⚠

Variant 3. Adult. Known or suspected pheochromocytoma. Initial staging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen and pelvis without and with IV contrast	Usually Appropriate	0
CT abdomen and pelvis with IV contrast	Usually Appropriate	⚠⚠⚠
CT chest with IV contrast	Usually Appropriate	⚠⚠⚠
DOTATATE PET/CT skull base to mid-thigh	Usually Appropriate	⚠⚠⚠
DOTATATE PET/MRI skull base to mid-thigh	Usually Appropriate	⚠⚠⚠
MIBG scan whole body with SPECT or SPECT/CT area of interest	Usually Appropriate	⚠⚠⚠
FDG-PET/MRI skull base to mid-thigh	May Be Appropriate	⚠⚠⚠
MIBG scan whole body	May Be Appropriate	⚠⚠⚠
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	⚠⚠⚠⚠
Radiography chest	Usually Not Appropriate	⚠
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	0
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	⚠⚠⚠
CT chest without and with IV contrast	Usually Not Appropriate	⚠⚠⚠
CT chest without IV contrast	Usually Not Appropriate	⚠⚠⚠
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	⚠⚠⚠⚠

Variant 4. Adult. Known or suspected pheochromocytoma. Restaging or surveillance.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen and pelvis without and with IV contrast	Usually Appropriate	0
CT abdomen and pelvis with IV contrast	Usually Appropriate	⚠⚠⚠
CT chest with IV contrast	Usually Appropriate	⚠⚠⚠
DOTATATE PET/CT skull base to mid-thigh	Usually Appropriate	⚠⚠⚠
DOTATATE PET/MRI skull base to mid-thigh	Usually Appropriate	⚠⚠⚠
FDG-PET/MRI skull base to mid-thigh	May Be Appropriate (Disagreement)	⚠⚠⚠
MIBG scan whole body	May Be Appropriate	⚠⚠⚠
MIBG scan whole body with SPECT or SPECT/CT area of interest	May Be Appropriate (Disagreement)	⚠⚠⚠
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	⚠⚠⚠⚠
Radiography chest	Usually Not Appropriate	⚠
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	0
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	⚠⚠⚠
CT chest without and with IV contrast	Usually Not Appropriate	⚠⚠⚠
CT chest without IV contrast	Usually Not Appropriate	⚠⚠⚠
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	⚠⚠⚠⚠

Table 1. Appropriateness category names and definitions.

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Table 2. Relative radiation level designations.

RRL	Adult Effective Dose Estimate Range (mSv)	Pediatric Effective Dose Estimate Range (mSv)
O	0	0
⊕	<0.1	<0.03
⊕⊕	0.1-1	0.03-0.3
⊕⊕⊕	1-10	0.3-3
⊕⊕⊕⊕	10-30	3-10
⊕⊕⊕⊕⊕	30-100	10-30

Note: Relative radiation level (RRL) assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “varies.”

SUMMARY OF LITERATURE REVIEW

Introduction/Background

There are 2 primary carcinomas that can arise from the adrenal gland: adrenocortical carcinoma (ACC) and malignant pheochromocytoma. Both malignancies are rare. ACC incidence is estimated at 0.5 to 2.0 new cases per million people per year [1,2], and adrenal pheochromocytoma 2 to 8 new cases per million people per year [3]. The tumors differ significantly in their risk factors, clinical course, and treatments.

ACC accounts for <5% of adrenal incidentalomas. The prognosis of ACC is poor, with overall survival rates of 15% to 44% at 5-years [4]. Overall prognosis is worsened in high-grade tumors, with a large percentage of patients presenting late with stage IV disease (47%) [5]. Most ACC tumors arise sporadically, with a small number associated with hereditary syndromes, including Li-Fraumeni syndrome, Lynch syndrome, multiple endocrine neoplasm type 1, and familial adenomatous polyposis. Treatments include surgery, chemotherapy, immunotherapy, and, for later stages, chemoradiotherapy.

Pheochromocytoma is a potentially malignant neuroendocrine tumor arising from the chromaffin cells of the adrenal medulla. Extra-adrenal pheochromocytomas are referred to as paragangliomas and are not addressed in this document. Pheochromocytomas represent 8.5% (1%-14%) of adrenal incidentalomas [6]. Most pheochromocytomas are asymptomatic [7]. Ninety percent of solitary pheochromocytomas are sporadic, with the remaining 5% to 10% resulting from germline mutation. Multiple pheochromocytomas (with or without paragangliomas) are associated with germline/somatic mutations in >70% of cases. There have been 22 isolated susceptibility genes identified, the most prevalent gene mutations being associated with the well-known succinate dehydrogenase (SDHx) deficiency, multiple endocrine neoplasm type 2, Von-Hippel Lindau, and neurofibromatosis type 1 syndromes. The primary treatment of pheochromocytoma is surgical resection, although theranostic intervention has begun to play a role in treatment. The median overall survival rate is 18 years [8].

Anatomical and functional imaging screening protocols, and theranostic treatment protocols for hereditary syndromes are beyond the scope of this document. A brief review of the role of Gallium-68 DOTATATE PET/CT in the initial staging and follow-up of diagnosed pheochromocytoma or adrenocortical carcinoma is discussed within the relevant subheadings. For a complete guide to nuclear medicine workup of pheochromocytoma and paragangliomas, particularly in known hereditary or de novo genetic mutation syndromes, a review of the European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of pheochromocytoma and paraganglioma is suggested [9].

DISCUSSION OF PROCEDURES BY VARIANT

Variant 1: Adult. Known or suspected adrenocortical carcinoma. Initial staging.

The goal of imaging is to stage a known or suspected ACC, which encompasses assessing the local extent of disease and distant metastases. The information gathered from initial staging with imaging will help provide the most appropriate treatment in patients with suspected or confirmed ACC. This will improve patient outcomes by guiding the most appropriate management plan early, and thereby lessening the length of illness and expediting the patient's recovery time.

In the following discussion, an area of interest can refer to the following: head, neck, chest, abdomen, pelvis, upper extremity, and lower extremity.

CT Abdomen and Pelvis With IV Contrast. The National Cancer Comprehensive Network (NCCN) and the European Network for the Study of Adrenal Tumors (ENSAT) guidelines support the use of CT of the abdomen and pelvis with intravenous (IV) contrast for the staging of known or suspected ACC [10-12]. Features of benignancy include macroscopic fat within the mass, Hounsfield units of ≤ 10 , signal drop-out on out-of-phase MRI compared

with in-phase and no enhancement [13]. Suspected ACCs do not demonstrate these benign features and are usually heterogeneous and >4 cm in size [14]. However, in rare cases, ACC can contain fat and considered when the mass is heterogeneous [10], and generally in symptomatic lesions >6 cm with <5% fat content [15]. Further information on the workup of adrenal masses can be found in ACR Appropriateness Criteria® topic on “Adrenal Mass Evaluation” [13]. There is limited published data on the performance of CT abdomen and pelvis with IV contrast on the staging of ACC. One study compared abdominal CT and abdominal MRI in determining liver involvement by right-sided ACCs and found that CT and MRI performed similarly. Using the criteria of bulge or contour disruption, the sensitivity, specificity, and accuracy for CT was 100%, 91%, and 93%, and for MRI was 100%, 86%, and 90%, respectively [16].

CT Abdomen and Pelvis Without and With IV Contrast. There is no relevant literature to support the use of CT abdomen and pelvis without and with IV contrast in the staging of known or suspected ACC.

CT Abdomen and Pelvis Without IV Contrast. There is no relevant literature to support the use of CT abdomen and pelvis without IV contrast in the staging of known or suspected ACC.

CT Chest With IV Contrast. Although metastases from ACC to the lung and mediastinal and supraclavicular lymph nodes are a common site of spread to the chest [10,17], there is currently no literature on the performance of CT chest in the staging of known or suspected ACC. However, the NCCN and ENSAT guidelines recommend including a CT chest or MRI of the abdomen and pelvis in the staging of known or suspected ACC [10,11].

CT Chest Without and With IV Contrast. There is no relevant literature to support the use of CT chest without and with IV contrast in the staging of known or suspected ACC.

CT Chest Without IV Contrast. NCCN guidelines recommend the inclusion of a CT chest in the staging of known or suspected ACC, and it can be performed with or without IV contrast [11]. There is no other relevant literature to support the use of CT chest without IV contrast in the staging of known or suspected ACC.

DOTATATE PET/CT Skull Base to Mid-Thigh. There is no relevant literature to support the use of DOTATATE PET/CT skull base to mid-thigh in the staging of known or suspected ACC.

DOTATATE PET/MRI Skull Base to Mid-Thigh. There is no relevant literature to support the use of DOTATATE

PET/MRI skull base to mid-thigh in the staging of known or suspected ACC.

FDG-PET/CT Skull Base to Mid-Thigh. The NCCN and ENSAT guidelines support the use of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT in the staging of known or suspected ACC [10,11]. There is a small body of literature on its performance. One retrospective study involving 30 patients over a 10-year period found that FDG-PET/CT performed better than whole body CT with a sensitivity, specificity, and accuracy of 100% with FDG-PET/CT compared with 65.2%, 97.6%, and 92.7% for CT, respectively [18]. In this study, FDG-PET/CT upstaged 4 (13.3%) and downstaged 3 (10%) of the cases, and CT showed 3 false-positives and 8 false-negatives that were correctly identified on FDG-PET/CT. Another retrospective study also showed 100% sensitivity, specificity, and accuracy of FDG-PET/CT compared with 92.6%, 100%, and 96.4%, respectively, for CT [19]. One prospective study compared FDG-PET to CT of the chest, abdomen, and pelvis, but this also included patients for restaging and surveillance [20]. This study showed a sensitivity of 90% for FDG-PET and 88% for CT and concluded that both studies are complementary to one another. In instances where ACC is suspected and not confirmed, CT would be the better initial test.

FDG-PET/MRI Skull Base to Mid-Thigh. There is no relevant literature to support the use of FDG-PET/MRI skull base to mid-thigh in the staging of known or suspected ACC. However, based on the expert opinion of this panel, FDG-PET/MRI may be considered appropriate for use in staging of known or suspected ACC, as an equivalent to FDG-PET/CT.

MIBG Scan Whole Body. There is no relevant literature to support the use of meta-iodobenzylguanidine (MIBG) scan whole body in the staging of known or suspected ACC.

MIBG Scan Whole Body With SPECT or SPECT/CT Area of Interest. There is no relevant literature to support the use of MIBG scan whole body with single-photon emission CT (SPECT) or SPECT/CT of the area of interest in staging known or suspected ACC.

MRI Abdomen and Pelvis Without and With IV Contrast. The NCCN and ENSAT guidelines support the use of MRI abdomen and pelvis without and with IV contrast as an alternative to CT of the abdomen and pelvis with IV contrast [10,11], although there is limited published performance of this procedure. One study compared abdominal CT and abdominal MRI in determining liver involvement by right-sided ACC and found that CT and MRI performed similarly. Using the criteria of bulge or contour disruption, the sensitivity, specificity, and

accuracy for CT was 100%, 91%, and 93%, and for MRI was 100%, 86%, and 90%, respectively [16].

MRI Abdomen and Pelvis Without IV Contrast. There is no relevant literature to support the use of MRI abdomen and pelvis without IV contrast in the staging of known or suspected ACC.

Radiography Chest. There is no relevant literature to support the use of chest radiography in the staging of known or suspected ACC. However, imaging of the chest is recommended and should be performed with CT [10,11].

Variant 2: Adult. Known or suspected adrenocortical carcinoma. Restaging or surveillance.

The goal of imaging is to restage or surveil a known or suspected ACC. This includes evaluation of the site of initial disease and assessment for distant metastases. Restaging refers to the process of reassessing a patient's disease status after treatment to determine how the disease has changed in response to treatment. Surveillance refers to ongoing monitoring to detect any signs of recurrence after successful treatment or remission. The information gathered from restaging or surveillance imaging will help provide the most appropriate treatment for these patients. This will improve patient outcomes by guiding the most appropriate management plan early and thereby lessening the length of illness and expediting the patient's recovery time.

In the following discussion, an area of interest can refer to the following: head, neck, chest, abdomen, pelvis, upper extremity, and lower extremity.

CT Abdomen and Pelvis With IV Contrast. CT of the abdomen and pelvis with IV contrast is useful for restaging and surveillance of known or suspected ACC [10,11]. Recommended surveillance protocols are every 3 months for 2 years and then every 3 to 6 months for 3 years. Continued surveillance beyond 5 years is recommended and should be tailored to the patient [10].

CT Abdomen and Pelvis Without and With IV Contrast. There is no relevant literature to support the use of CT abdomen and pelvis without and with IV contrast in the restaging or surveillance of known or suspected ACC.

CT Abdomen and Pelvis Without IV Contrast. There is no relevant literature to support the use of CT abdomen and pelvis without IV contrast in the restaging or surveillance of known or suspected ACC.

CT Chest With IV Contrast. Metastasis to the lung is a common site of recurrence [10]. The NCCN and ENSAT guidelines support including CT chest with CT or MRI of

the abdomen and pelvis in restaging or surveillance of known or suspected ACC [10,11].

CT Chest Without and With IV Contrast. There is no relevant literature to support the use of CT chest without and with IV contrast in the restaging or surveillance of known or suspected ACC.

CT Chest Without IV Contrast. The NCCN guidelines support inclusion of CT chest in the restaging or surveillance of known or suspected ACC and it can be performed with or without IV contrast [11]. There is no other relevant literature to support the use of CT chest without IV contrast in the restaging or surveillance of known or suspected ACC.

DOTATATE PET/CT Skull Base to Mid-Thigh. There is no relevant literature to support the use of DOTATATE PET/CT skull base to mid-thigh in the restaging or surveillance of known or suspected ACC.

DOTATATE PET/MRI Skull Base to Mid-Thigh. There is no relevant literature to support the use of DOTATATE PET/MRI skull base to mid-thigh in the restaging or surveillance of known or suspected ACC.

FDG-PET/CT Skull Base to Mid-Thigh. There is a small body of literature on the performance of FDG-PET/CT skull base to mid-thigh in restaging and surveillance of known or suspected ACC. NCCN guidelines suggest that FDG-PET/CT can be an alternative to abdominal and pelvic CT or MRI [11]. Krishnaraju et al [18] compared FDG-PET/CT to contrast-enhanced CT skull to mid-thigh in assessing recurrence and surveillance of known or suspected ACC. They found that the sensitivity was 95.6% for FDG-PET/CT and 91.3% for CT, and the specificity was 100% for FDG-PET/CT and 94.7% for CT. Another retrospective study showed sensitivity, specificity, and accuracy of 98.4%, 100%, and 99.5% for FDG-PET/CT and 96.8%, 98.6%, and 98.0% for CT, respectively [19]. There has been one prospective study that compared FDG-PET to CT of the chest, abdomen, and pelvis, but this also included patients for staging [20]. This study showed a sensitivity of 90% for FDG-PET and 88% for CT and concluded that both studies are complementary to one another.

FDG-PET/MRI Skull Base to Mid-Thigh. There is no relevant literature to support the use of FDG-PET/MRI skull base to mid-thigh in the restaging or surveillance of known or suspected ACC. However, based on the expert opinion of this panel, FDG-PET/MRI is considered appropriate for use in staging of known or suspected ACC, as an equivalent to FDG-PET/CT.

MIBG Scan Whole Body. There is no relevant literature to support the use of MIBG scan whole body in the restaging or surveillance of known or suspected ACC.

MIBG Scan Whole Body With SPECT or SPECT/CT Area of Interest. There is no relevant literature to support the use of MIBG scan whole body with SPECT or SPECT/CT on the area of interest in the restaging or surveillance of known or suspected ACC.

MRI Abdomen and Pelvis Without and With IV Contrast. Although there is limited published performance of MRI abdomen and pelvis without and with IV contrast in the restaging or surveillance of known or suspected ACC, the NCCN and ENSAT guidelines support its use as an alternative to CT of the abdomen and pelvis with IV contrast [10,11] or FDG-PET/MRI skull base to mid-thigh [11].

MRI Abdomen and Pelvis Without IV Contrast. There is no relevant literature to support the use of MRI abdomen and pelvis without IV contrast in the restaging or surveillance of known or suspected ACC.

Radiography Chest. There is no relevant literature to support the use of chest radiography in the restaging or surveillance of known or suspected ACC. However, imaging of the chest is recommended and should be performed with CT [10,11].

Variant 3: Adult. Known or suspected pheochromocytoma. Initial staging.

The goal of imaging is to stage a known or suspected pheochromocytoma. This encompasses assessment of local extent of disease and distant metastases. The information gathered from initial staging with imaging will help provide the most appropriate treatment in patients with or suspected pheochromocytoma. This will improve patient outcomes by guiding the most appropriate management plan early and thereby lessening the length of illness and expediting the patient's recovery time.

Prospective studies comparing the performance of anatomical imaging with functional imaging in the staging of known or suspected pheochromocytoma are lacking. One small study with 14 patients with sporadic pheochromocytoma who underwent PET/CT using various radiotracers, showed that fluorine-18-L-dihydroxyphenylalanine (F-DOPA) PET/CT performed better than CT but not MRI for pheochromocytoma detection [21]. For the initial staging of known or suspected pheochromocytoma, both anatomical and functional imaging are suggested by the NCCN guidelines [11]. However, in certain cases of low risk, nonhereditary, <5cm metanephrine-secreting tumors, anatomical staging with CT or MRI without functional imaging is sufficient [22].

The small volume of literature available on the sensitivity and specificity of functional imaging agents DOTATATE PET, FDG-PET, and F-DOPA PET on staging of known or suspected pheochromocytoma are either specific to a genetic mutation group or include all paragangliomas. Note that DOTATATE is approved for use, but F-DOPA currently is not FDA approved for use in the United States.

In the following discussion, an area of interest can refer to the following: head, neck, chest, abdomen, pelvis, upper extremity, and lower extremity.

CT Abdomen and Pelvis With IV Contrast. The NCCN guidelines supports the inclusion of CT of the abdomen and pelvis with IV contrast for the staging of known or suspected pheochromocytoma [11]. Currently, there is no literature describing the performance of CT abdomen and pelvis with IV contrast in the initial staging of known or suspected pheochromocytoma.

CT Abdomen and Pelvis Without and With IV Contrast. CT abdomen and pelvis without and with IV contrast with delayed 15-minute imaging can be used to characterize an adrenal mass [11], but there is no relevant literature to support the use of CT abdomen and pelvis without and with IV contrast in the staging of known or suspected pheochromocytoma.

CT Abdomen and Pelvis Without IV Contrast. There is no relevant literature to support the use of CT abdomen and pelvis without IV contrast in the staging of known or suspected pheochromocytoma.

CT Chest With IV Contrast. Although literature on the performance of CT chest with IV contrast in the staging of pheochromocytomas is lacking, the NCCN guidelines support including it in the staging of known or suspected pheochromocytoma [11].

CT Chest Without and With IV Contrast. There is no relevant literature to support the use of CT chest without and with IV contrast in the staging of known or suspected pheochromocytoma.

CT Chest Without IV Contrast. NCCN guidelines support inclusion of CT chest in the staging of known or suspected pheochromocytoma and it can be performed with or without IV contrast [11]. There is no other relevant literature to support the use of CT chest without IV contrast in the staging of known or suspected pheochromocytoma.

DOTATATE PET/CT Skull Base to Mid-Thigh. Whole body functional imaging with a somatostatin analogue (SSA) is useful in adrenal lesions biochemically confirmed or suspected to be pheochromocytoma [9]. DOTATATE is considered the first-line agent in the United States, as F-DOPA is not FDA-

approved for use. F-DOPA PET/CT is also a first-line agent in detecting pheochromocytomas excluding known SDHx mutation carriers [9,23]. Both DOTATATE and F-DOPA are favored over FDG and MIBG. In SDHx mutation carriers, patients with suspected multifocal or metastatic disease, DOTATATE PET/CT is the first-line functional imaging investigation [9].

DOTATATE PET/MRI Skull Base to Mid-Thigh. There is insufficient published literature for DOTATATE PET/MRI in the initial evaluation of pheochromocytoma. However, based on the expert opinion of this panel, FDG-PET/MRI is considered appropriate for use in staging of known or suspected ACC, as an equivalent to FDG-PET/CT.

FDG-PET/CT Skull Base to Mid-Thigh. Radionuclide imaging is recommended; however, FDG-PET/CT should be considered third-line after DOTATATE PET/CT and F-DOPA PET/CT for the detection of sporadic and inherited pheochromocytomas, excluding SDHx carriers [9]. FDG-PET/CT is the second-line functional imaging recommendation, after DOTATATE PET/CT, in SDHx carriers, suspected multifocal or metastatic disease [9].

FDG-PET/MRI Skull Base to Mid-Thigh. There is a paucity of literature on the usefulness of FDG-PET/MRI for the staging of confirmed or suspected pheochromocytoma. One study that included pheochromocytomas and paragangliomas showed that integrated PET/MRI, MRI provided added value to FDG-PET but not much to DOTATATE PET in identifying lesions [24].

MIBG Scan Whole Body. Radionuclide imaging is recommended; however, MIBG should be considered third-line after DOTATATE PET/CT and F-DOPA PET/CT. MIBG may lead to underestimation of metastatic disease and result in inappropriate treatment [9]. An I-123-MIBG scan is considered very useful for selecting potential candidates for I-131-MIBG therapy [9]. An MIBG scan with SPECT or SPECT/CT is preferred over planar only I-123-MIBG, for the ability of SPECT to localize sites of uptake and more accurately distinguish between physiologic and pathologic findings.

MIBG Scan Whole Body With SPECT or SPECT/CT Area of Interest. Radionuclide imaging is recommended; however, MIBG should be considered third-line after DOTATATE PET/CT and F-DOPA PET/CT. MIBG may lead to underestimation of metastatic disease and result in inappropriate treatment [9]. An I-123-MIBG scan is considered very useful for selecting potential candidates for I-131-MIBG therapy [9]. An MIBG scan with SPECT or SPECT/CT is preferred over planar only I-123-MIBG, for the ability of SPECT to localize sites of uptake and more

accurately distinguish between physiologic and pathologic findings.

MRI Abdomen and Pelvis Without and With IV Contrast. The NCCN guidelines support using MRI abdomen and pelvis without and with IV contrast as an alternative to CT for the staging of known or suspected pheochromocytoma [11]. Currently, there is no literature that has investigated the performance of MRI abdomen and pelvis with IV contrast in the initial staging of known or suspected pheochromocytoma.

MRI Abdomen and Pelvis Without IV Contrast. There is no relevant literature to support the use of MRI abdomen and pelvis without IV contrast in the staging of known or suspected pheochromocytoma.

Radiography Chest. There is no relevant literature to support the use of chest radiography in the staging of known or suspected pheochromocytoma. However, imaging of the chest is recommended and should be performed with CT [11].

Variant 4: Adult. Known or suspected pheochromocytoma. Restaging or surveillance.

The goal of imaging is to restage or surveil a known or suspected pheochromocytoma. This includes evaluation of the site of initial disease and assessment for distant metastases. Restaging refers to the process of reassessing a patient's disease status after treatment to determine how the disease has changed in response to treatment. Surveillance refers to ongoing monitoring to detect any signs of recurrence after successful treatment or remission. The information gathered from restaging or surveillance imaging will help provide the most appropriate treatment for these patients. This will improve patient outcomes by guiding the most appropriate management plan early and thereby lessening the length of illness and expediting the patient's recovery time.

Prospective studies comparing the performance of anatomical imaging with functional imaging in restaging or surveillance of pheochromocytoma are lacking. Thus, both types of imaging are suggested and considered complementary [11].

In the following discussion, an area of interest can refer to the following: head, neck, chest, abdomen, pelvis, upper extremity, and lower extremity.

CT Abdomen and Pelvis With IV Contrast. The NCCN guidelines support considering the use of CT of the abdomen and pelvis with IV contrast for the restaging or surveillance of known or suspected pheochromocytoma [11]. However, there is no literature describing the

performance of CT abdomen and pelvis with IV contrast in the restaging or surveillance of known or suspected pheochromocytoma.

CT Abdomen and Pelvis Without and With IV Contrast. There is no relevant literature to support the use of CT abdomen and pelvis without and with IV contrast in the restaging or surveillance of known or suspected pheochromocytoma.

CT Abdomen and Pelvis Without IV Contrast. There is no relevant literature to support the use of CT abdomen and pelvis without IV contrast in the restaging or surveillance of known or suspected pheochromocytoma.

CT Chest With IV Contrast. Although literature on the performance of CT chest with IV contrast in the restaging or surveillance of pheochromocytomas is lacking, the NCCN guidelines support including CT chest in the restaging or surveillance of known or suspected pheochromocytoma [11].

CT Chest Without and With IV Contrast. There is no relevant literature to support the use of CT chest without and with IV contrast in the restaging or surveillance of known or suspected pheochromocytoma.

CT Chest Without IV Contrast. The NCCN guidelines recommend considering inclusion of CT chest in the restaging or surveillance of known or suspected pheochromocytoma and it can be performed with or without IV contrast [11]. There is no other relevant literature to support the use of CT chest without IV contrast in the restaging or surveillance of known or suspected pheochromocytoma.

DOTATATE PET/CT Skull Base to Mid-Thigh. There is no published literature specific to the performance of restaging and surveillance of pheochromocytoma. Most of the available literature has focused on detection and initial staging, or has combined initial staging, restaging, and surveillance patient cohorts. The European Association of Nuclear Medicine and Society of Nuclear Medicine and Molecular Imaging support consideration of lifetime functional imaging every 2 to 3 years in patient cohorts with increased metastatic potential, including those with SDHB mutations, alpha thalassemia/mental retardation syndrome X-linked mutations, large tumors (>5 cm), noradrenergic biochemical phenotype, and high methoxytyramine level [9].

DOTATATE PET/MRI Skull Base to Mid-Thigh. There is no relevant literature on the performance of DOTATATE PET/MRI specific to restaging or surveillance of pheochromocytoma. However, based on the expert opinion of this panel, DOTATATE PET/MRI is considered appropriate for use in

the restaging or surveillance of known or suspected pheochromocytoma as an equivalent to FDG-PET/CT.

FDG-PET/CT Skull Base to Mid-Thigh. FDG-PET/CT skull base to mid-thigh can be considered for restaging or surveillance of pheochromocytoma [11]. There is a paucity of literature on its performance, with reported sensitivities of 86% to 100% and specificity of 100% [25]. In one study, FDG-PET/CT was shown to perform better than CT alone and MIBG SPECT [25].

FDG-PET/MRI Skull Base to Mid-Thigh. There is no relevant literature on the performance of FDG-PET/MRI in the context of restaging or surveillance of pheochromocytoma. However, based on the expert opinion of this panel, FDG-PET/MRI may be considered appropriate for use in the restaging or surveillance of known or suspected pheochromocytoma, as an equivalent to FDG-PET/CT. Nonetheless, DOTATE PET is preferred as a first-line agent.

MIBG Scan Whole Body. There is no published literature specific to the performance on restaging and surveillance of pheochromocytoma with MIBG whole body scan. Most of the available literature has focused on detection and initial staging or has combined initial staging with restaging and surveillance cohorts. An I-123-MIBG scan is considered very useful for selecting potential candidates for I-131-MIBG therapy [9]. An I-123-MIBG scan with SPECT or SPECT/CT is preferred over planar only I-123-MIBG, for the ability of SPECT to localize sites of uptake and more accurately distinguish between physiologic and pathologic findings.

MIBG Scan Whole Body With SPECT or SPECT/CT Area of Interest. MIBG whole body with SPECT is supported over MIBG whole body scan for its ability to localize sites of uptake and more accurately distinguish between physiologic and pathologic findings. An I-123-MIBG scan is considered very useful for selecting potential candidates for I-131-MIBG therapy [9]. An I-123-MIBG scan with SPECT or SPECT/CT is preferred over planar only I-123-MIBG, for the ability of SPECT to localize sites of uptake and more accurately distinguish between physiologic and pathologic findings.

MRI Abdomen and Pelvis Without and With IV Contrast. The NCCN guidelines suggest considering the use of MRI abdomen and pelvis without and with IV contrast as an alternative to CT for restaging or surveillance of known or suspected pheochromocytoma [11]. Currently, there is no literature that has investigated the performance of MRI abdomen and pelvis with IV contrast in the restaging or surveillance of known or suspected pheochromocytoma.

MRI Abdomen and Pelvis Without IV Contrast. Administration of contrast with CT or MRI is preferred.

Radiography Chest. There is no relevant literature to support the use of chest radiography in the restaging or surveillance of known or suspected pheochromocytoma. However, imaging of the chest is useful and should be performed with CT [11].

SUMMARY OF HIGHLIGHTS

This is a summary of the key recommendations from the variant tables. Refer to the complete narrative document for more information.

- **Variant 1:** For initial staging of known or suspected ACC, MRI of the abdomen and pelvis without and with IV contrast or CT of the abdomen and pelvis with IV contrast, CT of the chest with IV contrast, and FDG-PET/CT or FDG-PET/MRI are recommended to assess for local extent and distant metastases. CT abdomen and pelvis and MRI abdomen and pelvis are equivalent alternatives. These are complementary to CT chest and FDG-PET/CT or FDG-PET/MRI. FDG-PET/CT and FDG-PET/MRI are equivalent alternatives.
- **Variant 2:** For restaging or surveillance of known or suspected ACC, MRI of the abdomen and pelvis without and with IV contrast or CT of the abdomen and pelvis with IV contrast, CT of the chest with IV contrast, and FDG-PET/CT or FDG-PET/MRI are recommended to evaluate for recurrence.
- **Variant 3:** For initial staging of known or suspected pheochromocytoma, MRI of the abdomen and pelvis without and with IV contrast or CT of the abdomen and pelvis with IV contrast, CT of the chest with IV contrast, DOTATATE PET/CT or DOTATATE PET/MRI are recommended to assess for local extent and distant metastases. MIBG scan whole body with SPECT or SPECT/CT area of interest is an acceptable alternative for initial staging of known or suspected pheochromocytoma, in particular to determine eligibility for I-131 MIBG therapy. CT abdomen and pelvis and MRI abdomen and pelvis are equivalent alternatives. These are complementary to CT chest and DOTATATE PET/CT or DOTATATE PET/MRI. DOTATATE PET/CT or DOTATATE PET/MRI are equivalent alternatives.
- **Variant 4:** For restaging or surveillance of known or suspected pheochromocytoma, MRI of the abdomen and pelvis without and with IV contrast or CT of the

abdomen and pelvis with IV contrast, CT of the chest with IV contrast, DOTATATE PET/CT or DOTATATE PET/MRI are recommended to evaluate for recurrence. CT abdomen and pelvis and MRI abdomen and pelvis are equivalent alternatives. These are complementary to CT chest and DOTATATE PET/CT or DOTATATE PET/MRI. DOTATATE PET/CT or DOTATATE PET/MRI are equivalent alternatives.

SUPPORTING DOCUMENTS

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents, please visit <https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria>.

GENDER EQUALITY AND INCLUSIVITY CLAUSE

The ACR acknowledges the limitations in applying inclusive language when citing research studies that predates the use of the current understanding of language inclusive of diversity in sex, intersex, gender, and gender-diverse people. The data variables regarding sex and gender used in the cited literature will not be changed. However, this guideline will use the terminology and definitions as proposed by the National Institutes of Health [26].

RELATIVE RADIATION LEVEL INFORMATION

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table 2). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR

Appropriateness Criteria® Radiation Dose Assessment
Introduction document [27].

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