

# ACR Appropriateness Criteria<sup>®</sup> Staging and Follow-Up of Pancreatic Neuroendocrine Tumors

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## Abstract

Accurate staging and appropriate follow-up imaging of pancreatic neuroendocrine tumors (PNET) are essential for guiding management and optimizing outcomes. This document provides evidence-based recommendations for the imaging evaluation of patients with PNET across six clinical variants: local staging, staging for metastatic disease, surveillance postresection, follow-up after treatment of liver-dominant and non-liver dominant disease, and follow-up of untreated disease. Contrast-enhanced CT is usually appropriate in most scenarios and commonly used as the first-line imaging modality in assessing tumor size, locoregional extent, vascular involvement, and metastatic spread. MRI is also usually appropriate, particularly for liver evaluation. MRI with hepatobiliary contrast agents and

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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.

diffusion-weighted imaging improves detection and characterization of liver metastases, especially in liver-dominant disease. DOTATATE PET/CT is usually appropriate for staging and treatment planning in patients with suspected or known metastatic disease. FDG-PET/CT is reserved for select cases, such as high-grade tumors.

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, pancreatic neuroendocrine tumor, staging, surveillance, treatment response

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## ACR Appropriateness Criteria® Staging and Follow-Up of Pancreatic Neuroendocrine Tumors. [Variants 1 to 6](#) and [Tables 1](#) and [2](#).

### Variant 1. Adult. Local staging of pancreatic neuroendocrine tumor.

| Procedure                                          | Appropriateness Category          | Relative Radiation Level |
|----------------------------------------------------|-----------------------------------|--------------------------|
| CT abdomen and pelvis with IV contrast             | Usually Appropriate               | ⦿⦿⦿                      |
| DOTATATE PET/CT skull base to mid-thigh            | Usually Appropriate               | ⦿⦿⦿                      |
| CT abdomen and pelvis without and with IV contrast | Usually Appropriate               | ⦿⦿⦿⦿                     |
| US abdomen endoscopic                              | May Be Appropriate                | ○                        |
| MRI abdomen without and with IV contrast           | May Be Appropriate (Disagreement) | ○                        |
| MRI abdomen without and with IV contrast with MRCP | May Be Appropriate (Disagreement) | ○                        |
| MRI abdomen without IV contrast with MRCP          | May Be Appropriate                | ○                        |
| FDG-PET/CT skull base to mid-thigh                 | May Be Appropriate                | ⦿⦿⦿⦿                     |
| MRI abdomen without IV contrast                    | Usually Not Appropriate           | ○                        |
| CT abdomen and pelvis without IV contrast          | Usually Not Appropriate           | ⦿⦿⦿                      |

**Variant 2. Adult. Staging of pancreatic neuroendocrine tumor. Evaluation for metastatic disease.**

| 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      | ⚠⚠⚠                      |
| DOTATATE PET/CT skull base to mid-thigh              | Usually Appropriate      | ⚠⚠⚠                      |
| CT chest abdomen pelvis with IV contrast             | Usually Appropriate      | ⚠⚠⚠⚠                     |
| MRI abdomen and pelvis without IV contrast           | May Be Appropriate       | 0                        |
| CT abdomen and pelvis without and with IV contrast   | May Be Appropriate       | ⚠⚠⚠⚠                     |
| CT chest abdomen pelvis without and with IV contrast | May Be Appropriate       | ⚠⚠⚠⚠                     |
| FDG-PET/CT skull base to mid-thigh                   | May Be Appropriate       | ⚠⚠⚠⚠                     |
| US abdomen endoscopic                                | Usually Not Appropriate  | 0                        |
| CT abdomen and pelvis without IV contrast            | Usually Not Appropriate  | ⚠⚠⚠                      |
| CT chest abdomen pelvis without IV contrast          | Usually Not Appropriate  | ⚠⚠⚠⚠                     |

**Variant 3. Adult. Pancreatic neuroendocrine tumor. Imaging after surgical resection, no suspected or known recurrence. Surveillance.**

| Procedure                                            | Appropriateness Category          | Relative Radiation Level |
|------------------------------------------------------|-----------------------------------|--------------------------|
| CT abdomen and pelvis with IV contrast               | Usually Appropriate               | ⚠⚠⚠                      |
| CT chest abdomen pelvis with IV contrast             | Usually Appropriate               | ⚠⚠⚠⚠                     |
| MRI abdomen and pelvis without and with IV contrast  | May Be Appropriate (Disagreement) | 0                        |
| MRI abdomen and pelvis without IV contrast           | May Be Appropriate                | 0                        |
| DOTATATE PET/CT skull base to mid-thigh              | May Be Appropriate                | ⚠⚠⚠                      |
| CT abdomen and pelvis without and with IV contrast   | May Be Appropriate (Disagreement) | ⚠⚠⚠⚠                     |
| CT chest abdomen pelvis without and with IV contrast | May Be Appropriate                | ⚠⚠⚠⚠                     |
| US abdomen endoscopic                                | Usually Not Appropriate           | 0                        |
| CT abdomen and pelvis without IV contrast            | Usually Not Appropriate           | ⚠⚠⚠                      |
| CT chest abdomen pelvis without IV contrast          | Usually Not Appropriate           | ⚠⚠⚠⚠                     |
| FDG-PET/CT skull base to mid-thigh                   | Usually Not Appropriate           | ⚠⚠⚠⚠                     |

**Variant 4. Adult. Pancreatic neuroendocrine tumor. Follow-up imaging after treatment. Liver-dominant disease.**

| Procedure                                            | Appropriateness Category          | Relative Radiation Level |
|------------------------------------------------------|-----------------------------------|--------------------------|
| MRI abdomen and pelvis without and with IV contrast  | Usually Appropriate               | ○                        |
| CT abdomen and pelvis without and with IV contrast   | Usually Appropriate               | ⦿⦿⦿⦿                     |
| CT chest abdomen pelvis with IV contrast             | Usually Appropriate               | ⦿⦿⦿⦿                     |
| CT chest abdomen pelvis without and with IV contrast | Usually Appropriate               | ⦿⦿⦿⦿                     |
| MRI abdomen and pelvis without IV contrast           | May Be Appropriate (Disagreement) | ○                        |
| MRI abdomen without and with IV contrast with MRCP   | May Be Appropriate (Disagreement) | ○                        |
| MRI abdomen without IV contrast with MRCP            | May Be Appropriate (Disagreement) | ○                        |
| CT abdomen and pelvis with IV contrast               | May Be Appropriate (Disagreement) | ⦿⦿⦿                      |
| DOTATATE PET/CT skull base to mid-thigh              | May Be Appropriate (Disagreement) | ⦿⦿⦿                      |
| US abdomen endoscopic                                | Usually Not Appropriate           | ○                        |
| CT abdomen and pelvis without IV contrast            | Usually Not Appropriate           | ⦿⦿⦿                      |
| CT chest abdomen pelvis without IV contrast          | Usually Not Appropriate           | ⦿⦿⦿⦿                     |
| FDG-PET/CT skull base to mid-thigh                   | Usually Not Appropriate           | ⦿⦿⦿⦿                     |

**Variant 5. Adult. Pancreatic neuroendocrine tumor. Follow-up imaging after treatment. Non-liver dominant disease.**

| Procedure                                            | Appropriateness Category          | Relative Radiation Level |
|------------------------------------------------------|-----------------------------------|--------------------------|
| MRI abdomen and pelvis without and with IV contrast  | Usually Appropriate               | ○                        |
| CT abdomen and pelvis with IV contrast               | Usually Appropriate               | ⦿⦿⦿                      |
| DOTATATE PET/CT skull base to mid-thigh              | Usually Appropriate               | ⦿⦿⦿                      |
| CT chest abdomen pelvis with IV contrast             | Usually Appropriate               | ⦿⦿⦿⦿                     |
| MRI abdomen and pelvis without IV contrast           | May Be Appropriate                | ○                        |
| MRI abdomen without and with IV contrast with MRCP   | May Be Appropriate (Disagreement) | ○                        |
| MRI abdomen without IV contrast with MRCP            | May Be Appropriate                | ○                        |
| CT abdomen and pelvis without and with IV contrast   | May Be Appropriate                | ⦿⦿⦿⦿                     |
| CT chest abdomen pelvis without and with IV contrast | May Be Appropriate                | ⦿⦿⦿⦿                     |
| FDG-PET/CT skull base to mid-thigh                   | May Be Appropriate                | ⦿⦿⦿⦿                     |
| US abdomen endoscopic                                | Usually Not Appropriate           | ○                        |
| CT abdomen and pelvis without IV contrast            | Usually Not Appropriate           | ⦿⦿⦿                      |
| CT chest abdomen pelvis without IV contrast          | Usually Not Appropriate           | ⦿⦿⦿⦿                     |

**Variant 6. Adult. Pancreatic neuroendocrine tumor. Follow-up imaging of untreated disease.**

| Procedure                                           | Appropriateness Category          | Relative Radiation Level |
|-----------------------------------------------------|-----------------------------------|--------------------------|
| MRI abdomen and pelvis without and with IV contrast | Usually Appropriate               | ○                        |
| MRI abdomen without and with IV contrast with MRCP  | Usually Appropriate               | ○                        |
| CT abdomen and pelvis with IV contrast              | Usually Appropriate               | ⦿⦿⦿                      |
| CT abdomen and pelvis without and with IV contrast  | Usually Appropriate               | ⦿⦿⦿⦿                     |
| MRI abdomen and pelvis without IV contrast          | May Be Appropriate                | ○                        |
| MRI abdomen without IV contrast with MRCP           | May Be Appropriate                | ○                        |
| DOTATATE PET/CT skull base to mid-thigh             | May Be Appropriate (Disagreement) | ⦿⦿⦿                      |
| US abdomen endoscopic                               | Usually Not Appropriate           | ○                        |
| CT abdomen and pelvis without IV contrast           | Usually Not Appropriate           | ⦿⦿⦿                      |
| FDG-PET/CT skull base to mid-thigh                  | 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) |
|-------|-------------------------------------------|-----------------------------------------------|
| ○     | 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

Pancreatic neuroendocrine neoplasms (PNET) are rare, accounting for up to 7% of pancreatic tumors [1,2]. The incidence of gastroenteropancreatic neuroendocrine neoplasms has steadily risen over the past 40 years, likely because of increasing detection [3,4], reaching 5.45 per 100,000 in 2015 in the United States [4]. PNET represent 16.3% of gastroenteropancreatic neuroendocrine neoplasms [4]. According to the World Health Organization 2017 classification, PNET are divided into well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinoma (NEC) [5]. Pancreatic neuroendocrine tumors (PNET) can be further graded into three grades (G1, G2, and G3) based on the mitotic rate and the fraction of Ki-67–positive tumor cells (Ki-67 index) [5]. NEC are rare and high-grade and are by definition poorly differentiated. They have worse outcomes and require different therapeutic strategies and staging, and therefore recent classifications separate NEC from neuroendocrine tumors. This document is primarily focused on PNET, with no further discussion of NEC.

Less than one-third of PNET are functioning [6,7], secreting various hormones often leading to the clinical presentation. Insulinomas followed by gastrinomas are the most common types of functioning PNET. Other types include glucagonomas, Verner-Morrison syndrome, somatostatinomas, and rarely other hormone secreting tumors [8]. Most PNET are sporadic, but some are associated with familial syndromes. Patients with multiple endocrine neoplasia type 1 and Von Hippel-Lindau have a high incidence of PNET, which warrants screening of affected patients [8,9]. There is also an association with neurofibromatosis type 1 as well as tuberous sclerosis; however, the incidence in those groups remains relatively low, and therefore surveillance is not typical in those patients [8,9]. The majority of PNET are nonfunctioning and are often larger at diagnosis, with a higher likelihood of metastasis [1,9]. The increase in incidence of PNET can possibly be attributed to increased detection of nonfunctioning PNET incidentally on imaging. Whereas imaging is an important component of the workup (plus a biochemical workup as clinically indicated), pathologic examination remains the reference standard for diagnosis [2]. Endoscopic ultrasound (EUS) with fine-needle aspiration is the approach of choice for diagnosis and histologic grading of the tumor in most setting [7].

Multiple staging systems have been historically used for PNET [9]. In 2017, the eighth edition of the American Joint Committee on Cancer adopted a different staging system for PNET separate from that used for exocrine

pancreatic cancer, which is more consistent with that of the European Neuroendocrine Tumor Society [10,11]. This staging was maintained in the subsequent 9th edition [12]. Imaging plays a key role in the preoperative staging of PNET, which is important for appropriate management. For tumor staging, the T stage is defined as follows: T1 tumors are <2 cm in size and confined to the pancreas; T2 tumors measure between 2 cm and 4 cm and are confined to the pancreas; T3 tumors are >4 cm in size or there is growth of tumor into the duodenum or common bile duct; and in T4 disease, there is tumor invasion into adjacent organs or there is growth into blood vessels.

PNET have overall more indolent biology with far better outcomes compared with NEC and pancreatic adenocarcinoma. The median overall survival is 67 months for all PNET [4]. For tumors with distant disease and regional disease, the median overall survival is 2 years and 10.8 years, respectively [4]. For localized tumors, that median could not be reached (ie, exceeding 30 years) with a 5-year survival of 91.7% [4]. Surgical resection is considered the only curative therapy [13]. The extent of the surgery depends on the tumor size and staging. Patients with limited liver metastases may also benefit from surgical resection of the metastases with curative intent; however, there is a high recurrence rate [2,14]. Liver-directed therapies such as chemoembolization, ablation, and radioembolization may be of value for hepatic metastases [2,14]. Most PNET express high affinity receptors for somatostatin, making somatostatin analogs the treatment of choice to control tumor growth for patients with locoregional advanced disease and/or metastatic disease with significant tumor burden or progression [14]. Patients who progress on somatostatin analogs can be treated with peptide receptor radionuclide therapy, Lu-177 DOTATATE, if the tumor expresses somatostatin receptors [14]. Other systemic therapy options include oral targeted agents such as everolimus and sunitinib [14]. Recent data suggest cabozantinib also has activity, although this agent is not yet FDA-approved for this indication [15]. Chemotherapy is also routinely implemented, with temozolomide-based therapy most commonly used [15,16].

## DISCUSSION OF PROCEDURES BY VARIANT

### Variant 1: Adult. Local staging of pancreatic neuroendocrine tumor

In this clinical scenario, the patient has been diagnosed with PNET and is presenting for evaluation of the locoregional extent of the tumor, typically as part of the preoperative evaluation for possible surgical resection. The possibility of metastatic disease is considered unlikely in this clinical

scenario based on prior imaging and tumor factors such as small size and tumor grade.

**CT Abdomen and Pelvis With IV Contrast.** CT is often the initial modality for evaluation of patients with PNET and should be performed according to the pancreatic protocol, which includes a late arterial phase known as the pancreatic parenchymal phase as well as a portal venous phase. The reported lesion detection rate ranges from 69% to 94% [17]. The reported sensitivities for small tumors are broad, ranging from 30% to 80%, with significantly higher sensitivities reaching up to 95% for larger lesions [9]. PNET are most typically solid lesions with arterial phase hyperenhancement on CT and MRI necessitating the use of intravenous (IV) contrast; furthermore, a multiphase CT including arterial and portal venous phases is typically needed given that some tumors may only be visible on the arterial phase [2,9,18]. Tumor size estimated by CT was concordant with gross pathology [10]. Although vascular encasement and narrowing is less common with PNET, vascular involvement correlates with tumor grade and outcomes and has significant management implications [19-21]. PNET may exhibit a distinctive and underrecognized pattern of venous tumor thrombus in the splenic vein, superior mesenteric vein, and main portal vein, warranting particular attention to these vessels [6,22]. The prevalence of venous tumor thrombus is estimated to be as high as 33%, but it is underreported on imaging [6,22]. Precontrast images are typically not necessary but can be useful in confirming the presence of necrotic components and intratumor hemorrhage. There is no evidence to support the inclusion of the chest in the setting of staging local disease given the low likelihood of metastatic disease in this clinical scenario.

**CT Abdomen and Pelvis Without and With IV Contrast.** Although a CT performed with and without IV contrast has the same performance characteristics as a CT with IV contrast, precontrast images are typically not necessary and have not been shown to add to diagnostic/staging accuracy. However, precontrast images can be useful in confirming the presence of necrotic components and intratumor hemorrhage. There is no evidence to support the inclusion of the chest in the setting of staging local disease given the low likelihood of metastatic disease in this clinical scenario.

**CT Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that many PNET will only be visible after administration of contrast. Furthermore, evaluation of peripancreatic vasculature is not possible without IV contrast. There is no evidence to support the inclusion of the chest in the setting of

staging local disease given the low likelihood of metastatic disease in this clinical scenario.

**DOTATATE PET/CT Skull Base to Mid-Thigh.** Somatostatin receptor-PET imaging (SSTR-PET), such as DOTATATE PET/CT, is highly sensitive for neuroendocrine tumors, with reported sensitivities and specificities for PNET ranging from 86% to 100% and 79% to 100%, respectively [17,23], the exception being insulinoma, for which the sensitivity is as low as 25% [23]. DOTATATE PET/CT could play a role when there is a suspicion for PNET based on laboratory tests, particularly if not detected on conventional imaging or if not amenable to biopsy [1,24]. In the context of staging histologically confirmed PNET without metastatic disease, DOTATATE PET/CT offers the particular advantage of detecting lymph node metastases that are difficult to characterize by CT and MRI apart from size, as well as significantly improving the detection of bone metastases that are often missed on CT [17,25], making it a useful alternative tool for staging in this clinical scenario [1,24]. DOTATATE PET/CT was found to change the staging or cause a therapy modification in >50% of patients in one study [26]. In the scenario of a small primary lesion, <2 cm, with low-grade histology, the likelihood of metastatic disease is considered very low, and therefore DOTATATE PET/CT may not be necessary [1].

**FDG-PET/CT Skull Base to Mid-Thigh.** Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) uptake is typically minimal in low-grade well-differentiated PNET and is therefore unlikely to be of value in the initial staging of PNET being considered for resection, particularly when the suspicion for metastatic disease is low. FDG-PET can be considered in high-grade tumor without avidity on DOTATATE PET/CT, but that rare consideration would only arise after the initial workup, and therefore FDG-PET is not an initial test in local staging.

**MRI Abdomen Without and With IV Contrast.** Owing to its superior soft tissue and contrast resolution, MRI is valuable for the evaluation of PNET, with a reported sensitivity of 80% for small tumors <2 cm in size [9]. PNET are most typically solid lesions with arterial phase hyperenhancement on CT and MRI [27]. They typically demonstrate low T1 and high T2 signal and variable diffusion restriction [9]. However, it is important to recognize there could be significant variation in appearance. For example, 41.5% of PNET may not show arterial hyperenhancement [27]. Eighteen percent of PNET are cystic, most of which demonstrate a hyperenhancing rim, but a small proportion are purely cystic without enhancement [18]. Differentiation of cystic PNET and necrotic changes may be difficult on imaging [18,28].

Furthermore, many articles in the literature describe imaging features that are associated with aggressive behavior of the tumor, such as an ill-defined margin [29], relative hypoenhancement on the portal venous phase compared with the pancreatic parenchyma [5,20,29,30], lower arterial enhancement ratio [5,31,32], ductal dilatation [5,20], vascular involvement [19-21], nonbright T2 signal [19], and restricted diffusion [13,29,33]. Pancreatic ductal dilatation is uncommon with PNET, but it can occur in the setting of large tumor size and high-grade tumors [20] or by tumors that locally produce elevated serotonin leading to fibrotic stricture of the duct [9]. A rare but distinctive and underrecognized pattern of PNET spread is intraductal spread [6]. Involvement of the common bile duct would upgrade the T stage to T3. Therefore, the inclusion of MR cholangiopancreatography (MRCP) sequences is important for the evaluation of pancreatic ductal dilatation, intraductal growth, or involvement of the biliary duct. Kim et al [29] evaluated the staging accuracy of MRI for PNET and reported an accuracy for T-staging of 77% (n = 30) and 85% (n = 33) and an accuracy for N-staging of 92% (n = 36) and 87% (n = 34) for two readers with moderate interreader agreement. Tumor size estimated by MRI was concordant with gross pathology [10,29]. The inclusion of the pelvis is of no clear value in the setting of local staging.

**MRI Abdomen Without and With IV Contrast With MRCP.** Owing to its superior soft tissue and contrast resolution, MRI is valuable for the evaluation of PNET, with a reported sensitivity of 80% for small tumors <2 cm in size [9]. PNET are most typically solid lesions with arterial phase hyperenhancement on CT and MRI [27]. They typically demonstrate low T1 and high T2 signal and variable diffusion restriction [9]. However, it is important to recognize there could be significant variation in appearance. For example, 41.5% of PNET may not show arterial hyperenhancement [27]. Eighteen percent of PNET are cystic, most of which demonstrate a hyperenhancing rim, but a small proportion are purely cystic without enhancement [18]. Differentiation of cystic PNET and necrotic changes may be difficult on imaging [18,28]. Furthermore, many articles in the literature describe imaging features that are associated with aggressive behavior of the tumor, such as an ill-defined margin [29], relative hypoenhancement on the portal venous phase compared with the pancreatic parenchyma [5,20,29,30], lower arterial enhancement ratio [5,31,32], ductal dilatation [5,20], vascular involvement [19-21], nonbright T2 signal [19], and restricted diffusion [13,29,33]. Pancreatic ductal dilatation is uncommon with PNET, but it can occur in the setting of large tumor size and high-grade tumors [20] or by tumors that locally produce elevated serotonin

leading to fibrotic stricture of the duct [9]. A rare but distinctive and underrecognized pattern of PNET spread is intraductal spread [6]. Involvement of the common bile duct would upgrade the T stage to T3. Therefore, the inclusion of MRCP sequences is important for the evaluation of pancreatic ductal dilatation, intraductal growth, or involvement of the biliary duct. Kim et al [29] evaluated the staging accuracy of MRI for PNET and reported an accuracy for T-staging of 77% (n = 30) and 85% (n = 33) and an accuracy for N-staging of 92% (n = 36) and 87% (n = 34) for 2 readers with moderate interreader agreement. Tumor size estimated by MRI was concordant with gross pathology [10,29].

**MRI Abdomen Without IV Contrast.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. Furthermore, evaluation of peripancreatic vasculature is difficult without IV contrast. MRCP sequences are considered an important component of the MRI protocol in this clinical scenario. The inclusion of the pelvis is of no clear value in the setting of local staging.

**MRI Abdomen Without IV Contrast With MRCP.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. Furthermore, evaluation of peripancreatic vasculature is difficult without IV contrast. MRCP sequences are considered an important component of the MRI protocol in this clinical scenario.

**US Abdomen Endoscopic.** EUS has a reported sensitivity of 80% to 90% for the detection of PNET and can be particularly useful in patients with an unrevealing CT [9]. EUS has high spatial resolution, which allows for improved tumor visualization and its anatomic relations to the pancreatic duct. The distinct advantage of EUS is the ability to perform fine-needle aspiration, which is considered the approach of choice for obtaining an accurate diagnosis [7]. The field of view for EUS is limited, and therefore evaluation of regional lymphadenopathy is limited. Typically EUS would have been performed already for tissue sampling before dedicated imaging for local staging, but if not, EUS can be considered if additional delineation of the tumor relation to the pancreatic duct is needed.

## Variant 2: Adult. Staging of pancreatic neuroendocrine tumor. Evaluation for metastatic disease

In this clinical scenario, the patient has been diagnosed with PNET and is presenting for complete staging of the disease.

Metastatic disease may have already been suspected based on prior imaging, or the likelihood of metastases is not negligible based on tumor factors such as size or grade.

**CT Abdomen and Pelvis With IV Contrast.** CT is often the initial modality for the evaluation of patients with PNET and should be performed with a biphasic CT protocol, which includes a late arterial phase (also known as the pancreatic parenchymal phase) through the pancreas and liver as well as a portal venous phase through the abdomen and pelvis. The reported sensitivity and specificity of CT for lymph node metastases are 60% to 70% and 87% to 100%, respectively [17]. For soft tissue metastases, the sensitivity and specificity of CT are 62% to 67% and 98% to 100%, respectively [17]. For bone metastases the sensitivity and specificity of CT are 46% to 80% and 98% to 100%, respectively [17]. For liver metastases, the sensitivity and specificity of CT are 75% to 100% and 83% to 100%, respectively [17]. If liver metastases are already known or suspected, then a liver protocol CT should be considered. Precontrast imaging is unlikely to be helpful and is therefore not necessary. It is worth noting that a study that compared multiple imaging modalities with thin slice histopathology of hemihepatectomy has found that CT has only a 38% accuracy for detecting liver metastases preoperatively on a per-lesion basis [34]. Half of the metastatic lesions were not detected by any modality preoperatively, with MRI having the highest accuracy of 48% [34]. This would account for the known high recurrence rate after liver resection.

**CT Abdomen and Pelvis Without and With IV Contrast.** Although a CT performed with and without IV contrast has the same performance characteristics as a CT with IV contrast, precontrast images are typically not necessary. Precontrast images can be useful in confirming the presence of necrotic components and intratumor hemorrhage. Some institutions routinely include precontrast images as part of their multiphase protocols.

**CT Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that many PNET will only be visible after administration of contrast. Furthermore, evaluation of peripancreatic vasculature is not possible without IV contrast.

**CT Chest Abdomen Pelvis With IV Contrast.** Neither the National Comprehensive Cancer Network (NCCN) guidelines nor multiple North American and European consensus guidelines explicitly discuss the need for CT of the chest [1,8,17,23,25,35]; however, it can be obtained at the time of initial diagnosis when DOTATATE PET/CT is not performed [25].

**CT Chest Abdomen Pelvis Without and With IV Contrast.** Neither the NCCN guidelines nor multiple North American and European consensus guidelines explicitly discuss the need for CT of the chest [1,8,17,23,25,35]; however, it can be obtained at the time of initial diagnosis when DOTATATE PET/CT is not performed [25].

**CT Chest Abdomen Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that many PNET will only be visible after administration of contrast. Furthermore, evaluation of peripancreatic vasculature is not possible without IV contrast.

**DOTATATE PET/CT Skull Base to Mid-Thigh.** SSTR-PET, such as DOTATATE PET/CT, is highly sensitive for neuroendocrine tumors, with reported sensitivities and specificities for PNET ranging from 86% to 100% and 79% to 100%, respectively [17,23], the exception being insulinomas, for which the sensitivity is as low as 25% [23]. In the context of staging histologically confirmed PNET with suspected metastases, DOTATATE PET/CT offers the particular advantage of detecting lymph node metastases that are difficult to characterize by CT and MRI apart from size, as well as significantly improving the detection of bone metastases that are often missed on CT [17,25], and therefore should be considered for complete staging of these patients [1,24]. DOTATATE PET/CT was found to change the staging or cause a therapy modification in more than 50% of patients in 1 study [26]. DOTATATE PET/CT has the unique role of evaluating somatostatin receptor status for determining whether a patient may benefit from targeted peptide receptor radionuclide therapy [24].

**FDG-PET/CT Skull Base to Mid-Thigh.** FDG uptake is typically minimal in low-grade well-differentiated PNET and is therefore unlikely to be of value in the initial staging of PNET. FDG-PET can be considered in high-grade tumors that are negative on DOTATATE PET/CT.

**MRI Abdomen and Pelvis Without and With IV Contrast.** MRI is useful for the initial evaluation and staging of PNET, owing to its sensitivity in detecting the primary tumor and metastatic disease. MRI has a particular advantage in evaluating liver metastases. A study that compared multiple imaging modalities with thin slice histopathology of hemihepatectomy has found MRI to have the highest accuracy compared with CT, US, and somatostatin receptor scintigraphy [34]. In addition, the lesion may also be seen on other sequences, including fat-suppressed T2-weighted images and diffusion-weighted imaging (DWI). DWI in particular was found to be more sensitive for the detection of liver metastases than T2-weighted sequences and dynamic gadolinium-enhanced

MRI [36]. Hepatobiliary contrast agent-enhanced MRI has been shown to improve the detection of liver metastases [9,37,38]. Extrapolating from the ACR Appropriateness Criteria® topic on “Staging of Colorectal Cancer” [39] and expert opinion on neuroendocrine tumor staging [1,25], it is recommended to use hepatobiliary contrast agent-enhanced MRI in combination with DWI when liver resection and liver-directed therapy are being considered. MRCP sequences are useful in the complete assessment of the primary pancreatic tumor.

**MRI Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors; however, DWI in particular was found to be more sensitive for the detection of liver metastases than dynamic gadolinium-enhanced MRI [36], with one study suggesting that visualization of hepatic metastases using DWI alone is within the acceptable limits for clinical use [40]. T2 fast spin-echo was also shown in 1 study to be useful in detecting and monitoring the size of carcinoid hepatic metastases [41]. The combination of these sequences was found to improve the detection of liver metastases [36]. MRCP sequences are useful in the complete assessment of the primary pancreatic tumor.

**US Abdomen Endoscopic.** There is no literature to support the use of EUS for evaluation of distant metastatic disease in the setting of PNET. EUS for evaluation of PNET with metastases is limited due to the limited field of view.

### Variant 3: Adult. Pancreatic neuroendocrine tumor. Imaging after surgical resection, no suspected or known recurrence. Surveillance

Curative resection of PNET with no remaining gross or microscopic tumor and negative margins is referred to as an R0 resection. The prognosis for these patients is excellent, exceeding 90% disease-specific survival at 5 years; however, the rates of recurrence can be as high as 40% in 5 years, warranting close follow-up [1]. Knowledge of the appearance of the primary tumor on various imaging modalities before resection could guide the selection of the postresection surveillance modality. The recommended frequency of surveillance varied between every 3 to 12 months in the first year and then every 6 to 12 months for the following 10 years [35], with higher-grade tumors warranting shorter interval follow-up compared with lower-grade tumors.

**CT Abdomen and Pelvis With IV Contrast.** As in the primary diagnosis and staging of PNET, contrast-enhanced CT is commonly used in postresection surveillance. The

reported sensitivities for small tumors are broad, ranging from 30% to 80%, with significantly higher sensitivities reaching up to 95% for larger lesions [9]. The CT technique should be optimized by performing a multiphase CT including a late arterial phase and portal venous phase [35]. In the absence of a history of directed liver therapy, precontrast imaging is unlikely to be helpful and is therefore not necessary.

**CT Abdomen and Pelvis Without and With IV Contrast.** As in the primary diagnosis and staging of PNET, contrast-enhanced CT is commonly used in postresection surveillance. The CT technique should be optimized by performing a multiphase CT including a late arterial phase and portal venous phase [35]. In the absence of a history of directed liver therapy, precontrast imaging is unlikely to be helpful and is therefore not necessary, although some institutions include a precontrast phase in multiphase CT protocols by convention.

**CT Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that many PNET will only be visible after administration of contrast.

**CT Chest Abdomen Pelvis With IV Contrast.** As in the primary diagnosis and staging of PNET, contrast-enhanced CT is commonly used in postresection surveillance. The CT technique should be optimized by performing a multiphase CT including a late arterial phase and portal venous phase [35]. Imaging of the chest is optional for PNET [35].

**CT Chest Abdomen Pelvis Without and With IV Contrast.** As in the primary diagnosis and staging of PNET, contrast-enhanced CT is commonly used in postresection surveillance. The CT technique should be optimized by performing a multiphase CT including a late arterial phase and portal venous phase [35]. In the absence of a history of directed liver therapy, precontrast imaging is unlikely to be helpful and is therefore not necessary, although some institutions include a precontrast phase in multiphase CT protocols by convention. Imaging of the chest is optional for PNET [35].

**CT Chest Abdomen Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that many PNET will only be visible after administration of contrast.

**DOTATATE PET/CT Skull Base to Mid-Thigh.** SSTR-PET, such as DOTATATE PET/CT, is highly sensitive for neuroendocrine tumors, with reported sensitivities and specificities for PNET ranging from 86% to 100% and 79% to 100%, respectively [17,23], the exception being insulinoma,

for which the sensitivity is as low as 25% [23]. DOTATATE PET/CT is not recommended for routine surveillance [35] but could play a role when there is a suspicion for PNET recurrence not detected on conventional imaging [1,24,25,42]. If a patient did not undergo DOTATATE PET/CT before surgical resection, a single DOTATATE PET/CT examination should be considered to complete staging postoperatively [24].

**FDG-PET/CT Skull Base to Mid-Thigh.** FDG uptake is typically minimal in low-grade well-differentiated PNET and is therefore unlikely to be of value in postresection surveillance of PNET.

**MRI Abdomen and Pelvis Without and With IV Contrast.** As in the primary diagnosis and staging of PNET, contrast-enhanced MRI is commonly used in postresection surveillance. Owing to its superior soft tissue and contrast resolution, MRI is valuable for the evaluation of PNET, with a reported sensitivity of 80% for small tumors <2 cm in size [9]. In the absence of known liver metastases, some authors may prefer an extracellular contrast agent over a hepatobiliary contrast agent [1] because the arterial phase with hepatobiliary agents is negatively affected by the reduced concentration of gadolinium and by the higher likelihood of transient severe respiratory motion [43]. MRCP sequences may not be necessary in this context. Considering that follow-up imaging may be repeated over many years, the merit of the lack of ionizing radiation is a consideration that may favor MRI in this context, particularly for younger patients.

**MRI Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. If necessary, an MRI without IV contrast could still be useful in delineating the tumor. MRCP sequences may not be necessary in this context.

**US Abdomen Endoscopic.** EUS is not typically indicated in the context of postresection surveillance, due to its limited field of view and relatively invasive nature.

#### **Variant 4: Adult. Pancreatic neuroendocrine tumor. Follow-up imaging after treatment. Liver-dominant disease**

For PNET with liver-dominant metastases, the role of imaging would need to address the treatment response assessment of the liver-directed therapy, as well as the increased likelihood of recurrent disease in the liver. Many liver metastases can go undetected on pretreatment imaging with the percentage of undetected metastases >50% in some studies [34,36].

**CT Abdomen and Pelvis With IV Contrast.** The sensitivity and specificity of CT for liver metastases are reported to be 75% to 100% and 83% to 100% [17], although there is a recognition that many liver metastases go undetected [34,36]. In this clinical scenario, the CT should be performed using a liver protocol. The inclusion of precontrast images is valuable in this context to assess treatment response to liver-directed therapy and to differentiate true enhancement from intrinsic high attenuation related to the treatment.

**CT Abdomen and Pelvis Without and With IV Contrast.** The sensitivity and specificity of CT for liver metastases are reported to be 75% to 100% and 83% to 100% [17], although there is a recognition that many liver metastases go undetected [34,36]. In this clinical scenario, the CT should be performed using a liver protocol. The inclusion of precontrast images is valuable in this context to assess treatment response to liver-directed therapy and to differentiate true enhancement from intrinsic high attenuation related to the treatment.

**CT Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that many PNET will only be visible after administration of contrast.

**CT Chest Abdomen Pelvis With IV Contrast.** The sensitivity and specificity of CT for liver metastases are reported to be 75% to 100% and 83% to 100% [17], although there is a recognition that many liver metastases go undetected [34,36]. In this clinical scenario, the CT should be performed using a liver protocol. The inclusion of precontrast images is valuable in this context to assess treatment response to liver-directed therapy and to differentiate true enhancement from intrinsic high attenuation related to the treatment. Imaging of the chest is optional for PNET [35].

**CT Chest Abdomen Pelvis Without and With IV Contrast.** The sensitivity and specificity of CT for liver metastases are reported to be 75% to 100% and 83% to 100% [17], although there is a recognition that many liver metastases go undetected [34,36]. In this clinical scenario, the CT should be performed using a liver protocol. The inclusion of precontrast images is valuable in this context to assess treatment response to liver-directed therapy and to differentiate true enhancement from intrinsic high attenuation related to the treatment. Imaging of the chest is optional for PNET [35].

**CT Chest Abdomen Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that many PNET will only be visible after administration of contrast.

**DOTATATE PET/CT Skull Base to Mid-Thigh.** SSTR-PET, such as DOTATATE PET/CT, is highly sensitive for neuroendocrine tumors, with reported sensitivities and specificities for PNET ranging from 86% to 100% and 79% to 100%, respectively [17,23], the exception being insulinoma, for which the sensitivity is as low as 25% [23]. DOTATATE PET/CT is not recommended for routine surveillance [35] but could play a role when there is a suspicion for PNET recurrence not detected on conventional imaging [1,24,25,42]. If a patient did not undergo DOTATATE PET/CT before surgical resection, a single DOTATATE PET/CT examination should be considered to complete staging postoperatively [24].

**FDG-PET/CT Skull Base to Mid-Thigh.** FDG uptake is typically minimal in low-grade well-differentiated PNET and is therefore unlikely to be of value in postresection surveillance of PNET.

**MRI Abdomen and Pelvis Without and With IV Contrast.** MRI is particularly well suited for surveillance in a patient with liver-dominant disease. Liver metastases are usually hypointense on T1-weighted images and hyperintense on T2-weighted images and demonstrate arterial phase hyperenhancement [9]. Some metastases are only seen on the arterial phase, emphasizing the importance of a multiphase imaging technique [9]. Some studies have shown that DWI improved the detection of liver metastases [36,40]. Hepatobiliary contrast agent-enhanced MRI has been shown to improve the detection of liver metastases [9,37,38]. Similar to the guidelines of colon cancer staging [39], we recommend using hepatobiliary contrast agent-enhanced MRI in combination with DWI when liver resection and liver-directed therapy are being considered [1,25]. MRI is also particularly useful in assessing treatment response for liver-directed therapies. As is the case in hepatocellular carcinoma treatment response assessment, MRI may be preferred over CT. MRCP sequences may not be necessary in this context.

**MRI Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. If necessary, an MRI without IV contrast could still be useful in identifying liver metastases. Some studies have shown that DWI is useful in detecting liver metastases [36,40], with one study suggesting that visualization of hepatic metastases using DWI alone is within the acceptable limits for clinical use [40]. T2 fast spin-echo was also shown in 1 study to be useful in detecting and monitoring the size of carcinoid hepatic metastases [41]. MRCP sequences may not be necessary in this context.

**MRI Abdomen Without and With IV Contrast With MRCP.** MRI is particularly well suited for surveillance in a patient with liver-dominant disease. Liver metastases are usually hypointense on T1-weighted images and hyperintense on T2-weighted images and demonstrate arterial phase hyperenhancement [9]. Some metastases are only seen on the arterial phase emphasizing the importance of a multiphase imaging technique [9]. Some studies have shown that DWI improved the detection of liver metastases [36,40]. Hepatobiliary contrast agent-enhanced MRI has been shown to improve the detection of liver metastases [9,37,38]. Similar to the guidelines of colon cancer staging [39], we recommend using hepatobiliary contrast agent-enhanced MRI in combination with DWI when liver resection and liver-directed therapy are being considered [1,25]. MRI is also particularly useful in assessing treatment response for liver-directed therapies. As is the case in hepatocellular carcinoma treatment response assessment, MRI may be preferred over CT. MRCP sequences may not be necessary in this context.

**MRI Abdomen Without IV Contrast With MRCP.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. If necessary, an MRI without IV contrast could still be useful in identifying liver metastases. Some studies have shown that DWI is useful in detecting liver metastases [36,40], with 1 study suggesting that visualization of hepatic metastases using DWI alone is within the acceptable limits for clinical use [40]. T2 fast spin-echo was also shown in 1 study to be useful in detecting and monitoring the size of carcinoid hepatic metastases [41]. MRCP sequences may not be necessary in this context.

**US Abdomen Endoscopic.** EUS has no role in evaluating recurrent or treated disease in the liver.

#### **Variant 5: Adult. Pancreatic neuroendocrine tumor. Follow-up imaging after treatment. Non-liver dominant disease**

In patients with diffuse metastatic disease on systemic therapy, imaging plays the key role of assessing disease burden to determine response to treatment or progression on therapy.

**CT Abdomen and Pelvis With IV Contrast.** Contrast-enhanced CT is the most used modality for assessing diffuse metastatic PNET. A portal venous phase may be sufficient in this context, but the protocol can be adjusted depending on the dominant sites of the disease. Precontrast imaging is typically not needed.

**CT Abdomen and Pelvis Without and With IV Contrast.** Contrast-enhanced CT is the most used modality for assessing diffuse metastatic PNET. Precontrast imaging is typically not needed.

**CT Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast will significantly limit the visualization of metastatic PNET.

**CT Chest Abdomen Pelvis With IV Contrast.** Contrast-enhanced CT is the most used modality for assessing diffuse metastatic PNET. A portal venous phase may be sufficient in this context, but the protocol can be adjusted depending on the dominant sites of the disease. Precontrast imaging is typically not needed. Imaging of the chest is optional for PNET [35]. The inclusion of the chest depends on the distribution of the disease.

**CT Chest Abdomen Pelvis Without and With IV Contrast.** Contrast-enhanced CT is the most used modality for assessing diffuse metastatic PNET. A portal venous phase may be sufficient in this context, but the protocol can be adjusted depending on the dominant sites of the disease. Precontrast imaging is typically not needed. Imaging of the chest is optional for PNET [35]. The inclusion of the chest depends on the distribution of the disease.

**CT Chest Abdomen Pelvis Without IV Contrast.** Lack of IV contrast will significantly limit the visualization of metastatic PNET.

**DOTATATE PET/CT Skull Base to Mid-Thigh.** In the context of surveillance for patients with metastatic disease, DOTATATE PET/CT is not routinely indicated; however, DOTATATE PET/CT is useful in certain scenarios such as bone-dominant disease, nodal and peritoneal-dominant disease, clinical progression without disease growth on conventional imaging, a new indeterminate lesion, or monitoring of disease seen predominantly on DOTATATE PET/CT [1,8,24].

**FDG-PET/CT Skull Base to Mid-Thigh.** FDG uptake is typically minimal in low-grade well-differentiated PNET; however, FDG-PET/CT can be considered for response assessment in patients with baseline FDG-avid disease [42].

**MRI Abdomen and Pelvis Without and With IV Contrast.** MRI is an acceptable alternative to CT for the evaluation of patients with diffuse metastatic disease. There are no added benefits to using hepatobiliary contrast agents in this clinical scenario, with the added limitations of a potentially degraded arterial phase, due to a higher rate of transient severe respiratory motion [43]. Extracellular contrast MRI is therefore preferred in this clinical

scenario. MRCP sequences may not be necessary in this context.

**MRI Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. If necessary, an MRI without IV contrast could still be useful in identifying the tumor sites. DWI would be particularly useful in this case. MRCP sequences may not be necessary in this context.

**MRI Abdomen Without and With IV Contrast With MRCP.** MRI is an acceptable alternative to CT in patients for the evaluation of patients with diffuse metastatic disease. There are no added benefits to using hepatobiliary contrast agents in this clinical scenario, with the added limitations of potentially degraded arterial phase, due to a higher rate of transient severe respiratory motion [43]. Extracellular contrast MRI is therefore preferred in this clinical scenario. MRCP sequences may not be necessary in this context.

**MRI Abdomen Without IV Contrast With MRCP.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. If necessary, an MRI without IV contrast could still be useful in identifying the tumor sites. DWI would be particularly useful in this case [36,40]. MRCP sequences may not be necessary in this context.

**US Abdomen Endoscopic.** EUS has no role in evaluating metastatic PNET.

## Variant 6: Adult. Pancreatic neuroendocrine tumor. Follow-up imaging of untreated disease

Imaging surveillance is an acceptable management strategy for small (<2 cm), low-grade, nonfunctional tumors [35]. Patients with a tumor <1 cm with imaging characteristics consistent with PNET do not even require a biopsy to be placed on imaging surveillance [25].

**CT Abdomen and Pelvis With IV Contrast.** PNET are most typically solid lesions with arterial phase hyperenhancement on CT and MRI, necessitating the use of IV contrast; furthermore, a multiphase CT including arterial and portal venous phases is typically needed given that some tumors may only be visible on the arterial phase [2,9,18]. Tumor size estimated by CT was concordant with gross pathology [10]. Characteristic features of early hyperenhancement, homogenous enhancement, and a well-circumscribed appearance correlate with benign behavior. However, features such as an ill-defined margin [29], relative hypoenhancement on the portal venous phase compared with the pancreatic parenchyma [5,20,29,30], lower arterial

enhancement ratio [5,31,32], ductal dilatation [5,20], and vascular involvement [13,20,21] correlate with aggressive behavior and should warrant reconsideration of surveillance. Precontrast images are typically not necessary. There is no evidence to support the inclusion of the chest in the setting of surveillance of untreated small low-grade neuroendocrine tumors given the low likelihood of metastatic disease in this clinical scenario.

**CT Abdomen and Pelvis Without and With IV Contrast.** PNET are most typically solid lesions with arterial phase hyperenhancement on CT and MRI, necessitating the use of IV contrast; furthermore, a multiphase CT including arterial and portal venous phases is typically needed given that some tumors may only be visible on the arterial phase [2,9,18]. Precontrast images are typically not necessary. There is no evidence to support the inclusion of the chest in the setting of surveillance of untreated small low-grade neuroendocrine tumors given the low likelihood of metastatic disease in this clinical scenario.

**CT Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that many PNET will only be visible after administration of contrast. Furthermore, evaluation of peripancreatic vasculature is not possible without IV contrast.

**DOTATATE PET/CT Skull Base to Mid-Thigh.** For a small primary lesion (<2 cm), with low-grade histology, the likelihood of metastatic disease is considered very low, and therefore SSTR may not be necessary [1].

**FDG-PET/CT Skull Base to Mid-Thigh.** FDG uptake is typically minimal in low-grade well-differentiated PNET and is of no value in this clinical scenario.

**MRI Abdomen and Pelvis Without and With IV Contrast.** Owing to its superior soft tissue and contrast resolution, MRI has a relatively high sensitivity for small tumors <2 cm in size [9], which makes it well suited for the imaging surveillance of small untreated lesions. PNET are most typically solid lesions with arterial phase hyperenhancement on CT and MRI [27]. Characteristic features of early hyperenhancement, homogenous enhancement, and well-circumscribed appearance correlate with benign behavior. However, features such as ill-defined margin [29], relative hypoenhancement on the portal venous phase compared with the pancreatic parenchyma [5,20,29,38], lower arterial enhancement ratio [5,31,32], ductal dilatation [5,20], vascular involvement [19-21], nonbright T2 signal [13], and marked restricted diffusion [13,29,33] correlate with aggressive behavior and should warrant reconsideration of surveillance decision. Tumor size estimated by MRI was found to be concordant with gross pathology [10,29]. The

inclusion of MRCP sequences is useful in assessing the relationship of the tumor with the duct and possible intraductal growth or ductal occlusion, which would suggest aggressive behavior. The inclusion of the pelvis is of no clear value in the setting of surveillance of small low-grade tumors. Considering that follow-up imaging may be repeated over many years, the merit of the lack of ionizing radiation is a consideration that may favor MRI in this context, particularly for younger patients.

**MRI Abdomen and Pelvis Without IV Contrast.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. Furthermore, evaluation of peripancreatic vasculature is not possible without IV contrast. If necessary, an MRI without IV contrast could still be useful in delineating the tumor. DWI is particularly useful in that scenario. The inclusion of MRCP sequences is useful in assessing the relationship of the tumor, the duct, and possible intraductal growth or ductal occlusion, which would suggest aggressive behavior. The inclusion of the pelvis is of no clear value in the setting of surveillance of small low-grade tumors.

**MRI Abdomen Without and With IV Contrast With MRCP.** Owing to its superior soft tissue and contrast resolution, MRI has a relatively high sensitivity for small tumors <2 cm in size [9], which makes it well suited for imaging surveillance of small untreated lesions. PNET are most typically solid lesions with arterial phase hyperenhancement on CT and MRI [27]. Characteristic features of early hyperenhancement, homogenous enhancement, and a well-circumscribed appearance correlate with benign behavior. However, features such as an ill-defined margin [29], relative hypoenhancement on the portal venous phase compared with the pancreatic parenchyma [5,20,29,38], lower arterial enhancement ratio [5,31,32], ductal dilatation [5,20], vascular involvement [19-21], nonbright T2 signal [13], and marked diffusion restriction [13,29,33] correlate with aggressive behavior and should warrant reconsideration of surveillance. Tumor size estimated by MRI was found to be concordant with gross pathology [10,29]. The inclusion of MRCP sequences is useful in assessing the relationship of the tumor, the duct, and possible intraductal growth or ductal occlusion, which would suggest aggressive behavior.

**MRI Abdomen Without IV Contrast With MRCP.** Lack of IV contrast would be a significant limitation given that arterial phase hyperenhancement is the hallmark of many of these tumors. Furthermore, evaluation of peripancreatic vasculature is not possible without IV contrast. If necessary, an MRI without IV contrast could still be useful in delineating the tumor. DWI is particularly useful in that

scenario. The inclusion of MRCP sequences is useful in assessing the relationship of the tumor, the duct, and possible intraductal growth or ductal occlusion, which would suggest aggressive behavior.

**US Abdomen Endoscopic.** Although EUS is highly sensitive for small PNET [9], it is a relatively invasive procedure and its use for surveillance is not supported.

## 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 local staging of PNET, CT abdomen and pelvis with IV contrast and CT without and with IV contrast are usually appropriate due to their high lesion detection rates and ability to assess vascular involvement and venous tumor thrombus. DOTATATE PET/CT is usually appropriate as a complementary modality to CT and is useful in detecting lymph node and bone metastases not readily seen on CT or MRI, although its necessity may be limited in small, low-grade tumors (<2 cm) given the low likelihood of metastasis. MRI without and with IV contrast, particularly with MRCP, has high sensitivity (80% for tumors <2 cm) and the ability to characterize features of aggressiveness and ductal involvement. It may be appropriate because CT is typically the first-line modality and given the lack of consensus among experts about the role of MRI as an alternative to CT. Typically, EUS would have been performed already for tissue sampling before dedicated imaging for local staging, but if not, EUS may be appropriate if additional delineation of the tumor relation to the pancreatic duct is needed.
- **Variant 2 and 5:** For staging and evaluation for metastatic disease as well as follow-up after treatment of non-liver-dominant disease, CT abdomen and pelvis with IV contrast and CT chest, abdomen, and pelvis with IV contrast are usually appropriate, offering sensitivity for detecting nodal, liver, and soft tissue metastases, although detection of small liver metastases remains limited. The need for inclusion of the chest is not explicitly discussed in other clinical guidelines. MRI abdomen and pelvis with IV contrast is usually an appropriate alternative, particularly due to superior detection of liver metastases—enhanced with DWI—and hepatobiliary agents. DOTATATE PET/CT is usually appropriate due to its superior ability to detect nodal and bone metastases and to inform therapeutic decisions (eg, peptide receptor radionuclide therapy).

FDG-PET/CT may be appropriate in select settings (eg, high-grade tumors).

- **Variant 3:** For surveillance postsurgical resection with no known or suspected recurrence, CT abdomen and pelvis with IV contrast and CT chest, abdomen, and pelvis with IV contrast are usually appropriate, because they are widely used in surveillance and provide acceptable sensitivity when multiphase techniques are applied. MRI with IV contrast may be an appropriate alternative, offering good soft tissue contrast and usefulness in small tumors, but there is a lack of consensus on its role as a first-line modality.
- **Variant 4:** For follow-up after treatment of liver-dominant disease, MRI with IV contrast is usually appropriate due to its high sensitivity for liver metastases and superiority in treatment response assessment. Hepatobiliary contrast-enhanced MRI and DWI improve detection. Liver protocol CT is also a usually appropriate alternative. The inclusion of precontrast images is valuable in this context to assess treatment response. DOTATATE PET/CT may be appropriate, particularly when there is suspicion for recurrence not detected on conventional imaging or if DOTATATE PET/CT was not done preoperatively.
- **Variant 6:** For follow-up of untreated disease, MRI and CT with IV contrast are usually appropriate alternatives for imaging surveillance of small (<2 cm), low-grade, nonfunctional PNET. These tumors often display arterial phase hyperenhancement and characteristic imaging features associated with benign behavior. DOTATATE PET/CT may be appropriate complementary study but not routinely necessary in low-grade, small tumors with no high-risk features.

## 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 go to the ACR website at <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 [44].

## 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 [45].

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