Neuroendocrine and Adrenal Tumors, Version 2.2021

Manisha H. Shah, MD[1,*]; Whitney S. Goldner, MD[2,*]; Al B. Benson, III, MD[3]; Emily Bergsland, MD[4,*]; Lawrence S. Blaszkowsky, MD[5]; Pamela Brock, MS[1,*]; Jennifer Chan, MD[6,*]; Satya Das, MD, MSCI[7,*]; Paxton V. Dickson, MD[8]; Paul Fanta, MD[9]; Thomas Giordano, MD, PhD[10]; Thorvardur R. Halfdanarson, MD[11,*]; Daniel Halperin, MD[12,*]; Jin He, MD, PhD[13,*]; Anthony Heaney, MD, PhD[14,*]; Martin J. Heslin, MD[15]; Fouad Kandeel, MD, PhD[16]; Arash Kardan, MD[17]; Sajid A. Khan, MD[18]; Boris W. Kuvshinoff, II, MD, MBA[19]; Christopher Lieu, MD[20]; Kimberly Miller, RN[2]; Venu G. Pillarisetty, MD[21]; Diane Reidy, MD[22]; Sarimar Agosto Salgado, MD[23,*]; Shagufta Shaheen, MD[24,*]; Heloisa P. Soares, MD, PhD[25]; Michael C. Soulen, MD[26,*]; Jonathan R. Strosberg, MD[27]; Craig R. Sussman, MD[7]; Nikolaos A. Trikalinos, MD[28,*]; Nataliya A. Uboha, MD, PhD[29]; Namrata Vijayvergia, MD[30]; Terence Wong, MD, PhD[31,*]; Beth Lynn, RN, BS, CMSRN[32]; and Cindy Hochstetler, PhD[32]

ABSTRACT

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Neuroendocrine and Adrenal Gland Tumors focus on the diagnosis, treatment, and management of patients with neuroendocrine tumors (NETs), adrenal tumors, pheochromocytomas, paragangliomas, and multiple endocrine neoplasia. NETs are generally subclassified by site of origin, stage, and histologic characteristics. Appropriate diagnosis and treatment of NETs often involves collaboration between specialists in multiple disciplines, using specific biochemical, radiologic, and surgical methods. Specialists include pathologists, endocrinologists, radiologists (including nuclear medicine specialists), and medical, radiation, and surgical oncologists. These guidelines discuss the diagnosis and management of both sporadic and hereditary neuroendocrine and adrenal tumors and are intended to assist with clinical decision-making. This article is focused on the 2021 NCCN Guidelines principles of genetic risk assessment and counseling and recommendations for well-differentiated grade 3 NETs, poorly differentiated neuroendocrine carcinomas, adrenal tumors, pheochromocytomas, and paragangliomas.

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[1]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [2]Fred & Pamela Buffett Cancer Center; [3]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [4]UCSF Helen Diller Family Comprehensive Cancer Center; [5]Massachusetts General Hospital Cancer Center; [6]Dana-Farber/Brigham and Women's Cancer Center; [7]Vanderbilt-Ingram Cancer Center; [8]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [9]UC San Diego Moores Cancer Center; [10]University of Michigan Rogel Cancer Center; [11]Mayo Clinic Cancer Center; [12]The University of Texas MD Anderson Cancer Center; [13]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [14]UCLA Jonsson Comprehensive Cancer Center; [15]O'Neal Comprehensive Cancer Center at UAB; [16]City of Hope National Medical Center; [17]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [18]Yale Cancer Center/Smilow Cancer Hospital; [19]Roswell Park Comprehensive Cancer Center; [20]University of Colorado Cancer Center; [21]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [22]Memorial Sloan Kettering Cancer Center; [23]UT Southwestern Simmons Comprehensive Cancer Center; [24]Stanford Cancer Institute; [25]Huntsman Cancer Institute at the University of Utah; [26]Abramson Cancer Center at the University of Pennsylvania; [27]Moffitt Cancer Center; [28]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [29]University of Wisconsin Carbone Cancer Center; [30]Fox Chase Cancer Center; [31]Duke Cancer Institute; and [32]National Comprehensive Cancer Network.
*Discussion Writing Committee member.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

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The complete NCCN Guidelines for Neuroendocrine and Adrenal Tumors are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

Disclosures for the NCCN Neuroendocrine and Adrenal Tumors Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Neuroendocrine and Adrenal Tumors Panel members can be found on page 868. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

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- **The decision to offer genetic testing involves three related stages:**
  1) Pre-test counseling prior to ordering testing;
  2) Consideration of the most appropriate testing strategy; and
  3) Testing result disclosure and post-test counseling.
- **It is recommended that a genetic counselor, medical geneticist, endocrinologist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics be involved at each stage whenever possible. Clinicians without direct referral access to the appropriate expertise should be aware of the telehealth genetic counseling options available. These resources can be found through the National Society of Genetic Counselors (NSGC) "Find a Genetic Counselor" tool (www.nsgc.org).**

1) Pre-Test Counseling:

- **Pre-test counseling includes the following elements:**
  - **Evaluation of patient's knowledge, needs/concerns, and goals for familial risk assessment.**
  - **Detailed family history (including cancers/tumors and age at diagnosis, as well as clinical symptoms that can indicate an underlying endocrine neoplasia) in first-, second-, and third-degree family members on each side of the family.**
  - **Detailed past medical history and review of systems, including:**
    - **Documentation of prior genetic testing results for patients and their family members; and**
    - **Personal cancer/tumor history including age of diagnosis and treatment.**
  - **Focused physical examination (conducted by qualified clinician) when indicated.**
  - **Generation of differential diagnosis and educating the patient of inheritance pattern, penetrance, variable expressivity, and the possibility of genetic heterogeneity.**
  - **Discussion of possible genetic testing result outcomes, including positive (pathogenic or likely pathogenic), negative, and variants of unknown significance.**
  - **Discussion of the clinical implications of testing results to the patient.**
  - **Discussion of the clinical implications of testing results to potentially affected family members and their available options for pursuing risk assessment, testing, and management.**
  - **Cost of genetic testing.**
  - **Current legislation regarding genetic discrimination and the privacy of genetic information.**

Overview

Neuroendocrine tumors (NETs) are thought to arise from cells throughout the diffuse endocrine system. They comprise a broad family of tumors, the most common of which are in the gastrointestinal tract, lungs and bronchi (so-called *bronchopulmonary*), thymus, and pancreas. Sites of origin within the gastrointestinal tract include the stomach, small intestine, appendix, and rectum.[1,2] Other NETs include those arising in the parathyroid, thyroid, adrenal, and pituitary glands.

An analysis of the SEER database estimated that the incidence of NETs in the United States was 6.98 cases per 100,000 people in the year 2012.[2] This analysis suggested that the incidence of NETs is increasing, and that the prevalence of individuals with NETs in the United States may exceed 170,000.

Most NETs seem to be sporadic, and risk factors for sporadic NETs are poorly understood. NETs may also arise in the context of inherited genetic syndromes, including multiple endocrine neoplasia types 1 (MEN1), 2 (MEN2), and 4 (MEN4), and succinate dehydrogenase mutations. NETs have also been associated with other conditions, including von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis.[3,4]

Patients with NETs can have symptoms attributable to hormonal hypersecretion. These symptoms include intermittent flushing and diarrhea in patients with gastrointestinal NETs,[5] bronchospasm and wheezing in lung NETs,[5] hypertension in patients with pheochromocytoma or paraganglioma,[6] and symptoms attributable to secretion of insulin, glucagon, gastrin, and other peptides in patients with pancreatic NETs.[7] Patients with hormonal symptoms are considered to have "functional" tumors, and those without symptoms are considered to have "nonfunctional" tumors.

Histologic Classification and Staging of Neuroendocrine and Adrenal Tumors

NETs are generally subclassified by site of origin, stage, and histologic characteristics.

Histologic Classification

Neuroendocrine neoplasms (NENs) are divided into NETs and neuroendocrine carcinomas (NECs). The 2019 WHO classification of NENs includes significant updates.[8]

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2) Considerations When Determining the Most Appropriate Testing Strategy:

- The introduction of multigene testing for hereditary cancer/tumor predisposition syndromes has rapidly altered the clinical approach to genetic testing of at-risk patients and their families.
- Given the possible overlap in clinical presentation amongst hereditary endocrine neoplasias, multigene panel testing may be more efficient and cost-effective in many situations.
- As commercially available tests differ in the specific genes analyzed, variant classification, and other factors (eg, methods of DNA/RNA analysis or option to reflex from a narrow to a larger panel; provision of financial assistance for cascade testing of relatives), it is important to consider the indication for testing and the expertise of the laboratory when choosing the specific laboratory and test panel.
- The interpretation of genetic testing remains subjective and complex. The interpretations can differ based on interlaboratory classification rules, access to unique case-level data, and other evidence. Additionally, variants may need to be reconsidered and reclassified as additional data emerge in the field.
- Genetic testing performed to identify somatic mutations arising in malignant cells is often not designed to detect germline variants and may thus be inadequate for evaluation of an underlying hereditary endocrine neoplasia syndrome.
- Testing for unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

3) Post-Test Counseling Includes the Following Elements:

- Discussion of results and implications for patient and/or family members
- Interpretation of results in context of personal and family history
- Likely pathogenic variants are usually clinically managed similarly to pathogenic variants, while patients with variants of unknown significance (VUS) and likely benign variants should be managed based on the cancers/tumors in the family
- For patients with positive results:
  - Discussion of recommended medical management
  - Discussion of the importance of notifying family members and offering materials/resources for information and testing at-risk family members
  - For many hereditary endocrine neoplasia syndromes, testing of children is indicated since screening interventions often start in childhood or adolescence
  - Discussion of available resources such as high-risk clinics, disease-specific support groups, and research studies
  - For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis
  - Consider carrier status implications of certain autosomal recessive disorders
- For patients with negative results:
  - Discussion of possible etiologies for their personal/family history including sporadic, multifactorial, or unidentified hereditary factors
  - For patients with a clinical diagnosis of an endocrine neoplasia condition (such as MEN1) and negative genetic testing, consider following the related surveillance recommendations for patient and first-degree family members

Previously, the gastrointestinal NENs and the pancreatic NENs were classified separately; now they share a common classification scheme.[8,9] NETs are well-differentiated while NECs are poorly differentiated neoplasms. Well differentiated NETs are further classified into 3 categories: low-grade (G1); intermediate-grade (G2); high-grade (G3). All poorly differentiated NECs are G3, but not all G3 NENs are poorly differentiated. Some tumors can have mixed, both well and poorly differentiated histology and are termed as mixed neuroendocrine-nonneuroendocrine neoplasms.

Tumor differentiation and tumor grade often correlate with mitotic count and Ki-67 proliferation index. In fact, most commonly used histologic classification schemes, including the European Neuroendocrine Tumor Society (ENETS), WHO systems, and the International Agency for Research on Cancer, incorporate mitotic rate and Ki-67 index.[7,9–13] Numerous studies have confirmed that increased mitotic rate and high Ki-67 index are associated with a more aggressive clinical course and worse prognosis.[14–17] In gastrointestinal and pancreatic NETs, well-differentiated, low-grade tumors have a mitotic count of <2/10 high-power field (HPF) and/or a Ki-67 index of less than 3%. Well-differentiated, intermediate-grade tumors have a mitotic count of 2 to 20/10 HPF and/or a Ki-67 index of 3%–20%. In high-grade well-differentiated tumors, the mitotic count exceeds 20/10 HPF and/or the Ki-67 index exceeds 20%.

Grade is generally defined by mitotic count and/or Ki-67 index, whichever is higher. If both mitotic rate and Ki-67 index are used and these are discordant, it is currently recommended that the higher grade be used to assign classification.[18–20] Ki-67 immunohistochemistry should be analyzed and/or counted in the areas of highest activity referred to as *hot spots*. A key recommendation is that tumor differentiation, mitotic rate, and Ki-67 index should all be included in the pathology report. Doing so allows the treating physician to factor these data into the clinical picture to make appropriate treatment decisions in gastrointestinal and pancreatic NENs. The current grading of lung NENs does not rely on Ki-67.[21]

Staging

NETs are staged according to the AJCC tumor (T), node (N), metastasis (M) staging system. The AJCC introduced

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4) Criteria for Genetic Risk Evaluation for Hereditary Endocrine Neoplasia Syndromes

- **Recommend evaluation in a patient with any of the following:[a]**
  - **Adrenal cortical carcinoma (ACC)**
  - **Paraganglioma (PGL)/Pheochromocytoma (PCC)**
  - **Gastrinoma (duodenal/pancreatic or type 2 gastric NET)**
  - **Multifocal pancreatic neuroendocrine tumors.**
  - **Parathyroid adenoma or primary hyperparathyroidism before age 30, multiple parathyroid adenomas, multigland hyperplasia (without obvious secondary causes), or recurrent primary hyperparathyroidism**
  - **Clinical suspicion for MEN2 due to the presence of medullary thyroid cancer or other combination of MEN2-related features. See Overview of Hereditary Endocrine Neoplasia Syndromes (NE-E 4 of 7).**
  - **A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline (eg, tumor analysis shows mutation in *BRCA1/2* or mismatch repair gene).**
  - **Close blood relative with a known pathogenic variant/likely pathogenic variant in a cancer susceptibility gene.**
  - **A first-degree relative meeting one of the above criteria but not available for testing.**
  - **Recommend evaluation in a patient with clinical suspicion for MEN1 due to 2 or more of the following, or 1 AND a family history of 1 or more of the following:**
    - ◊ **Primary hyperparathyroidism**
    - ◊ **Duodenal/pancreatic neuroendocrine tumor**
    - ◊ **Pituitary adenoma**
    - ◊ **Foregut carcinoid (bronchial, thymic, or gastric)**
- **Consider evaluation in a patient with duodenal/pancreatic neuroendocrine tumor at any age.[b]**

[a] Genetic testing may be a consideration for patients with other combinations of tumors or cancers in the patient and/or their family members.
[b] Studies of unselected patients with pancreatic neuroendocrine tumors have identified germline variants in 16-17% of cases. However, these studies involved relatively small cohorts of patients. (Raj N, et. al. JCO Precis Oncol. 2018;2018:PO.17.00267; Scarpa A, et al. Nature. 2017 Mar 2;543(7643):65-71).

its first TNM staging system for the classification of NETs in its seventh edition of the AJCC Cancer Staging Manual.[22] The T and N definitions and other staging definitions were revised in the 8th edition of the AJCC Cancer Staging Manual.[23] The 8th edition also added the first staging system for thymic tumors and adrenal NETs (including staging for pheochromocytoma and paraganglioma).[23] NETs of the stomach, duodenum/ampulla, jejunum/ileum, appendix, colon/rectum, and pancreas have separate staging systems. The association of tumor stage with prognosis has been confirmed in analyses of the SEER database and the National Cancer Database.[24–30] An analysis of 691 patients with jejunal-ileocecal NETs treated at the Moffitt Cancer Center between 2000 and 2010 revealed 5-year survival rates of 100%, 100%, 91%, and 72% for stages I through IV, respectively, further validating the TNM staging system.[31] Of note, however, this analysis also suggested that, unlike other malignancies, primary tumor size and depth of invasion had little bearing on survival in early-stage disease.[32] Similar results were reported in a separate analysis of 6,792 small intestine NETs in the SEER database, which found that outcomes were similar for patients with T1 and T2 tumors.[33] These results have been supported in additional analyses, confirming that the presence of lymph node and distant metastases have the strongest effect on survival.[34,35]

The TNM staging system for the classification of pancreatic NETs in the eighth edition of the AJCC Cancer Staging Manual is separate from exocrine pancreatic carcinoma.[22,23] The primary tumor (T) is differentiated based on size and involvement of major vessels or other organs (see "Staging" in the algorithm, available at NCCN.org). A retrospective analysis of 425 patients with pancreatic NETs treated at the Moffitt Cancer Center between 1999 and 2010 validated the AJCC 2017 classification system, with 5-year overall survival (OS) rates of 92%, 84%, 81%, and 57% for stages I through IV, respectively ($P<.001$).[36] Although the trends of this analysis are consistent with population-based studies, the survival rates from this analysis were significantly higher than those seen in population-based studies.[37,38] For example, in the SEER database analysis of pancreatic NETs, the 5-year survival rate for patients with metastatic disease was only 19.5%.[38]

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Overview of Hereditary Endocrine Neoplasia Syndromes

Syndrome (Gene)[c]	Endocrine Neoplasia Manifestations	Other Manifestations	Surveillance
Hereditary paraganglioma/ pheochromocytoma syndrome (*MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127*)	Paraganglioma[c] Pheochromocytoma[c]	GIST (SDHx) Renal cell cancer (SDHx)	See NE-E (7 of 7) NCCN Guidelines for Kidney Cancer† (HRCC-B)
Multiple endocrine neoplasia type 1 (*MEN1*)[d,e]	Parathyroid adenoma/hyperplasia (>95%) Pancreatic (functioning) or duodenal neuroendocrine tumors (20%–80%) ▸ Gastrinoma 20%–61% ▸ Insulinoma 7%–31% ▸ Glucagonoma 1%–5% ▸ VIPoma/somatostatinoma <2% Pituitary adenomas (30%–40%) Gastric carcinoids (7%–35%) Bronchial/thymic carcinoids (<8%) Adrenal adenomas (27%–36%)	Angiofibromas Collagenomas Lipomas Meningiomas	See MEN1-2[e*] and MEN1-A[e*]
Multiple endocrine neoplasia type 2 (*RET*)[f]	Medullary thyroid cancer (≤98%) Pheochromocytoma (≤50%) Parathyroid adenoma/hyperplasia (≤25% MEN2A, rare in MEN2B)	MEN2A: • Cutaneous lichens amyloidosis • Hirschsprung disease MEN2B: • Intestinal ganglioneuromas • Mucosal neuromas • Marfanoid habitus	See MEN2-1* and NE-E (7 of 7)[g] NCCN Guidelines for Thyroid Cancer† (MEDU-4 and MEDU-5)

Note: This resource is not intended to be an exhaustive list of hereditary endocrine neoplasias. Specific scenarios may warrant consideration of less common conditions such as Carney complex, Carney triad, Currarino syndrome, or polycythemia-paraganglioma-somatostatinoma syndrome.

[c] Penetrance estimates and tumor locations vary significantly by gene. For patients with pathogenic variants in the SDHD, SDAHF2, and possibly MAX genes, tumor risks are mostly a concern when the variant is paternally inherited.
[d] 10% of cases have de novo MEN1 mutations.
[e] Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012;97:2990-3011.
[f] 50% of cases have de novo RET mutations; therefore, even if a family history is not suggestive of a hereditary syndrome, genetic testing for RET mutations should still be performed on the affected individual.
[g] Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the mamagement of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

Pathologic Reporting

In addition to information on histologic classification and stage, the margin status (positive or negative) and the presence of vascular or perineural invasion should be included in the pathology report; some studies have suggested that these factors may also have prognostic significance.[39,40]

Whether tumors are associated with symptoms of hormone hypersecretion ("functioning" or "nonfunctioning") is a clinical rather than histologic diagnosis. The presence of hormone-staining granules without a clinical syndrome does not make a tumor "functioning." Thus, functional status is usually not included in the pathology report.

Principles of Genetic Risk Assessment and Counseling

In the 2021 guidelines, the panel included a new principles of genetic risk assessment and counseling for hereditary endocrine neoplasias. This section outlines how to go about genetic counseling, provides an overview of clinical manifestations associated with these disorders, and advises the readers of resources that can be accessed for more information (eg, how to find a genetic counselor, see "Principles of Genetic Risk Assessment and Counseling," in the algorithm [NE-E]). Recommendations are provided regarding pretest counseling, considerations when determining the most appropriate testing strategy, posttest counseling, and criteria for genetic risk evaluation for hereditary endocrine neoplasia syndromes.

Genetic risk evaluation is recommended in patients with any of the following: (1) adrenocortical carcinoma (ACC); (2) paraganglioma/pheochromocytoma; (3) gastrinoma (duodenal/pancreatic or type 2 gastric NET); (4) multifocal pancreatic NETs; (5) parathyroid adenoma or primary hyperparathyroidism before age 30, multiple parathyroid adenomas, multigland hyperplasia (without obvious secondary causes), or recurrent primary hyperparathyroidism; (6) clinical suspicion for MEN2 due to the presence of medullary thyroid cancer or other combination of MEN2-related features; (7) a mutation identified on tumor genomic testing that has clinical implications if also identified in the germline (eg, tumor analysis shows a mutation in *BRCA1/2* or mismatch repair (MMR) gene);

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Overview of Hereditary Endocrine Neoplasia Syndromes

Syndrome (Gene)	Endocrine Neoplasia Manifestations	Other Manifestations	Surveillance
Multiple endocrine neoplasia type 4 *(CDKN1B)*[g]	Parathyroid adenoma/hyperplasia Pituitary adenomas Pancreatic or duodenal neuroendocrine tumors Papillary thyroid cancer	Meningiomas	Not available[e]
Neurofibromatosis type 1 *(NF1)*	Pheochromocytoma (3%) Pancreatic neuroendocrine tumors (rare)	Neurofibromas Skin lesions (CAL and freckling) Lisch nodules Gliomas GIST	NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic† AAP Health Supervision Guidelines[h]
Tuberous sclerosis complex *(TSC1 and TSC2)*	Pituitary adenomas (rare) Parathyroid adenoma/hyperplasia (rare) Pancreatic neuroendocrine tumors (rare)	Skin lesions CNS tumors/cancers Renal angiomyolipomas Clear cell renal cancer Cardiac rhabdomyomas Lymphangioleiomyomatosis	NCCN Guidelines for Kidney Cancer† (HRCC-B)
von Hippel Lindau syndrome (VHL)	Pheochromocytoma (10%–20%) Paraganglioma (10%–20%) Pancreatic neuroendocrine tumors (5%–17%)	Hemangioblastomas (retinal or CNS) Clear cell renal cancer Endolymphatic sac tumors Cystadenomas	See NE-E (7 of 7) and PanNET-6* VHLA Handbook[i] NCCN Guidelines for Kidney Cancer† (HRCC-B)

Note: This resource is not intended to be an exhaustive list of hereditary endocrine neoplasias. Specific scenarios may warrant consideration of less common conditions such as Carney complex, Carney triad, Currarino syndrome, or polycythemia-paraganglioma-somatostatinoma syndrome.

[e] Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012;97:2990-3011.
[g] MEN4 is a newly described endocrine neoplasia. Therefore, penetrance estimates and surveillance guidelines are not available. Given the clinical overlap with MEN1, consideration can be given to following MEN1-related surveillance recommendations in patients with MEN4.
[h] Miller, D. T., et al. (2019). Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics 143(5): e20190660.
[i] The VHL Alliance. The VHL Handbook: What you need to know about VHL. 6th ed. 2020.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

(8) a close blood relative with a known pathogenic variant/likely pathogenic variant in a cancer susceptibility gene; (9) a first-degree relative meeting one of the above criteria but not available for testing; and (10) clinical suspicion for MEN1 due to 2 or more of the following, or 1 of the following and a family history of 1 or more of the following: primary hyperparathyroidism, duodenal/pancreatic NET, pituitary adenoma, or foregut carcinoid (bronchial, thymic, or gastric). Genetic risk evaluation should be considered at any age in patients with duodenal/pancreatic NET.

Genetic syndromes covered in this section include hereditary paraganglioma/pheochromocytoma syndrome; MEN1, MEN2, and MEN4; neurofibromatosis type 1; tuberous sclerosis complex; and von Hippel Lindau syndrome. Some resources are also listed for hereditary cancer predisposition syndromes associated with ACCs such as Li-Fraumeni syndrome, Lynch syndrome, MEN1, and familial adenomatous polyposis (see "Principles of Genetic Risk Assessment and Counseling," NE-E). Additional screening recommendations are also provided for patients with hereditary paraganglioma/pheochromocytoma, MEN2, and von Hippel Lindau syndrome.

Well-Differentiated Grade 3 Neuroendocrine Tumors

Well-differentiated G3 NETs were introduced as a new category in the 2017 WHO classification update of pancreatic NENs, and in the 2019 WHO classification for digestive system (gastroenteropancreatic) NENs (including unknown primary tumors). These encompass tumors that have a high proliferation rate, with a mitotic index greater than 20 or a Ki-67 index greater than 20%, and a well-differentiated morphology.[41] These occur mostly in the pancreas, stomach, and colon, although they can occur at any primary site. Well-differentiated G3 tumors have a better prognosis than poorly differentiated NECs, but a worse prognosis when compared with G1–G2 well-differentiated NETs.[19] The results from 2 studies showed that patients with well-differentiated G3 NETs had a significantly higher median OS (41–99 vs 17 months) compared with patients with poorly differentiated NECs.[42,43]

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Hereditary Cancer Predisposition Syndromes Associated with ACC

Syndrome (Gene)	Other Cancer/Tumor Associations	Surveillance Recommendations
Li-Fraumeni syndrome (*TP53*)	Sarcoma, brain cancer, breast cancer, leukemia	NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic†
Lynch syndrome (*MLH1, EPCAM/MSH2, MSH6, PMS2*)	Colon, endometrial, gastric, ovarian, and other cancers	NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic† NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal†
Multiple endocrine neoplasia type 1 (*MEN1*)	Parathyroid adenoma/hyperplasia, duodenal/pancreatic neuroendocrine tumors, pituitary adenomas, bronchial/thymic carcinoids	See MEN1-2* and MEN1-A*
Familial adenomatous polyposis (*APC*)	Colon polyposis/cancer, duodenal/periampullary polyposis/cancer, thyroid cancer	NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal†

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

Evaluation of Well-Differentiated Grade 3 Neuroendocrine Tumors

Imaging with multiphasic abdominal/pelvic CT or MRI scans with contrast, with or without chest CT scans (if clinically indicated), and somatostatin-receptor (SSR)-based PET imaging (SSR-PET) is recommended. Unless otherwise indicated, the preferred SSR-based imaging in this discussion includes SSR-PET/CT or SSR-PET/MRI imaging using 68Ga-DOTATATE, 68Ga-DOTATOC, or 64Cu-DOTATATE. SSR scintigraphy using ^{111}In-octreotide (with SPECT/CT) is appropriate only if SSR-PET is not available. SSR-PET imaging is more sensitive than SSR scintigraphy for determining SSR status.

SSR-based PET imaging should include PET/CT or PET/MRI of the skull base to midthigh with intravenous contrast (both arterial and portal venous phase), when possible. Data are limited on the optimal timing of SSR scans after administration of somatostatin analogs. FDG-PET/CT scans can be performed as appropriate if SSR PET imaging is negative. There are some instances where FDG PET is useful in patients with positive SSR PET. Biochemical evaluation should be performed if the patient has symptoms suggestive of a secretory tumor. Pathology review is recommended, and assessment of p53, Rb, and p16, by histopathologic analysis or molecular profiling, can be considered if there is uncertainty about the tumor's degree of differentiation, because a mutation in these genes would suggest a poorly differentiated NEC.[44–46] SSR 2A staining may also be helpful.[47] Genetic counseling and testing for inherited genetic syndromes is recommended only for duodenal or pancreatic NETs.

Primary Treatment of Well-Differentiated Grade 3 Neuroendocrine Tumors

Treatment recommendations are based on the biology of the tumor. A tumor with favorable biology typically possesses Ki-67 less than 55%, is slow-growing, and may yield a positive SSR-based PET result. A tumor with unfavorable biology typically has Ki-67% greater than or equal to 55%, is faster-growing, and may yield a negative SSR-based PET result. Importantly, the data informing the appropriate Ki-67 cutoff are limited and variability/heterogeneity of Ki-67 in a given tumor and over time in serial biopsies make decision-making less straightforward in this entity

PRINCIPLES OF GENETIC RISK ASSESSMENT AND COUNSELING HEREDITARY ENDOCRINE NEOPLASIAS

PCC/PGL-specific Screening Recommendations for Patients with Confirmed Hereditary Syndromes[h-k]

Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome[l]

- **Surveillance starting at 6–8 years of age:**
  - **Blood pressure monitoring at all medical visits.**
  - **Annual measurement of plasma free metanephrines or 24-hour urine for fractionated metanephrines.**
  - **Cross-sectional imaging of skull base to pelvis every 2 years. Whole body MRI (if available) or other non-radiation–containing imaging procedures. If whole body MRI not available, may consider abdominal MRI, skull base and neck MRI, and chest CT.[m]**

Multiple endocrine neoplasia type 2[n]

- **Surveillance starting by age 11 years for children in the American Thyroid Association high risk (ATA-H) and highest risk (ATA-HST) categories and by age 16 years in children in the ATA-moderate risk (ATA-MOD) category:**
  - **Annual measurement of plasma free metanephrines or 24-hour urine for fractionated metanephrines.**
  - **Adrenal imaging with CT or MRI is indicated in patients with positive biochemical results.**

von Hippel Lindau syndrome (VHL)

- **Blood pressure monitoring at all medical visits starting at age 2 years.**
- **Annual measurement of plasma-free metanephrines (preferred) or 24-hour urine for fractionated metanephrines starting at age 5 years.**
- **Abdominal MRI (preferred) or CT with and without IV contrast every 2 years starting at age 15 years.**

Surgical Recommendations for Patients with Confirmed Hereditary Syndromes

- **Preoperative alert: Patients with a suspected or known diagnosis of a hereditary PGL/PCC syndrome should have blood and/or urine screening for tumors prior to any surgical procedures.**
- **Patients with hereditary PGL/PCC, multiple endocrine neoplasia type 2, and VHL have an appreciable risk for bilateral tumors. Consideration should be given to cortical-sparing adrenalectomy.**

[h] Redman SP, Erez A, Druker H, et al. Von Hippel Lindau and Hereditary Pheochromocytoma/Paraganglioma Syndroms: Clinical Features, Genetics, and Surveillance Recommendations in Childhood. Clin Cacer Res. 2017;23(12):e68-e75.doi:10.1158/1078-0432.CCR-17-0547.

[i] Muth A, Crona J, Gimm O, et al. Genetic testing and surveillance guidelines in hereditary pheochromocytoma and paraganglioma. J Intern Med. 2019;285(2):187-204. doi:10.1111/joim.12869.

[j] Tufton N, Sahdev A, Akker SA. Radiological Surveillance Screening in Asymptomatic Succinate Dehydrogenase Mutation Carriers. J Endocr Soc. 2017;1(7):897-907. Published 2017 Jun 6. doi:10.1210/js.2017-00230.

[k] Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. N Engl J Med. 2019;381(6):552-565. doi:10.1056/NEJMra1806651

[l] SDHD, SDHAF2, and MAX patients are most at risk if the pathogenic variant was paternally inherited. Recommend following the above recommendations if the parent of origin is unknown. Consider screening for patients with maternally inherited variants as case reports of tumor occurrence exist.

[m] Available data suggests SDHAF2 patients are primarily at risk for head and neck tumors and MAX patients are primarily at risk for adrenal tumors. Therefore, consideration can be given to more targeted imaging in these cohorts.

[n] Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567-610.

compared with other NENs. The combination of clinical course and histopathologic workup should dictate therapy, not solely Ki-67. For locoregional (resectable) disease, resection is recommended, along with regional lymphadenectomy, if feasible, regardless of tumor biology.[48] Patient factors should be considered.

For resectable locoregional disease with unfavorable biology, a clinical trial is preferred. Neoadjuvant chemotherapy can also be given on a case-by-case basis, and options include temozolomide with or without capecitabine, oxaliplatin-based therapy (FOLFOX or CAPEOX), cisplatin/etoposide, or carboplatin/etoposide. Temozolomide may have more activity in tumors arising in the pancreas. Following the completion of neoadjuvant chemotherapy, the patient should undergo resection with regional lymphadenectomy if feasible.

For resectable locally advanced or metastatic disease with favorable biology, resection of the primary and metastatic sites may be performed, if feasible. The treatment of unresectable locally advanced or metastatic tumors depends on the degree of tumor burden. If the patient is asymptomatic with low tumor burden, observation with a short interval follow-up scan is an option for select patients; otherwise, octreotide or lanreotide is recommended if the patient is SSR-positive and/or has hormonal symptoms. There are multiple treatment modalities if the patient has a clinically significant tumor burden or evidence of disease progression. Octreotide or lanreotide is recommended if the patient is SSR-positive and/or has hormonal symptoms. Enrollment in a clinical trial is preferred. Other recommended treatment options include peptide receptor radionuclide therapy (PRRT) with 177Lu-dotatate, everolimus, sunitinib (pancreas only), chemotherapy, or liver-directed therapy (for liver-predominant disease). Chemotherapy options consist of temozolomide with or without capecitabine,[49] oxaliplatin-based therapy (FOLFOX, CAPEOX), cisplatin/etoposide, or carboplatin/etoposide. Pembrolizumab (category 2B) is also an option for patients with advanced tumor mutational burden-high (TMB-H) tumors (≥10 mutations/Mb), as determined by an FDA-approved test, that have progressed after prior treatment and have no satisfactory alternative treatment options.[50,51] There is some concern with the TMB cutoff. In some cancers, compared

PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

2019 WHO Classification and Grading Criteria for Neuroendocrine Neoplasms of the Gastrointestinal Tract and Hepatopancreatobiliary Organs

Terminology	Differentiation	Grade	Mitotic rate[a] (mitoses/2 mm²)	Ki-67 index[a] (percent)
NET, G1	Well-differentiated	Low	<2	<3
NET, G2	Well-differentiated	Intermediate	2 to 20	3 to 20
NET, G3	Well-differentiated	High	>20	>20
Neuroendocrine carcinoma (NEC), small cell type (SCNEC)	Poorly differentiated	High[b]	>20	>20
NEC, large cell type (LCNEC)	Poorly differentiated	High[b]	>20	>20
Mixed neuroendocrine-non-neuroendocrine neoplasm	Well or poorly differentiated[c]	Variable[c]	Variable[c]	Variable[c]

Reprinted with permission from: WHO Classification of Tumours. Digestive System Tumours, 5th ed, Klimstra DS, Kloppel G, La Rosa S, Rindi G, the WHO Classification of Tumours Editorial Board (Ed), the WHO classification of neuroendocrine neoplasms of the digestive system, p.16, Copyright © 2019 International Agency for Research on Cancer.

[a] Mitotic rates are to be expressed as the number of mitoses/2 mm2 (equaling 10 high-power fields at 40× magnification and an ocular field diameter of 0.5 mm) as determined by counting in 50 fields of 0.2 mm² (ie, in a total area of 10 mm²); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labeling (hot spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher grade category.
[b] Poorly differentiated NECs are not formally graded but are considered high grade by definition.
[c] In most MiNENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately.

with a TMB-low status, a TMB-H status did not result in a higher objective response rate (ORR) in patients treated with an immune checkpoint inhibitor,[52] especially after additional cohort stratification.[53] See "Principles of Peptide Receptor Radionuclide Therapy (PRRT) with 177Lu-dotatate" in the algorithm (available online, in these guidelines, at NCCN.org) for practical guidance and information, including patient eligibility, patient preparation for treatment, dose and administration of 177Lu-dotatate, posttreatment instructions, and timing of somatostatin analogs.

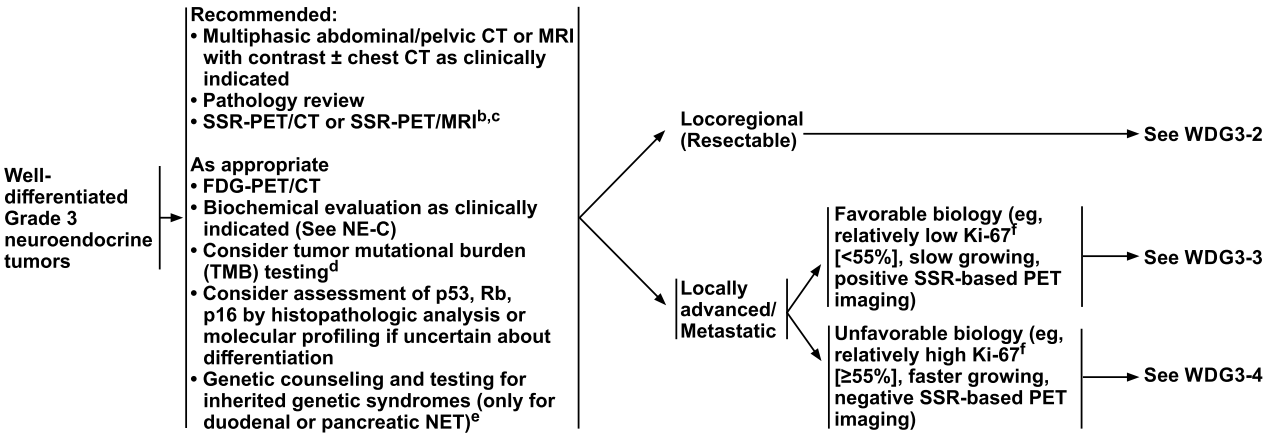
In the event of locally advanced or metastatic disease with unfavorable biology, a clinical trial is a preferred option. Other recommended options include chemotherapy (as described previously) and the combination of nivolumab and ipilimumab (category 2B).[54] Pembrolizumab is also an option for patients with advanced TMB-H tumors, as determined by an FDA-approved test, that have progressed after prior treatment and have no satisfactory alternative treatment options.[50,51] Additional chemotherapy options in this setting include irinotecan-based therapies (eg, FOLFIRI, cisplatin/irinotecan, FOLFIRINOX). The addition of liver-directed therapies, including embolization, selective internal radiation therapy, ablation, and stereotactic body radiation therapy, can be considered in selected cases with residual liver-predominant disease after systemic therapy. Palliative RT is recommended for symptomatic bone metastases.

Evolving data suggest that well-differentiated tumors with intermediate Ki-67 levels (in the 20%–55% range) may not respond as well to platinum/etoposide as those with higher Ki-67 (>55%).[55] A few studies reported that treatment with platinum-based chemotherapy yielded almost no response (0%–2% response rate).[42,43,56]

Surveillance of Well- Differentiated Grade 3 Neuroendocrine Tumors

Surveillance for resectable locoregional, locally advanced, or metastatic disease consists of a routine patient history and physical examination along with appropriate imaging studies (abdominal/pelvic MRI scans with contrast or abdominal/pelvic multiphasic CT, and chest CT scans as clinically indicated) every 12 to 24 weeks for the first 2 years and every 6 to 12 months thereafter, for up to 10 years.

Well-Differentiated, Grade 3 Neuroendocrine Tumors



[a] See Principles of Imaging (NE-B*).
[b] PET/CT or PET/MRI of skull base to mid-thigh with IV contrast when possible. Data are limited on the optimal timing of scans following administration of SSAs.
[c] SSR PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC.
[d] FDA-approved test recommended for determination of TMB.
[e] See Principles of Genetic Risk Assessment and Counseling (NE-E).
[f] There are limitations in terms of the data for what the appropriate cutoff should be, as well as variability/heterogeneity of Ki-67 in a given tumor and over time in serial biopsies. The clinical course and histopathologic workup combined should dictate therapy, not solely Ki-67.

*Available online, in these guidelines, at NCCN.org.

WDG3-1

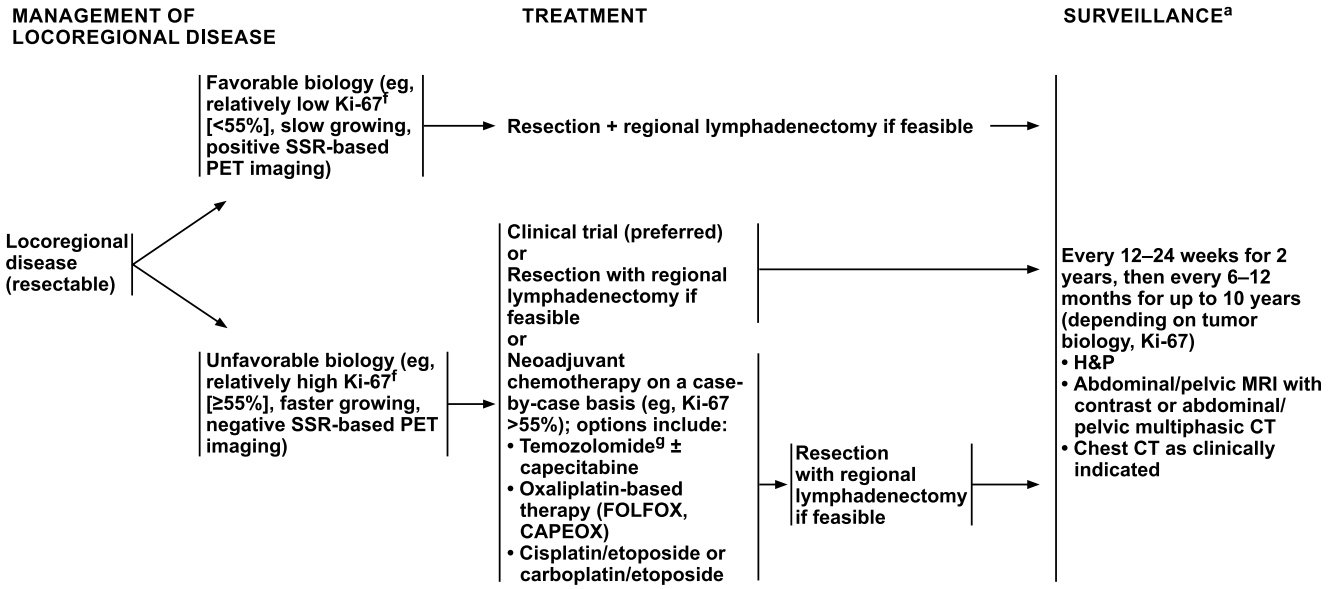
Surveillance for resectable locoregional disease depends on the tumor biology and Ki-67%. Patients with unresectable locally advanced or metastatic disease with favorable biology should be monitored every 12 to 24 weeks (depending on tumor biology), with a history and physical and a chest CT with or without contrast and an abdominal/pelvic MRI with contrast or a chest/abdominal/pelvic multiphasic CT scan. SSR-PET/CT or SSR-PET/MRI or FDG PET/CT scans and biochemical markers are also recommended as clinically indicated. Patients with unresectable locally advanced or metastatic disease with unfavorable biology should follow the same surveillance recommendations (except for SSR imaging) but should be followed every 8 to 12 weeks (depending on tumor biology).

Poorly Differentiated Neuroendocrine Carcinomas/Large or Small Cell Carcinomas or Unknown Primary

Although rare, extrapulmonary poorly differentiated NECs can occur in a wide variety of organs. They are characterized by a high mitotic index and high Ki-67 index. The most aggressive of these tumors histologically resemble classic small cell carcinoma of the lung. The most frequent organs involved are the cervix, esophagus, pharynx and larynx, colon, rectum, prostate, pancreas, and bladder.[57] Most extrapulmonary poorly differentiated NECs are aggressive and require combined multimodality treatment, usually following a treatment paradigm that parallels the treatment of small cell lung cancer. These tumors are rarely associated with a hormonal syndrome. Gastrointestinal tumors with mixed histology of poorly differentiated adenocarcinoma can be treated according to the NCCN Guidelines for Colon Cancer and Pancreatic Adenocarcinoma (available at NCCN.org).

Results from a SEER database analysis of NECs found that 9% were extrapulmonary.[57] The median survival for all NECs was 7.7 months. Compared with other primary NECs (26.0%), the survival was lower for lung NECs (5.6%) and gastrointestinal NECs (13.1%) at 5 years. The median survival of patients with gastrointestinal NECs was 7.5

Well-Differentiated, Grade 3 Neuroendocrine Tumors



[a] See Principles of Imaging (NE-B*).
[f] There are limitations in terms of the data for what the appropriate cutoff should be, as well as variability/heterogeneity of Ki-67 in a given tumor and over time in serial biopsies. The clinical course and histopathologic workup combined should dictate therapy, not solely Ki-67.
[g] May have more activity in tumors arising in pancreas.

*Available online, in these guidelines, at NCCN.org.

WDG3-2

months, with patients with small intestine tumors doing better (25.1 months) than patients with pancreatic tumors (5.7 months). The median survival for patients with unknown primary NECs was 2.5 months.

Evaluation of Poorly Differentiated/Large or Small Cell Carcinomas or Unknown Primary

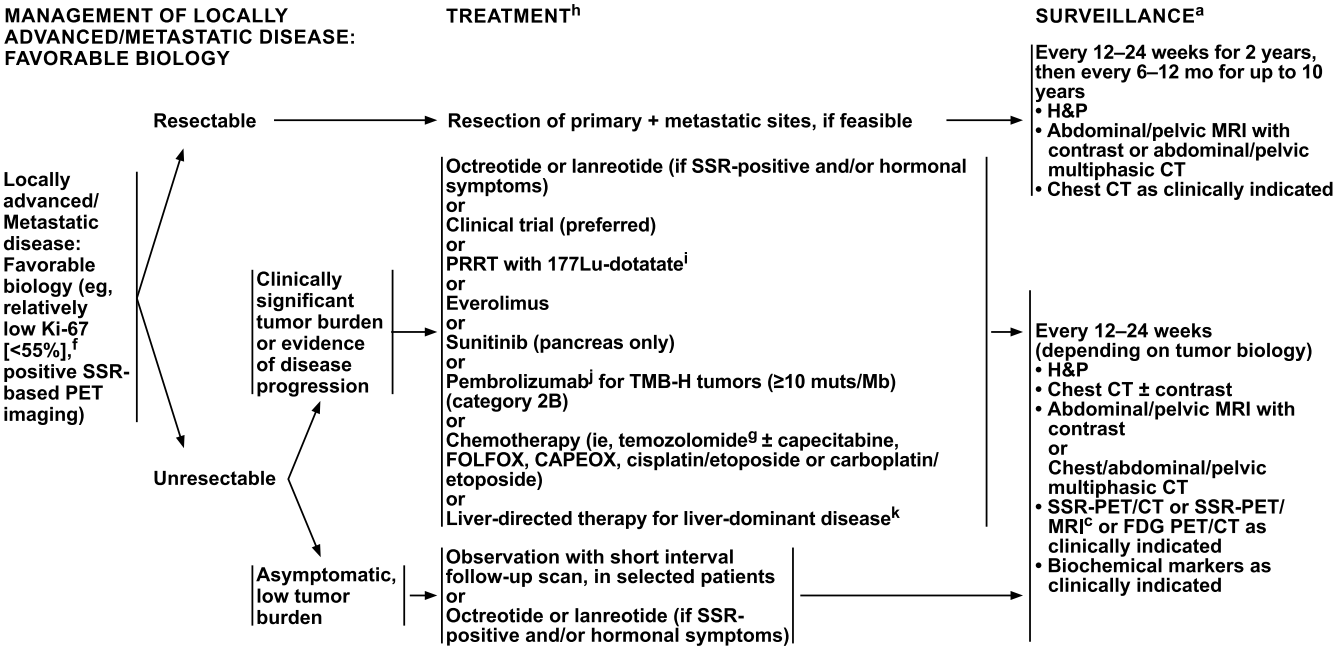
CT scans of the chest, abdomen, and pelvis or CT scans of the chest and MRI of the abdomen and pelvis are recommended as baseline staging studies. Brain imaging with MRI or CT scan with contrast and FDG-PET should be performed as clinically indicated and should be considered routinely in poorly differentiated NECs of the thorax and neck. Biochemical markers are recommended if symptoms are suggestive of a secretory tumor. SSR imaging is not part of the routine evaluation of poorly differentiated NECs. Tumor biomarkers such as microsatellite instability (MSI), MMR, and TMB testing (by an FDA-approved test) should be considered as they can aid in assessing targeted therapy options.

Primary Treatment of Extrapulmonary Poorly Differentiated/Large or Small Cell Neuroendocrine Carcinomas or Unknown Primary

For resectable poorly differentiated/large or small cell NECs, poorly differentiated of unknown primary, treatment options depend on the disease site. Such options include surgical resection and adjuvant chemotherapy with or without radiotherapy, neoadjuvant chemotherapy with or without radiation and resection, chemotherapy alone, radiotherapy alone, and definitive chemoradiation (with cisplatin/etoposide or carboplatin/etoposide). For unresectable locoregional disease, concurrent or sequential radiotherapy in combination with chemotherapy, or chemotherapy alone are recommended. If metastatic disease is present, chemotherapy alone is recommended.

Cytotoxic chemotherapy regimens, such as cisplatin/etoposide[58,59] or carboplatin/etoposide,[60] FOLOFOX,[61] FOLFIRI,[62] and temozolomide with or without capecitabine,[63] are generally used as primary treatment of

Well-Differentiated, Grade 3 Neuroendocrine Tumors



[a] See Principles of Imaging (NE-B*).
[c] SSR PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC.
[f] There are limitations in terms of the data for what the appropriate cutoff should be, as well as variability/heterogeneity of Ki-67 in a given tumor and over time in serial biopsies. The clinical course and histopathologic workup combined should dictate therapy, not solely Ki-67.
[g] May have more activity in tumors arising in pancreas.
[h] Clinical trials preferred due to a lack of data from prospective clinical trials to guide therapy.
[i] Consider trial of SSA before PRRT. Preliminary data suggest reduced efficacy if high Ki-67 and/or FDG-PET avid. See Principles of PRRT with 177Lu-DOTATATE (NE-G*).
[j] Pembrolizumab is an option for patients with advanced tumor mutational burden-high (TMB-H) tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.
[k] See Principles of Liver-Directed Therapy for Neuroendocrine Tumor Metastases (NE-H*).

*Available online, in these guidelines, at NCCN.org.

WDG3-3

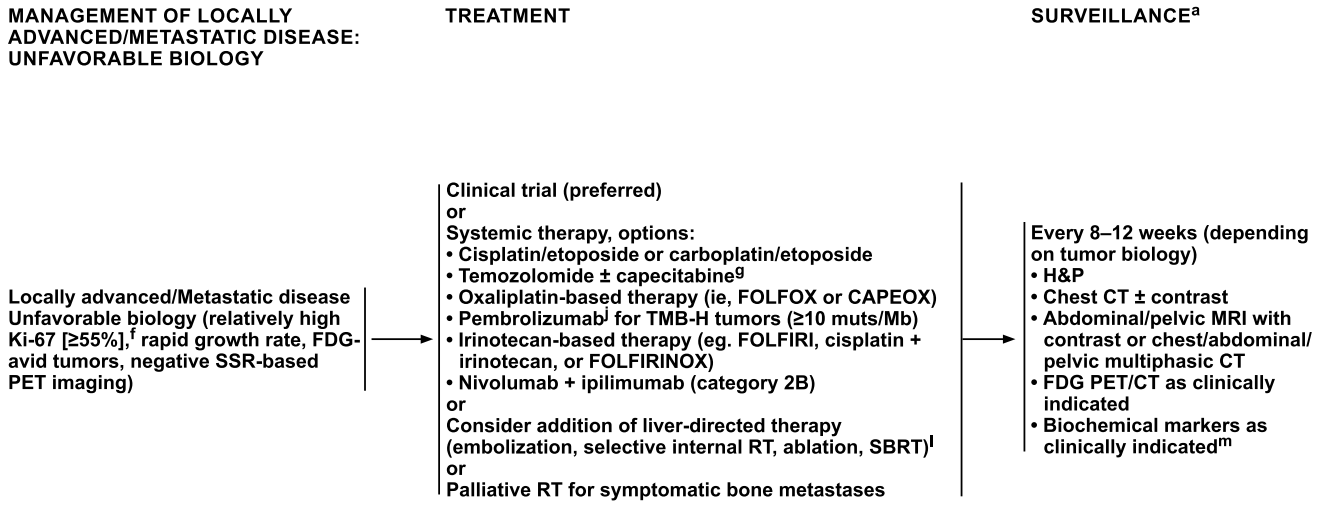
resectable, locoregional unresectable, or metastatic disease. For locoregional unresectable or metastatic disease, additional chemotherapy options include cisplatin/irinotecan,[59] carboplatin/irinotecan, and FOLFIRINOX.[64,65] The efficacy of second-line or later lines of chemotherapy is very limited and survival is short.[66] The combination of ipilimumab and nivolumab (category 2B) can be considered if the disease progresses following chemotherapy.[54,67] The results of one phase II study (S1609 DART) revealed an ORR of 44% in patients with nonpancreatic high-grade NECs (including lung primaries) treated with combined ipilimumab and nivolumab.[67] Subsequent data from an additional cohort of patients (n=19) with high-grade NENs (median Ki-67 80%) revealed an ORR of 26% and a 6-month progression-free survival (PFS) of 32%.[68] The median PFS was 2.0 months and the median OS was 8.7 months. The subgroup analysis of the CA209-538 trial, centered on patients with advanced NENs that received the combined treatment, demonstrated an ORR of 24%.[54] The median PFS was 4.8 months and the OS was 14.8 months. Immune-related toxicity occurred in 66% of cases. Importantly, preliminary data from the multicohort phase II study (n=123) of durvalumab plus tremelimumab for patients with NENs of gastroenteropancreatic or lung origin suggested only modest activity (irRECIST ORR 9.1%) in G3 gastroenteropancreatic NENs.[69]

Finally, pembrolizumab can also be considered for patients with MMR-deficient, MSI-high, or advanced TMB-high (as determined by an FDA-approved test) tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.[50,51,70]

Surveillance of Poorly Differentiated/Large or Small Cell Carcinomas or Unknown Primary

For patients with resectable disease, surveillance after treatment completion consists of a routine history and physical along with appropriate imaging studies (chest CT with or without contrast and abdominal/pelvic MRI with contrast or chest/abdominal/pelvic multiphasic CT)

Well-Differentiated, Grade 3 Neuroendocrine Tumors



[a] See Principles of Imaging (NE-B*).
[f] There are limitations in terms of the data for what the appropriate cutoff should be, as well as variability/heterogeneity of Ki-67 in a given tumor and over time in serial biopsies. The clinical course and histopathologic workup combined should dictate therapy, not solely Ki-67.
[g] May have more activity in tumors arising in pancreas and with.
[j] Pembrolizumab is an option for patients with advanced tumor mutational burden-high (TMB-H) tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.
[l] Consider liver-directed therapy in selected cases with residual liver-predominant disease after systemic therapy. See Principles of Liver-Directed Therapy for Neuroendocrine Tumor Metastases (NE-H*).
[m] See Principle of Biochemical Testing (NE-C*).

*Available online, in these guidelines, at NCCN.org.

WDG3-4

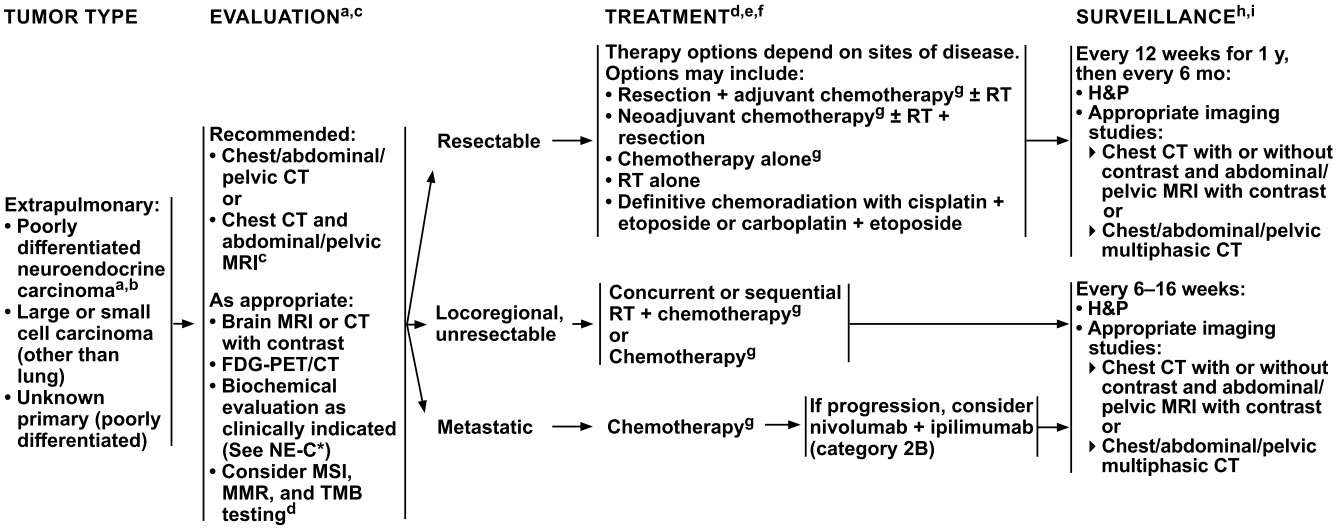
every 12 weeks for the first year and every 6 months thereafter. However, patients with locoregional, unresectable disease and with metastatic disease should be monitored more closely every 6 to 16 weeks with an history and physical and appropriate imaging studies as described.

Adrenal Gland Tumors

Adrenocortical carcinomas are rare (incidence, 0.7–2 per million).[71,72] ACC has a bimodal age distribution, with peak incidences in early childhood and the fourth to fifth decades of life. Women are more frequently affected (55%–60%).[71,73] Most cases are sporadic; however, ACCs have been observed in association with several hereditary syndromes, including Li-Fraumeni syndrome, Lynch syndrome, Beckwith-Wiedemann syndrome, MEN1, and familial adenomatous polyposis.[74–80] The underlying mechanisms of carcinogenesis in sporadic ACCs have not been fully elucidated; however, inactivating somatic mutations of the *p53* tumor suppressor gene (chromosome 17p13[81,82]) and alterations at the 11p15 locus (site of the *IGF2* gene[83,84]) seem to occur frequently.

Approximately 60% of patients present with evidence of adrenal steroid hormone excess, with or without virilization.[72] Signs and symptoms associated with hypersecretion of cortisol, called Cushing syndrome, include weight gain, weakness (primarily in proximal muscles), hypertension, psychiatric disturbances, hirsutism, centripetal obesity, purple striae, dorsocervical fat pad and supraclavicular fat pad enlargement, hyperglycemia, and hypokalemia. Aldosterone-secreting tumors may present with hypertension, weakness, and hypokalemia. Androgen-secreting tumors in women may induce hirsutism, virilization, deepening of the voice, and oligo/amenorrhea.[72] In men, estrogen-secreting tumors may induce gynecomastia and testicular atrophy. Hormonally inactive ACCs typically produce symptoms related to tumor burden, including abdominal pain, back pain, early satiety, and weight loss.[72]

Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell



[a] This page is for PDNEC and not high-grade NET. Not all high-grade (Ki-67 >20%) neuroendocrine neoplasms are poorly differentiated. See WDG3-1.
[b] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[c] Somatostatin scintigraphy with SPECT/CT is not part of the routine evaluation of poorly differentiated neuroendocrine carcinomas, but may be considered for morphologically well-differentiated tumors with higher proliferation index, as appropriate. See Principles of Imaging (NE-B*).
[d] Pembrolizumab can be considered for patients with mismatch repair-deficient (dMMR), microsatellite instability-high (MSI-H), or advanced tumor mutational burden-high (TMB-H) tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.
[e] Combination of immune checkpoint inhibitors + chemotherapy is investigational for all patients with extrapulmonary poorly differentiated neuroendocrine carcinomas.
[f] See Surgical Principles for Management of Neuroendocrine Tumors (NE-D*).
[g] See Principles of Systemic Anti-Tumor Therapy (NE-F).
[h] Earlier, if symptoms.
[i] See NCCN Guidelines for Survivorship†.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

PDNEC-1

Evaluation and Treatment of Adrenal Gland Tumors

All patients with adrenal gland tumors need biochemical evaluation and appropriate imaging. Biochemical evaluation to evaluate for hyperaldosteronism, Cushing syndrome, pheochromocytoma, and suspected ACC should be done with every adrenal mass. Comprehensive guidelines for the workup of adrenal tumors, adrenal incidentalomas, hyperaldosteronism, Cushing syndrome, and pheochromocytoma and paraganglioma are published through the Endocrine Society[85–87] and the European Society of Endocrinology (ESE).[88,89]

NCCN recommends doing a morphologic evaluation of adrenal nodules with adrenal protocol CT, or MRI with or without contrast, to determine the size, heterogeneity, lipid content (with MRI), contrast washout (with CT), and margin characteristics. If the Hounsfield unit (HU) attenuation value is less than 10 on unenhanced CT, then the tumor is probably benign. If the HU attenuation value is greater than 10 on unenhanced CT, then enhanced CT and washout at 15 minutes is recommended. If the absolute washout value is greater than 60% at 15 minutes, the tumor is likely benign; if less than 60%, the tumor is possibly malignant.[90,91] Functional evaluation should be done as noted previously. Most ACCs secrete multiple hormones; therefore, if imaging is suspicious for adrenal cortical carcinoma, evaluation for sex steroid in addition to the previously noted evaluation is indicated. If several hormones are over-secreted, ACCs are more likely.

History of a primary cancer outside of the adrenal gland raises the question of metastatic disease to the adrenals. However, it is very important that pheochromocytoma is ruled out prior to considering diagnostic biopsy of the adrenal mass. In these patients, an image-guided needle biopsy can be considered only if clinical suspicion for pheochromocytoma is low and plasma or urine fractionated metanephrines are normal. False-negative biopsies are possible; therefore, proceeding directly to surgery should be considered in some cases. If the tumor is determined to be a metastasis from another site, treatment should be according to the appropriate NCCN disease-

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell (Extrapulmonary)

Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell (Extrapulmonary)		
Resectable disease: • Cisplatin + etoposide[10] • Carboplatin + etoposide[21] • FOLFOX • FOLFIRI • Temozolomide ± capecitabine	**Locoregional Unresectable/Metastatic Disease:** • Cisplatin + etoposide[10] • Carboplatin + etoposide[21] • Cisplatin + irinotecan • Carboplatin + irinotecan • FOLFOX • FOLFIRI • FOLFIRINOX[22,23] • Temozolomide ± capecitabine • Nivolumab + ipilimumab (category 2B) (only for metastatic disease with progression)[24] • Pembrolizumab[h]	**Chemoradiation (concurrent/sequential) for locoregional unresectable disease** • Cisplatin + etoposide • Carboplatin + etoposide

[h] Pembrolizumab can be considered for patients with mismatch repair-deficient (dMMR), microsatellite instability-high (MSI-H), or advanced tumor mutational burden-high (TMB-H) tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.

*Available online, in these guidelines, at NCCN.org.

References*

specific treatment guideline (to see the NCCN Guidelines Table of Contents, go to www.NCCN.org). If biopsy reveals adrenal cortical tissue, then morphologic and functional evaluation should proceed as described here.

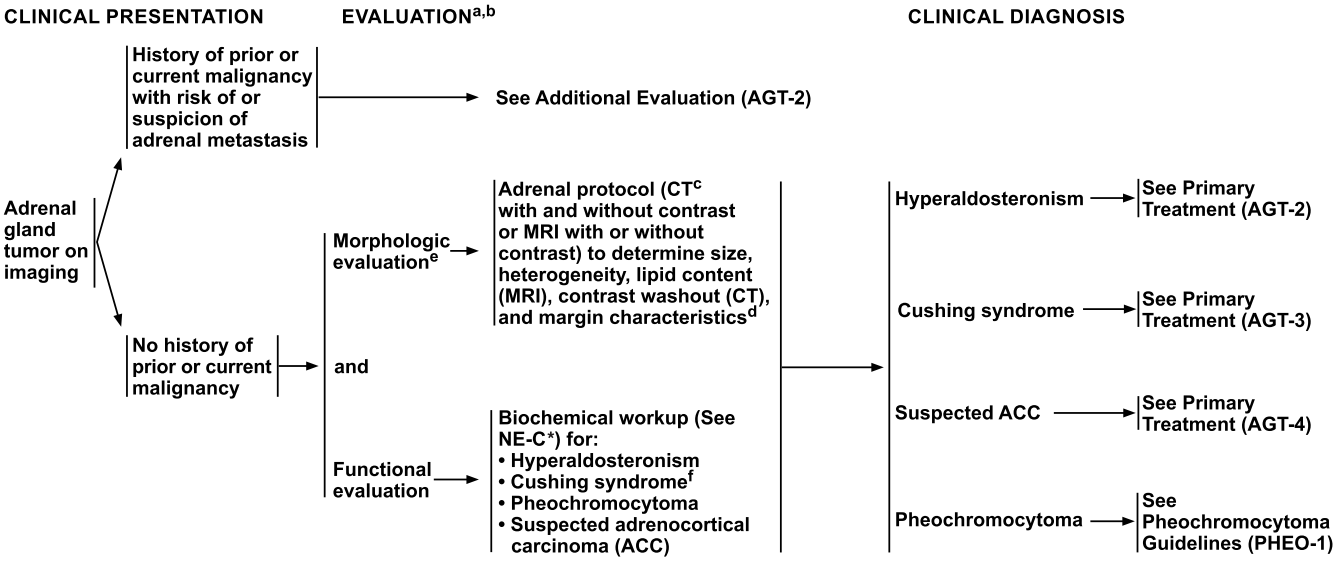
Evaluation and Treatment of Hyperaldosteronism

When hyperaldosteronism (also called *primary aldosteronism*) is suspected, plasma aldosterone and plasma renin activity should be assessed. Patients with primary aldosteronism have elevated plasma levels of aldosterone and low levels of renin activity. The plasma aldosterone-to-renin ratio in patients with primary hyperaldosteronism is usually greater than 30.[87] Confirmatory testing is often recommended for equivocal results. Twenty-four-hour urine for aldosterone, following salt loading or a saline suppression test, as well as sodium and potassium levels should be considered for definitive diagnosis. Serum electrolytes should also be measured, because excessive aldosterone production causes both retention of sodium and excretion of potassium. The Endocrine Society has developed detailed guidelines for the detection, diagnosis, and treatment of primary aldosteronism,[87] and these guidelines have been modified over time.[92,93]

Hyperaldosteronism is rarely associated with malignancy, but malignancy should be suspected if the tumor has an irregular or inhomogeneous morphology, is lipid-poor, does not wash out on contrast-enhanced CT, is larger than 4 cm, or is secreting more than one hormone. When malignant hyperaldosteronism is suspected, an open adrenalectomy is recommended, because these tumors are prone to rupture.[89]

Benign hyperaldosteronism is much more common and can be caused by a unilateral adrenal adenoma or bilateral adrenal hyperplasia. Adrenal vein sampling for aldosterone and cortisol can be considered for distinguishing these two causes of benign hyperaldosteronism and should be considered if the patient is a surgical candidate, because CT imaging cannot always differentiate between an adenoma and hyperplasia. It may be reasonable, however, to exclude adrenal vein sampling in patients younger than 40 years when imaging only shows one affected gland, because bilateral hyperplasia is rare in this population. Minimally invasive adrenalectomy is recommended for

Adrenal Gland Tumors



[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-C*).
[c] If unenhanced is <+ 10 HU, then the tumor is probably benign. If unenhanced is >+ 10 HU, then use enhanced and washout. If >60% absolute washout in 15 minutes, the tumor is likely to be benign; if <60%, the tumor is possibly malignant. (Caoili E, et al. Radiology 2002;222:629-633.)
[d] See Principles of Imaging (NE-B*).
[e] For benign-appearing lesions, refer to the following guidelines for the management of adrenal incidentalomas: Zeiger MA, Thompson GB, Duh QY, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2009;15 Suppl 1:1-20; Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 2016;175:G1-G34.
[f] For benign-appearing lesions, refer to the Endocrine Society's Clinical Practice Guidelines for the Treatment of Cushing's Syndrome (Nieman LK, et al. J Clin Endocrinol Metab 2015;100:2807-2831).

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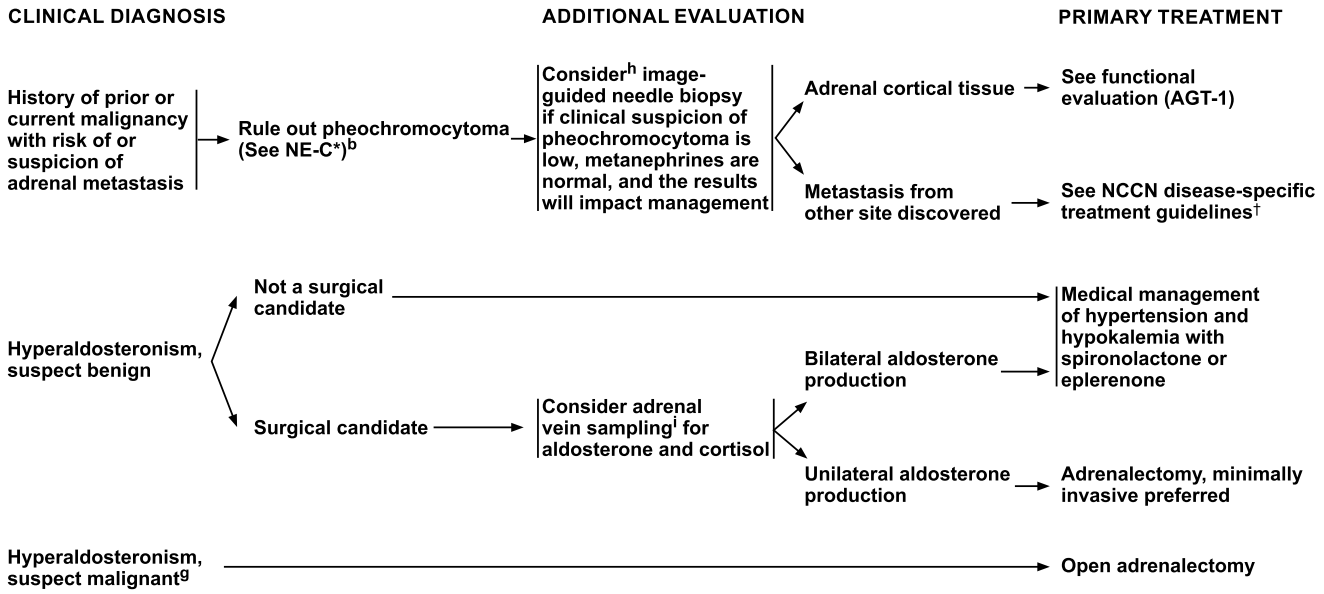
adenoma, whereas medical management with spironolactone or eplerenone for hypertension and hypokalemia is recommended for patients with bilateral adrenal hyperplasia and for nonsurgical candidates.

Evaluation and Treatment of Cushing Syndrome

Patients who present with symptoms of Cushing syndrome should be evaluated for evidence of hypercortisolemia with one of the following tests: (1) overnight 1-mg dexamethasone suppression test; (2) 2 to 3 midnight salivary cortisol measurements; or (3) free cortisol in a 24-hour urine sample.[86,94] Elevated levels of cortisol are indicative of Cushing syndrome. Plasma ACTH should be checked to determine if it is ACTH dependent or ACTH independent (ACTH <5 pg/mL). Adrenal masses that secrete cortisol are not mediated by ACTH (ACTH independent), and ACTH dependent tumors can arise in the pituitary or ectopic NET sources. If a clear pituitary adenoma is not visible by MRI, inferior petrosal sinus vein sampling can be considered to differentiate between pituitary and ectopic causes in ACTH-dependent Cushing syndrome. Endocrinology referral should be considered for the biochemical workup, localization of hypercortisolemia, and medical therapy for hypercortisolism until more definitive therapy can be arranged.

Cushing syndrome can be associated with either benign adrenal tumors (adrenal adenoma) or malignant adrenal tumors. Malignancy should be suspected if the tumor is larger than 4 cm or is inhomogeneous with irregular margins and/or has local invasion and other malignant imaging characteristics. Some centers may use 6 cm as a cutoff instead of 4 cm. FDG PET/CT scans, chest CT scans with or without contrast, and CT or MRI scans with contrast of the abdomen and pelvis are recommended. Benign adrenal tumors (ie, <4 cm, contralateral gland normal, circumscribed tumor, other benign imaging characteristics) should be resected. It is important that patients who have cortisol-secreting adrenal tumor receive perioperative glucocorticoids since the contralateral adrenal secretion will be transiently suppressed. For more details,

Adrenal Gland Tumors



[b] See Principles of Biochemical Testing (NE-C*).
[g] Suspect malignancies with irregular/inhomogeneous morphology, lipid-poor, do not wash-out, tumor >4 cm, or secretion of more than one hormone.
[h] False negatives are possible; may consider proceeding directly to surgery in selected cases.
[i] Adrenal vein sampling can be considered for distinguishing single unilateral adenomas from bilateral hyperplasia. CT imaging is not always reliable. Some NCCN Member Institutions recommend sampling in all cases of primary aldosteronism. However, it may be reasonable to exclude adrenal vein sampling in patients <40 y. Cortisol measurement in the catheterization samples is used to confirm proper catheter placement.

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please see the Endocrine Society's Clinical Practice Guidelines for the Treatment of Cushing Syndrome.[95]

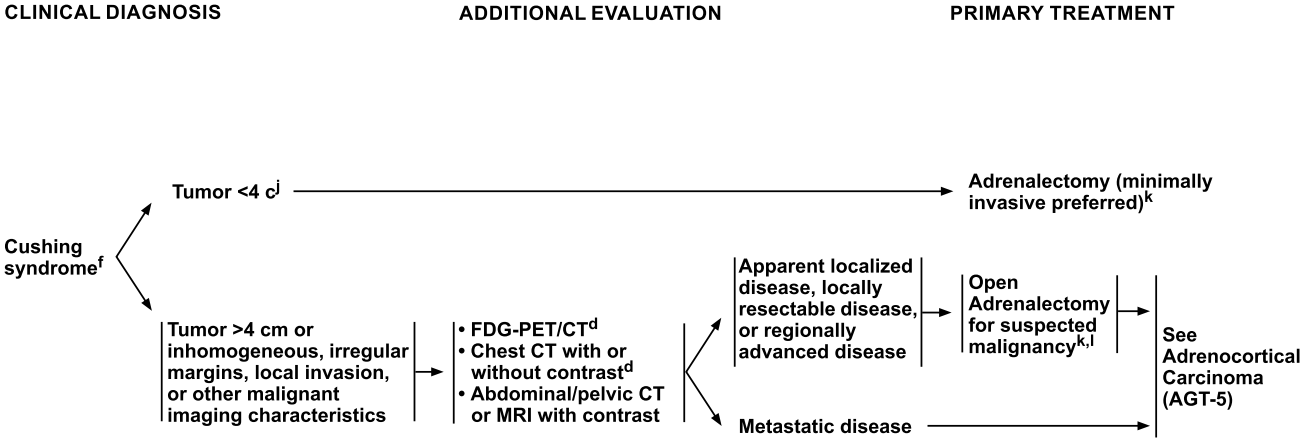
Treatment of Nonfunctioning, Benign Adrenal Tumors

Adrenal tumors that do not secrete hormones are often discovered incidentally during scans for unrelated reasons (*incidentalomas)*. It is still important to evaluate for biochemical secretion of hormones for hyperaldosteronism, Cushing syndrome, and pheochromocytoma and paraganglioma as listed previously to confirm they are nonsecreting. Please refer to the American Association of Clinical Endocrinology and American Association of Endocrine Surgeons (AACE/AAES) guidelines[96] and the ESE guidelines[89] for the management of adrenal incidentalomas. Most nonfunctioning tumors are benign and can be left untreated. Masses showing radiographic features of myelolipoma are considered benign. In addition, tumors smaller than 4 cm that are homogenous, with smooth margins, and that appear lipid-rich according to CT or MRI criteria are also usually benign. A minimally invasive adrenalectomy is preferred for these tumors if resection is indicated due to tumor growth. If malignancy is suspected and the disease is localized, locally resectable, or regionally advanced, an open adrenalectomy is recommended.

Evaluation of Adrenocortical Carcinoma

ACC should be strongly suspected in tumors larger than 4 cm with irregular margins or that are internally heterogeneous and if they secrete multiple hormones.[72] On CT scans with IV contrast, adjacent lymph nodes or liver metastases may be present. On unenhanced CTs, the HU number is typically higher in carcinomas than in adenomas, and a threshold value of 10 HU has been proposed as a means of distinguishing benign from malignant adrenal tumors.[72] If the HU attenuation value is less than 10 on unenhanced CT, then the tumor is probably benign. If the HU attenuation value is greater than 10 on unenhanced CT, then enhanced CT and washout at 15 minutes is recommended. If the absolute washout value is greater than 60% at 15 minutes, the tumor is likely benign; if less than 60%, the

Adrenal Gland Tumors



[d] See Principles of Imaging (NE-B*).
[f] For benign-appearing lesions, refer to the Endocrine Society's Clinical Practice Guidelines for the Treatment of Cushing's Syndrome (Nieman LK, et al. J Clin Endocrinol Metab 2015;100:2807-2831).
[j] Some centers may use 6 cm as cutoff.
[k] Perioperative management should include stress-dose steroids (eg, methylprednisolone or hydrocortisone).
[l] May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.

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tumor is possibly malignant.[90,91] MRIs more clearly document local invasion and involvement of the inferior vena cava than CT scans.[72] Whether CT or MRI scans are performed, they should be performed using an adrenal protocol to determine size, heterogeneity, lipid content (MRI), contrast washout (CT), and margin characteristics.

FDG PET/CT, chest CT scans with or without contrast, CT or MRI scans with contrast of the abdomen and pelvis, and a biochemical workup are also recommended for resectable, unresectable, or suspected metastatic disease.

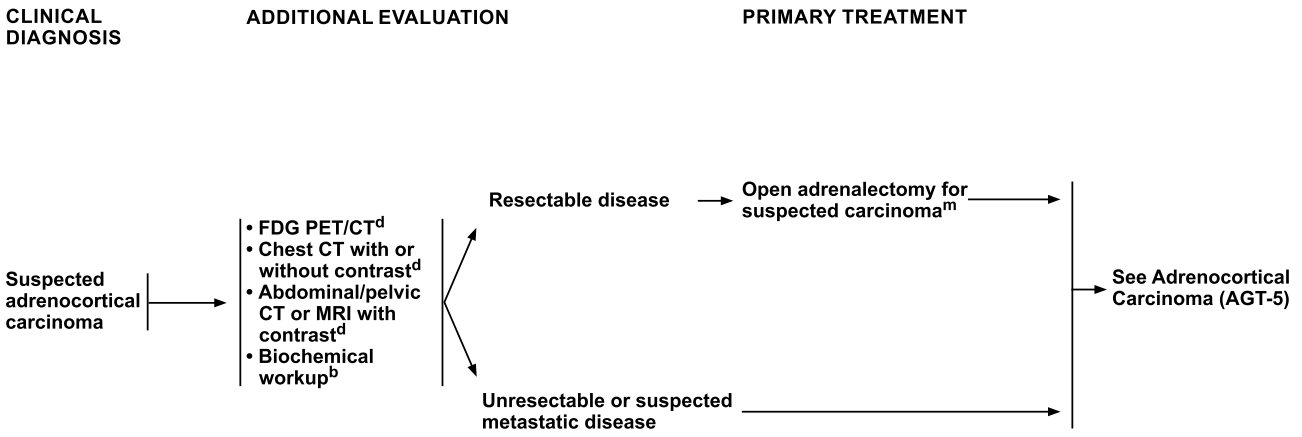
One study found that 5.8% of adults with ACC tested positive for Li Fraumeni syndrome (*TP53* gene) and genetic testing should be routinely offered to all patients with ACC.[97] Another analysis found that approximately 3% of patients with ACC have Lynch syndrome, leading the authors to recommend that patients with ACC also undergo genetic testing for Lynch syndrome.[79] Patients with ACC may also consider MSI, MMR, and TMB (by an FDA-approved test) testing. Genetic counseling and testing for inherited genetic syndromes is also recommended.

Treatment and Surveillance of Nonmetastatic Adrenocortical Carcinoma

Surgical resection of the tumor with removal of adjacent lymph nodes is recommended in patients with localized ACC, and may require removal of adjacent structures such as the liver, kidney, pancreas, spleen, and/or diaphragm for complete resection. Open adrenalectomy is recommended in tumors with a high risk of being malignant because of increased risk for local recurrence and peritoneal spread when performed laparoscopically.[98] It is thus important to achieve negative margins and avoid breaching the tumor capsule.

Because of the rarity of ACCs, no randomized, prospective trials of adjuvant therapy have been published. Most retrospective reports have examined the use of adjuvant mitotane, an oral adrenocorticolytic agent.[99] A recent systematic review and meta-analysis of the benefits of mitotane after resection of ACC in patients without distant metastasis included five retrospective studies reporting on 1249 patients.[100] The meta-analysis found benefit of

Adrenal Gland Tumors



[b] See Principles of Biochemical Testing (NE-C*).
[d] See Principles of Imaging (NE-B*).
[m] If size is resectable by laparoscopy, may explore with a minimally invasive approach with planned conversion for evidence of local invasion. The decision for open versus minimally invasive surgery is based on tumor size and degree of concern regarding potential malignancy, and local surgical expertise.

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adjuvant mitotane, with significantly longer recurrence-free survival and OS, suggesting that adjuvant mitotane may be an effective postoperative strategy. The randomized phase III ADIUVO trial is currently underway to assess the efficacy of adjuvant mitotane in patients with ACCs considered to be at low to intermediate risk for progression (ClinicalTrials.gov identifier: NCT00777244). Disease-free survival is the primary endpoint.

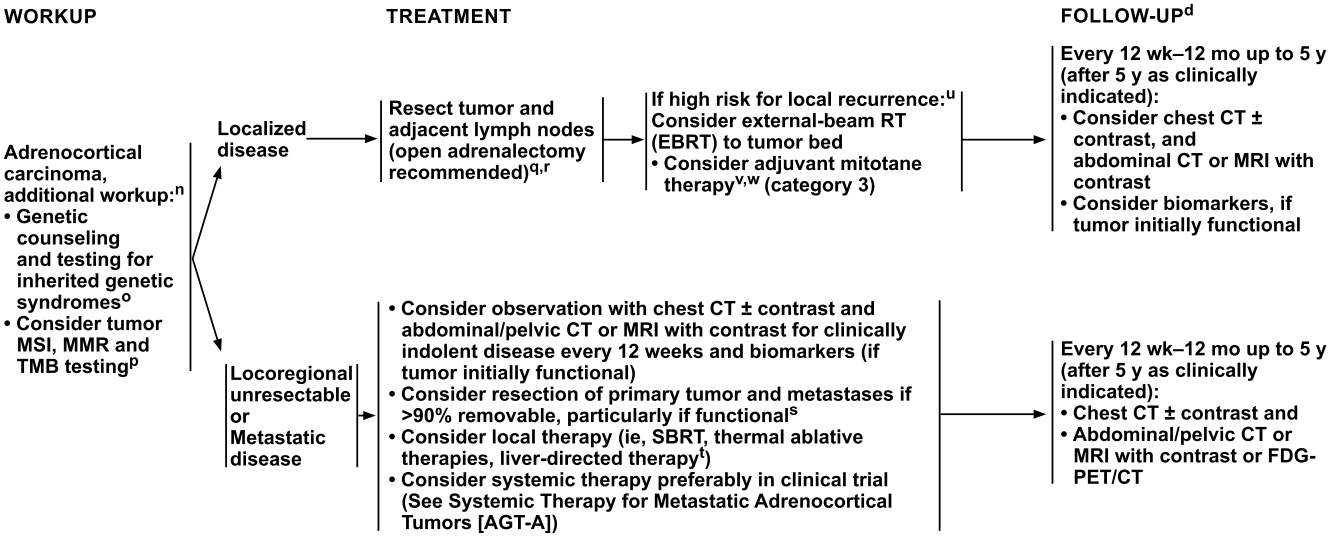
Based on the available data, adjuvant therapy can be considered if the patient is at high risk for local recurrence based on positive margins, ruptured capsule, large size, and high grade. Adjuvant external beam RT to the tumor bed can be considered in these cases, particularly if concern exists regarding tumor spillage or close margins after surgery. Adjuvant mitotane therapy can also be considered after resection of ACC, although its use in this setting is controversial (category 3). Mitotane blood levels should be monitored. Some institutions recommend target levels of 14 to 20 mcg/mL if tolerated. Steady-state levels may be reached several months after initiation of mitotane. Because of the adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone with or without fludrocortisone) should be prescribed to treat adrenal insufficiency if it is used; corticosteroids may be required for the rest of the patient's life. Because of the potential risks and uncertain benefits of adjuvant mitotane, several NCCN Member Institutions do not advocate its use in the adjuvant treatment of patients with resected ACCs.

A follow-up should be performed every 12 weeks to 12 months for up to 5 years, and then as clinically indicated. Recurrences after 5 years are thought to be very rare. A chest CT scan, with or without contrast, and an abdominal CT or MRI scan with contrast and biomarkers (if the tumor is initially functional) should be considered.

Management of Locoregional Unresectable or Metastatic Adrenocortical Carcinoma

Resection may be considered if greater than 90% of the tumor and metastases can be removed. In the case of bulky

Adrenal Gland Tumors



[d] See Principles of Imaging (NE-B*).
[n] Staging workup, see AGT-4.
[o] See Principles of Genetic Risk Assessment and Counseling (NE-E).
[p] FDA-approved test recommended for determination of TMB.
[q] May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.
[r] It is important to achieve negative margins and avoid breaching the tumor capsule. There may be an increased risk for local recurrence and peritoneal spread when done with a minimally invasive approach.
[s] If bulky disease, or <90% is removable, surgery can be reconsidered following response to systemic therapy.
[t] See Principles of Liver-Directed Therapy for Neuroendocrine Tumor Metastases (NE-H*).
[u] High-risk local recurrence features include: positive margins, Ki-67 >10%, rupture of capsule, large size, and high grade.
[v] Monitor mitotane blood levels. Some institutions recommend target levels of 14–20 mcg/mL if tolerated. Steady-state levels may be reached several months after initiation of mitotane. Life-long hydrocortisone replacement may be required with mitotane.
[w] Mitotane may have more benefit for control of hormone symptoms than control of tumor.

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disease or if less than 90% of the tumor is removable, surgery can be reconsidered following a response to systemic therapy. Observation with chest CT scans with or without contrast, abdominal/pelvic CT or MRI scans with contrast, and relevant biomarkers (if the tumor is initially functional) every 12 weeks can also be considered for clinically indolent disease, with systemic treatment initiated at tumor progression. For locoregional unresectable or metastatic disease, local therapy may be considered (ie, SBRT, thermal ablative therapies, liver-directed therapies).

Systemic therapy should be considered, preferably in a clinical trial. Choices of systemic therapy for advanced ACC are mitotane monotherapy or various combinations of cisplatin, carboplatin, etoposide, doxorubicin, streptozocin, and mitotane. Mitotane monotherapy has been studied in the setting of locally advanced or metastatic disease.[101–103] Partial response rates are thought to be 10%–30% at most.[104] Pembrolizumab can also be considered as a single agent or in combination with mitotane. These regimens were preference stratified. Preferred regimens include cisplatin or carboplatin in combination with etoposide, with or without doxorubicin, and with or without mitotane. Pembrolizumab, with or without mitotane, and mitotane monotherapy are listed as "other recommended" regimens. Streptozocin, with or without mitotane, is listed as "useful in certain circumstances."

A small phase II study investigating the use of pembrolizumab in patients with advanced ACCs found an ORR of 23% and a disease control rate of 52%.[105] The median OS was 24.9 months. Another small study with 16 patients with advanced ACC demonstrated an ORR of 14% (95% CI, 2%–43%).[106] One phase II study reported a 15% ORR and a 54% clinical benefit rate.[107]

Several studies have evaluated the combination of mitotane with other cytotoxic agents, including cisplatin and etoposide. One of the larger studies analyzed the combination of mitotane (4 g/day) with cisplatin, etoposide, and doxorubicin in 72 patients with unresectable adrenal carcinoma, yielding an ORR of 49% (according to WHO criteria) and a complete hormonal response in 16 of 42

Adrenal Gland Tumors

SYSTEMIC THERAPY FOR LOCOREGIONAL UNRESECTABLE/METASTATIC ADRENOCORTICAL CARCINOMA[x]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cisplatin + etoposide[1] ± doxorubicin ± mitotane[v,w,2] • Carboplatin + etoposide ± doxorubicin ± mitotane[v,w]	• Pembrolizumab[3,4] ± mitotane[v,w] • Mitotane monotherapy[v,w]	• Streptozocin ± mitotane[v,w,2]

References
[1] Williamson SK, Lew D, Miller GJ, et al. Phase II evaluation of cisplatin and etoposide followed by mitotane at disease progression in patients with locally advanced or metastatic adrenocortical carcinoma: a Southwest Oncology Group Study. Cancer 2000;88:1159-1165.
[2] Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med. 2012;366(23):2189-2197. doi:10.1056/NEJMoa1200966
[3] Raj N, Zheng Y, Kelly V, et al. PD-1 blockade in advanced adrenocortical carcinoma. J Clin Oncol 2020;38:71-80.
[4] Habra MA, Stephen B, Campbell M, et al. Phase II clinical trial of pembrolizumab efficacy and safety in advanced adrenocortical carcinoma. J Immunother Cancer 2019;7:253.

[v] Monitor mitotane blood levels. Some institutions recommend target levels of 14–20 mcg/mL if tolerated. Steady-state levels may be reached several months after initiation of mitotane. Life-long hydrocortisone ± fludrocortisone replacement may be required with mitotane.
[w] Mitotane may have more benefit for control of hormone symptoms than control of tumor.
[x] See Discussion for further information regarding the phase III FIRM-ACT trial.

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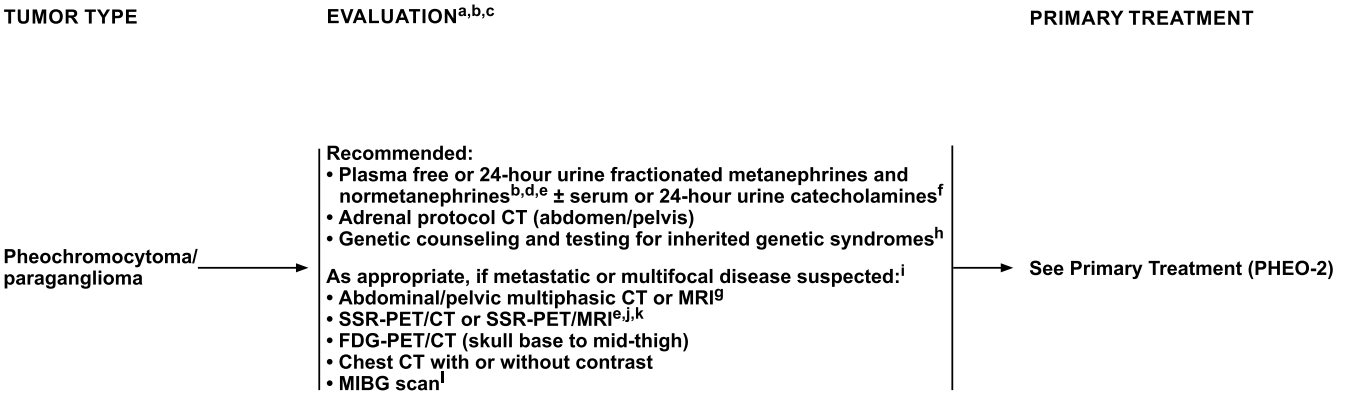
patients with functioning tumors.[108] Another study examined the combination of mitotane with streptozocin and reported an ORR of 36%.[109] Of 12 patients in this study with advanced disease, 3 (25%) were converted to a resectable status with this therapy and remained disease-free or with stable disease 3 to 18 years after surgery; 1 (8%) had stable disease for 3 months, and the other 8 (67%) showed no response.

Analysis of results from the international randomized controlled phase III FIRM-ACT trial comparing treatment of metastatic ACC with etoposide, doxorubicin, cisplatin, and mitotane versus treatment with streptozotocin and mitotane with a crossover design found no difference between the regimens in the primary endpoint of OS (14.8 vs 12.0 months; hazard ratio [HR], 0.79; 95% CI, 0.61–1.02; P=.07).[110] However, response rates and PFS were improved with the 4-drug regimen and an OS benefit was seen in those who did not cross over to the other combination (17.1 vs 4.7 months). Rates of serious adverse events were similar in the 2 arms.

However, the toxicity of concurrent chemotherapy plus mitotane should be considered when making treatment decisions, and mitotane monotherapy may still be appropriate in selected cases. The optimal doses and duration of mitotane treatment of metastatic disease have not yet been standardized, but some institutions recommend target levels of 14 to 20 mcg/mL, if tolerated. Higher doses may be difficult for patients to tolerate, whereas lower doses may be less effective.[104] Steady-state levels may be reached several months after initiation of mitotane. As noted previously, because of the adrenolytic effects of mitotane, replacement doses of corticosteroids (hydrocortisone with or without fludrocortisone) should be prescribed to treat adrenal insufficiency. This replacement therapy may be required for the remainder of the patient's lifetime. A follow-up with chest CT scans, with or without contrast, and abdominal/pelvic CT or MRI scans, with contrast, or FDG-PET/CT scans should be performed every 12 weeks to 12 months, up to 5 years, and then as clinically indicated.

Pheochromocytoma/Paraganglioma



[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Principles of Biochemical Testing (NE-C*).
[c] Consider medical alert ID for hormonally secreting pheochromocytomas and paragangliomas in situ or metastatic disease.
[d] Review concurrent medication(s) for those that may interfere with plasma metanephrines evaluation. Elevations that are 3 times above the upper limit of normal are diagnostic.
[e] For cervical paraganglioma, consider measuring serum and/or 24-hour urine fractionated catecholamines (for dopamine).
[f] Both catecholamines and metanephrines/normetanephrines can produce false-positive results (see NE-C*).
[g] See Principles of Imaging (NE-B*).
[h] See Principles of Genetic Risk Assessment and Counseling (NE-E).
[i] Data on the role of functional imaging in pheochomocytoma/paraganglioma are evolving and the preferred method remains unclear.
[j] PET/CT or PET/MRI of skull base to mid-thigh with IV contrast when possible.
[k] SSR PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC.
[l] MIBG scans are less sensitive than FDG-PET and 68Ga-dotatate for metastatic and multifocal paragangliomas/pheochromocytomas. Obtain MIBG scan if considering treatment with I131-MIBG.

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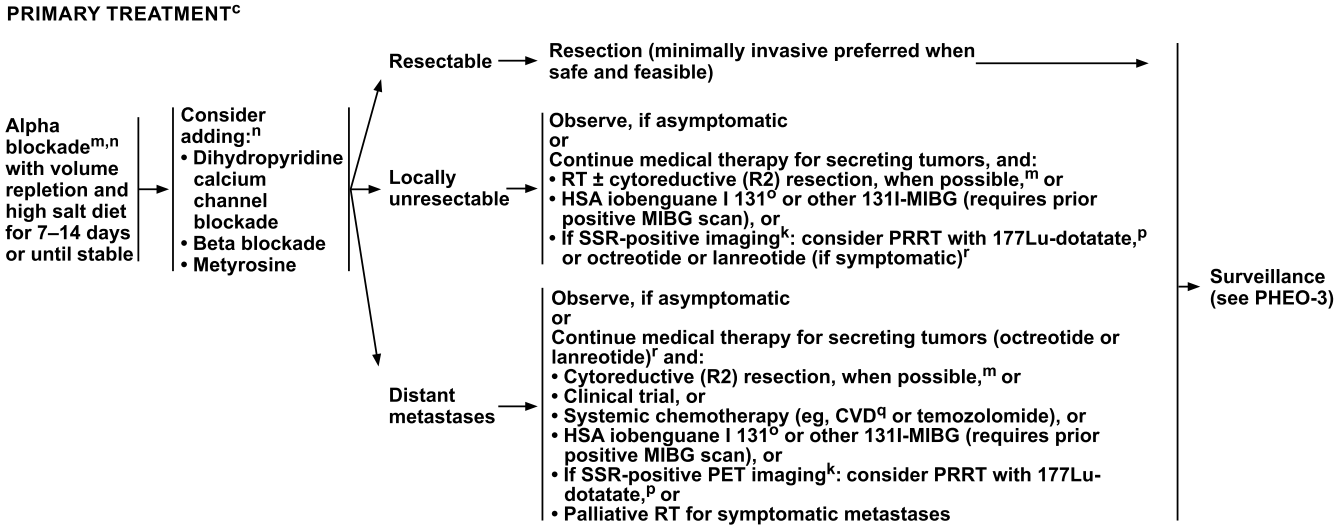
Pheochromocytomas/Paragangliomas

Pheochromocytomas are neoplasms of the chromaffin cells of the adrenal medulla in 80%–90% of cases. Ectopic/extra-adrenal pheochromocytomas that arise from sympathetic and para-aortic sympathetic ganglia are called paragangliomas.[85] Pheochromocytomas and paragangliomas occur in 0.05%–0.1% of hypertensive patients, and their combined annual incidence in the United States is estimated to be between 500 and 1,600 cases.[111] Approximately 10%–15% of pheochromocytomas and paragangliomas are malignant, but it could be up to 40%.[88,112] Pheochromocytomas release catecholamines (epinephrine and norepinephrine) and their metabolites metanephrine and normetanephrine, resulting in hypertension, arrhythmia, and/or hyperglycemia. About 40% of paragangliomas secrete catecholamines. Head and neck paragangliomas only secrete catecholamines about 5% of the time and often it is dopamine.

The peak incidence of occurrence for pheochromocytomas is between the third and fifth decades of life, but they generally occur at a younger age and are more likely to be bilateral in patients with familial disease. Paragangliomas are more likely to be malignant than pheochromocytomas in the adrenal medulla (about 40% vs 10%). Pheochromocytomas and paragangliomas associated with a familial syndrome tend to be more aggressive and more likely to metastasize than sporadic tumors.[113] In fact, a study showed that 87.5% of patients presenting with these tumors prior to age 20 harbored a germline mutation in one of several genes tested if they also had metastatic disease.[114] For those without metastases, the rate of identification of these mutations was still high, at 64.7%. The OS of patients with pheochromocytomas and paragangliomas can be heterogeneous, but a systematic review and meta-analysis of 7 studies of 738 patients reported survival to be 63% at 5 years.[115] Predicting who will go on to develop metastasis is difficult, but some studies have reported that almost half of patients have not progressed a year after diagnosis.[116] Delays at a median of 5.5 years with a range from 0.3 to 53.4 years between initial

Pheochromocytoma/Paraganglioma



[c] Consider medical alert ID for hormonally secreting pheochromocytomas and paragangliomas in situ or metastatic disease.
[k] SSR PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC.
[m] Alpha 1 selective receptor blockers include terazosin, doxazosin, and prazosin, and non-selective receptor blockers include phenoxybenzamine. Therapy for 7–14 days is recommended prior to surgical therapy. Nonselective alpha blockade phentolamine (IV) can be used intraoperatively.
[n] Alpha blockade is first-line therapy for all hormonally secreting pheochromocytomas and paragangliomas. After alpha blockade, if additional blood pressure (bp) support is needed, the addition of dihydropyridine calcium channel blockers can be used. This is not recommended as monotherapy unless the patient cannot tolerate alpha blockade. Metyrosine can also be used in addition to alpha blockade to stabilize bp. Beta blockade can be added to alpha blockade for tachycardia. B1 selective blockers or nonselective beta blockers can be used. Combination beta/alpha blockers are not recommended.
[o] HSA iobenguane I 131 is an FDA-approved option.
[p] Data are limited on the use of PRRT with 177Lu-dotatate in this setting. See Principles of PRRT with 177Lu-dotatate (NE-G*).
[q] CVD = cyclophosphamide, vincristine, and dacarbazine
[r] For symptom control, octreotide 150–250 mcg SC TID or octreotide LAR 20–30 mg IM or lanreotide 90–120 mg SC every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10–14 days after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms. For details on the administration of short-acting and/or long-acting octreotide with 177Lu-dotatate, see NE-G*.

*Available online, in these guidelines, at NCCN.org.

diagnosis and metastasis have been reported in a retrospective study spanning 55 years of patients with pheochromocytomas or paragangliomas, and many such patients survive long term after treatment of metastatic disease.[117] Thus, patients presenting during childhood, adolescence, or young adulthood require careful, lifelong surveillance (see "Surveillance of Pheochromocytomas/Paragangliomas," page 864).

Evaluation for Pheochromocytomas/Paragangliomas

A patient with possible pheochromocytoma should be evaluated with fractionated metanephrines and normetanephrines in 24-hour urine or free metanephrines in plasma. Elevated levels of metanephrines or normetanephrines are suggestive of pheochromocytoma or paraganglioma. In general, adrenal pheochromocytomas more commonly secrete metanephrines and paragangliomas secrete normetanephrines, with a few exceptions.[85] Concurrent medications should be reviewed before testing for those that interfere with plasma or blood metanephrine/normetanephrine evaluation, including acetaminophen, certain beta- and alpha-adrenoreceptor blocking drugs, serotonin-reuptake inhibitors, and monoamine oxidase inhibitors.[118] Elevations in metanephrine or normetanephrine levels that are 3 times above the upper limit of normal are diagnostic. Urine or plasma catecholamines are no longer routinely recommended for the evaluation of pheochromocytoma as 15%–20% of patients with pheochromocytoma have normal levels of urine catecholamines due to intermittent secretion in some tumors and insignificant secretion by others.[119] Measurement of serum and/or 24-hour urine fractionated catecholamines can be considered since rare tumors preferentially secrete catecholamines, and cervical paragangliomas can secrete dopamine.

Adrenal protocol CT scans (abdomen/pelvis) are recommended. Other imaging studies, including abdominal/pelvic multiphasic CT or MRI scans, SSR-based imaging (PET/CT or PET/MRI), FDG-PET/CT scans (skull base to midthigh), chest CT scans with or without contrast,

Pheochromocytoma/Paraganglioma

SURVEILLANCE[s]

Resectable disease (post-resection) →

12 wk–12 mo post-resection:[t]
- H&P, blood pressure, and markers[b]
- Consider chest CT (± contrast) and abdominal/pelvic CT or MRI with contrast

>1 y post-resection up to 10 y:
- H&P, blood pressure, and markers[b]
  - Years 1–3: every 6–12 mo[s]
  - Years 4+ up to 10 y: annually[s]
- Consider chest CT (± contrast) and abdominal/pelvic CT or MRI with contrast

>10 y:
- Consider surveillance as clinically indicated

Locally unresectable disease or Distant metastases →

Every 12 wk–12 mo:[t]
- H&P, blood pressure, and markers[b]
- Consider imaging:
  - Chest/abdominal/pelvic CT with contrast
    or
  - Chest CT (± contrast) and abdominal/pelvic MRI without contrast (if risk for hypertensive episode)
    or
  - FDG-PET/CT
    or
  - SSR-PET/CT[k] or SSR-PET/MRI[k]

[b] See Principles of Biochemical Testing (NE-C*).
[j] PET/CT or PET/MRI of skull base to mid-thigh with IV contrast when possible.
[k] SSR PET tracers include: 68Ga-DOTATATE, 64Cu-DOTATATE, 68Ga-DOTATOC.
[s] See NCCN Guidelines for Survivorship†.
[t] Earlier, if symptoms; less frequently if stable disease and no new symptoms.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

and metaiodobenzylguanidine (MIBG) scans should be performed as appropriate if metastatic or multifocal disease is suspected. CT scans are most helpful for adrenal masses and paragangliomas. However, there are some instances where extra-adrenal paragangliomas are seen better with MRI scans.

Genetic Counseling/Testing in Pheochromocytomas/Paragangliomas

Although many pheochromocytomas and paragangliomas are thought to be sporadic, increasing evidence shows that a number of pheochromocytomas and paragangliomas are in fact associated with inherited genetic syndromes.[111,120] Pheochromocytomas occur in patients with MEN2A, MEN2B, and other familial diseases such as neurofibromatosis and von Hippel-Lindau syndrome (see "Principles of Genetic Risk Assessment and Counseling," NE-E). Paragangliomas are also associated with polycythemia-paraganglioma-somatostatinoma syndrome due to somatic mutations in the *HIF2A* gene.[121,122] In addition to germline mutations associated with these syndromes (ie, *RET*, *NF1*, *VHL*), germline mutations in *SDHB*, *SDHA*, *SDHAF2*, *SDHD*, *SDHC*, *TMEM127*, *MAX*, *FH*, and *MDH2* have also been associated with an increased incidence of pheochromocytomas and paragangliomas.[112,120–126] *SDHB* gene mutations are associated with a 40%–60% risk of developing metastatic disease.[112] Patients younger than 45 years of age or those with multifocal, bilateral, or recurrent lesions are more likely to have a heritable mutation, although many individuals with a hereditary syndrome present with solitary disease and no family history.[126] Because a significant proportion of patients with a pheochromocytoma or paraganglioma have a heritable mutation,[120] genetic counseling is recommended in patients with such a diagnosis and in those with a family history of these tumors, with genetic testing when appropriate. The Endocrine Society has published guidelines that include a genetic testing decision algorithm.[85]

Individuals with known germline mutations associated with pheochromocytomas and paragangliomas should undergo lifelong biochemical and clinical surveillance, beginning around ages 6 to 8 years.[126] The type and timing of the surveillance should be based on which gene is affected and take into account known genotype-phenotype relationships. MRI may be the preferable imaging modality for tumor detection in these individuals to limit radiation exposure.

Primary Treatment of Pheochromocytomas/Paragangliomas

Surgical resection is the mainstay of treatment of both benign and malignant pheochromocytomas and paragangliomas. Surgery or stress can cause a sudden release of large amounts of catecholamines, causing very significant and sometimes life-threatening hypertension. Therefore, patients with pheochromocytomas or paragangliomas should receive preoperative alpha-adrenergic blockade with aggressive volume repletion and high-salt diet for 7 to 14 days or until stable. Alpha 1-selective receptor blockers include terazosin, doxazosin, and prazosin, and nonselective receptor blockers include phenoxybenzamine. If additional blood pressure control is needed after alpha blockade, the addition of dihydropyridine calcium channel blockers can be considered. Calcium channel blockers are not recommended as monotherapy unless the patient cannot tolerate alpha blockade. Metyrosine can be used in addition to alpha blockade to control blood pressure. Beta blockade (B1-selective blockers or nonselective beta-blockers) can also be added to alpha blockade to control tachycardia. Generally, alpha- and beta-blockers should be administered independently, and use of combination beta-/alpha-blockers is not recommended. Nonselective alpha blockade phentolamine (intravenous) can be used intraoperatively for additional blood pressure control.

Resection is the recommended treatment of patients with resectable tumors. A minimally invasive approach, when safe and feasible, is the preferred treatment of adrenal medullary tumors, including pheochromocytomas.[127–129]

For locally unresectable tumors, observation is recommended, if asymptomatic. Radiation therapy is recommended with cytoreductive resection, when possible. Alternatively, if tumors are positive on MIBG scan,[130,131] treatment with high-specific-activity (HSA) iobenguane I-131 or other iodine-131-MIBG therapy is recommended. If tumors are SSR-positive on imaging, PRRT with 177Lu-dotatate or treatment with octreotide or lanreotide (if symptomatic) may be considered. The panel advises diligence to ensure that the maximum cumulative radiation dose is not reached for these patients. In addition, medical therapy as described previously should be continued for unresectable secreting tumors.

The results of a phase 2, open-label, multicenter study investigating HSA iobenguane I-131 to treat patients with malignant, recurrent, and/or unresectable pheochromocytoma or paraganglioma[132,133] revealed that the primary endpoint, which was a reduction in antihypertension medication by at least half, was met by 25% of all patients who received at least one therapeutic dose (n=68) and 32% of patients who received 2 therapeutic doses (n=50).[134] The objective tumor response was evaluated as a secondary endpoint. Overall, 23% of patients had partial response, which went up to 30% in patients who received 2 therapeutic doses, and 68% of patients had stable disease. The median OS was 37 months. The most commonly reported side effects in patients who received any dose of HSA iobenguane I-131 were nausea, myelosuppression, and fatigue. In 2018, HSA iobenguane I-131 became an FDA-approved option for patients who have an MIBG positive scan; have unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma; and require systemic anticancer therapy.

A study of 20 patients with high SSR expressing pheochromocytoma or paraganglioma treated with 177Lu-dotatate measured the effectiveness of PRRT in controlling hypertension.[135] Most patients receiving PRRT saw no increase or reduction in medication to treat hypertension. The median PFS was 39 months and median OS was not reached with a median follow-up time of 28 months. A systematic review and meta-analysis of 201 patients with inoperable or metastatic pheochromocytomas or paragangliomas determined that treatment with PRRT led to an ORR of 25% (95% CI, 19%–32%) and a disease control rate of 84% (95% CI, 77%–89%).[136] Clinical responses were reported in 61% of patients.

An ENETS Centre study with 22 patients with progressive or metastatic pheochromocytomas or paragangliomas treated patients with PRRT with either 90Y-dotatate or 177Lu-dotatate, and 131I-MIBG.[137] Patients treated with PRRT had increased PFS and treatment response compared with 131I-MIBG treatment, but no significant differences were seen in OS. Other case studies have been presented at conferences[138–140] or published[141,142] that have also shown improvements in patients with high SSR-expressing pheochromocytoma or paraganglioma treated with 177Lu-dotatate.

When distant metastases are present, observation is recommended if asymptomatic. Medical therapy with octreotide or lanreotide should be continued for secreting tumors. For the latter, cytoreductive resection is recommended when possible. Other options for treating unresectable, metastatic disease include: (1) clinical trial; (2) systemic chemotherapy (eg, cyclophosphamide/vincristine/dacarbazine [CVD] or temozolomide)[143–147]; (3) HSA iobenguane 131I or other iodine-131-MIBG therapy after positive MIBG scan[130,131,134]; (4) if SSR-positive PET

imaging, consider PRRT with 177Lu-dotatate; or 5) palliative radiation therapy for symptomatic metastases.

A retrospective review of 52 evaluable patients treated with various systemic chemotherapy regimens for metastatic pheochromocytomas or paragangliomas showed that patients with a response to chemotherapy (reduction in symptoms, antihypertensive medications, or tumor size) had a median survival of 6.4 years and nonresponders had a median survival of 3.7 years.[144] Approximately 33% of patients exhibited a tumor response.

A review of 48 patients with pheochromocytoma or paraganglioma treated with iodine-131-MIBG therapy at 4 centers showed that, although partial responses were rare, stable disease was achieved after 83.1% of treatments.[148] A meta-analysis of 17 studies that included a total of 243 patients with malignant paraganglioma or pheochromocytoma found a stable disease rate of 52% (95% CI, 0.41–0.62) after iodine-131-MIBG therapy.[149] Partial and complete responses were seen in 27% and 3% of patients, respectively.

Surveillance of Pheochromocytomas/Paragangliomas

Surveillance intervals for patients with pheochromocytomas or paragangliomas are similar to those for other NETs. Following complete resection, history and physical should be performed and blood pressure and tumor markers should be measured after 12 weeks to 12 months, then every 6 to 12 months for the first 3 years, and then annually for up to 10 years. After 10 years, surveillance should be considered as clinically indicated. In addition, chest CT scans with or without contrast, and abdominal/pelvic CT or MRI scans with contrast can be considered. Timing for these surveillance events and procedures can be earlier if symptoms dictate or less frequently if the disease is stable and there are no new symptoms. For locally unresectable disease or distant metastases, history and physical should be performed and blood pressure and relevant markers should be measured every 12 weeks to 12 months. Chest/abdominal/pelvic CT scans with contrast, chest CT scans (with or without contrast) and abdominal/pelvic MRI scans without contrast (if the patient is at risk for a hypertensive episode), FDG-PET/CT scans, or SSR-based imaging can be considered. In addition, individuals with hereditary paraganglioma/pheochromocytoma may require more frequent and longer follow-up (see "Principles of Genetic Risk Assessment and Counseling," NE-E in the algorithm).

Summary

In the 2021 update, a new section was created to provide recommendations for patients with well-differentiated G3 NETs. A principles of genetic risk assessment section was also added. Because NETs can be associated with inherited genetic syndromes, genetic counseling and testing should be recommended, as appropriate. Recent successes have shown that large randomized controlled trials studying treatments for NETs can provide practice-changing results. Rigorous studies will allow continued progress in the development of improved treatments for patients with NETs.

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Individual Disclosures for the NCCN Neuroendocrine and Adrenal Tumors Panel

Panel Member	Clinical Research Support/Data S afety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Al B. Benson, III, MD	None	None	None	Medical Oncology
Emily Bergsland, MD	Merck & Co., Inc.	Advanced Accelerator Applications	MORE Health Inc.	Medical Oncology
Lawrence S. Blaszkowsky, MD[a]	None	None	None	Hematology/Hematology Oncology
Pamela Brock, MS	Ohio State University	None	None	Cancer Genetics
Jennifer Chan, MD[a]	Eli Lilly and Company; Exelixis Inc.; Merck & Co., Inc.; sanofi-aventis U.S.; and Tarveda Therapeutics	Advanced Accelerator Applications; Bayer HealthCare; Lexicon Pharmaceuticals, Inc.; and Pfizer Inc.	None	Medical Oncology
Satya Das, MD, MSCI	None	Cancer Expert Now, and Ipsen	Ipsen	Medical Oncology
Paxton V. Dickson, MD	None	None	None	Surgery/Surgical Oncology
Paul Fanta, MD	None	None	None	Hematology/Hematology Oncology, and Medical Oncology
Thomas Giordano, MD, PhD	None	None	None	Pathology
Whitney S. Goldner, MD	Roche Laboratories, Inc.	None	None	Endocrinology
Thorvardur R. Halfdanarson, MD	Advanced Accelerator Applications; Agios, Inc.; Basilea Pharmaceutica AG; Thermo Fisher Scientific; Turnstone Biologics Inc.	Advanced Accelerator Applications; Curium;Ipsen; ITM; Lexicon Pharmaceuticals, Inc.; and ScioScientific, LLC	None	Hematology/Hematology Oncology; Internal Medicine; and Medical Oncology
Daniel Halperin, MD	Advanced Accelerator Applications; Genentech, Inc.; Incyte Corporation; Tarveda Therapeutics; TerSera Therapeutics, LLC; and Thermo Fisher Scientific	Advanced Accelerator Applications; Chimeric Therapeutics; Curium; Ipsen; Isotopen Technologien München AG; and McGraw Hill	None	Medical Oncology
Jin He, MD, PhD	None	None	None	Surgery/Surgical Oncology
Anthony Heaney, MD, PhD	Camarus AB; Chiasma, Inc.; Corcept Therapeutics; Ipsen; and Strongbridge Biopharma	Chiasma, Inc., and Corcept Therapeutics	None	Endocrinology
Martin J. Heslin, MD	None	None	Best Doctors, Inc.	Surgery/Surgical Oncology
Fouad Kandeel, MD, PhD	None	None	None	Endocrinology
Arash Kardan, MD	None	None	None	Nuclear Medicine
Sajid A. Khan, MD	None	None	None	Surgery/Surgical Oncology
Boris W. Kuvshinoff, II, MD, MBA	None	None	None	Surgery/Surgical Oncology
Christopher Lieu, MD	None	HalioDx, and Pfizer Inc.	None	Medical Oncology
Kimberly Miller, RN	None	None	None	Patient Advocacy
Venu G. Pillarisetty, MD	AstraZeneca Pharmaceuticals LP; Ipsen; Merck & Co., Inc.; and NGM Biopharmaceuticals, Inc.	Takeda Pharmaceuticals North America, Inc.	None	Surgery/Surgical Oncology
Diane Reidy, MD	Ipsen; Lexicon Pharmaceuticals, Inc.; Merck & Co., Inc.; and Novartis Pharmaceuticals Corporation	None	None	Medical Oncology
Sarimar Agosto Salgado, MD	Bayer HealthCare, and Lilly/Loxo Oncology	Blueprint Medicines, and Eisai Inc.	None	Endocrinology, and Internal Medicine
Manisha H. Shah, MD	Eli Lilly and Company, and Merck & Co., Inc.	None	None	Medical Oncology
Shagufta Shaheen, MD	None	Ipsen, and Virtual Advisory Board for ASCO Virtual Direct™ Highlights San Francisco	None	Medical Oncology
Heloisa P. Soares, MD, PhD	None	Advanced Accelerator Applications; Exelixis Inc.; Ipsen; Lexicon Pharmaceuticals, Inc.; Natera, Inc.; and QED Therapeutics	None	Medical Oncology
Michael C. Soulen, MD	Guerbet LLC; Pfizer Inc.; and Sirtex Medical	Genentech, Inc., and Instylla, Inc.	None	Interventional Radiology
Jonathan R. Strosberg, MD	None	None	Novartis Pharmaceuticals Corporation	Medical Oncology
Craig R. Sussman, MD	None	None	None	Endocrinology, and Internal Medicine
Nikolaos A. Trikalinos, MD	None	None	None	Hematology/Hematology Oncology, and Medical Oncology
Nataliya A. Uboha, MD, PhD	EMD Serono, Inc.; Ipsen; and Taiho Pharmaceutical Co., Ltd.	Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Incyte Corporation; QED Therapeutics; and Taiho Pharmaceutical Co., Ltd.	None	Medical Oncology
Namrata Vijayvergia, MD	None	None	HalioDx, and Lexicon Pharmaceuticals, Inc.	Medical Oncology
Terence Wong, MD, PhD	None	None	None	Diagnostic Radiology, and Nuclear Medicine

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Lawrence S. Blaszkowsky, MD: Pfizer Inc.
Jennifer Chan, MD: Merck & Co., Inc.