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Bronchial carcinoid tumors

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INTRODUCTION — Bronchial carcinoid tumors are a rare group of pulmonary neoplasms that are characterized by neuroendocrine differentiation and relatively indolent clinical behavior. Although originally referred to as bronchial adenomas, these tumors are now recognized as malignant neoplasms because of their potential to metastasize.

Like other carcinoid tumors, bronchial carcinoids are thought to be derived from the diffuse neuroendocrine system, which is made up of peptide- and amine-producing cells which have migrated from the embryologic neural crest. Carcinoids can arise at a number of sites throughout the body, including the thymus, lung, gastrointestinal tract, and ovary. The gastrointestinal tract is the most frequently involved site, while lung is the second most common. (See "Clinical characteristics of primary carcinoid tumors").

The clinical features, diagnosis, and treatment of pulmonary carcinoid tumors will be discussed here. Carcinoid tumors arising in other sites are discussed elsewhere. (See "Clinical characteristics of primary carcinoid tumors" and see "Treatment of carcinoid tumors and the carcinoid syndrome").

EPIDEMIOLOGY AND RISK FACTORS — Bronchial carcinoid tumors account for approximately 1 to 2 percent of all lung malignancies in adults and roughly 20 to 30 percent of all carcinoid tumors [1-4]. Bronchial carcinoids are the most common primary lung neoplasm of children, typically presenting in late adolescence. Typical carcinoids are about four times more common than atypical carcinoids.

Globally, incidence rates range from 0.2 to 2 per 100,000 population per year, and most series suggest a higher incidence in women as compared to men, and in whites compared to blacks [1-3,5-7].

- In a nationwide, registry-based Swedish series, the annual incidence rates of bronchial carcinoid among men and women were 0.2 and 1.3 per 100,000 population [3].
- In data from the United States Surveillance, Epidemiology and End Results (SEER) database, the annual incidence rates of bronchial carcinoids among white males and white females per 100,000 population between 1992 and 1999 were 0.52 and 0.89, respectively [2]. The corresponding values for black males and black females were 0.39 and 0.57, respectively.

Although several reports suggest that the incidence of bronchial carcinoid tumors might be increasing over time [2,3,7] , this is at least partly related to the heightened use of advanced medical viewing techniques that detect asymptomatic tumors.

The average age of an adult diagnosed with a typical bronchial carcinoid tumor is 45 years, while in many series, individuals with atypical carcinoids generally are approximately 10 years older [8-10] .

Risk factors — Whether there is an association between bronchial carcinoids and smoking is unclear. In many studies, between one-third and two-thirds of all patients have been smokers [11-15] . Some note a higher prevalence of smoking in patients with atypical carcinoids [5,14] .

Despite these reports, causality is not proven, and the epidemiologic data linking smoking with the development of atypical carcinoids are nowhere near as convincing as they are for bronchogenic cancers. (See "Cigarette smoking and other risk factors for lung cancer").

No other known carcinogens or exposure to environmental agents has been implicated in carcinogenesis.

Inherited predisposition — Although rare, familial carcinoids are reported. Patients with the autosomal dominant syndrome of multiple endocrine neoplasia type 1 (MEN 1) have a high frequency of endocrine malignancies, and foregut carcinoids (ie, thymus, lung, stomach, or duodenum) arise in approximately 2 percent of cases. (See "Definition and genetics of Multiple Endocrine Neoplasia type 1").

Familial pulmonary carcinoids not associated with the MEN syndrome have also been described [16] .

CLASSIFICATION, HISTOLOGY, AND HISTOCHEMISTRY — Histologically, bronchial carcinoids are part of a spectrum of neuroendocrine tumors arising in the lung which are characterized by strikingly different biologic behavior. At one end of the spectrum are typical carcinoids, which are low-grade, slowly-growing neoplasms which rarely metastasize to extrathoracic structures. At the other end of the spectrum are the high-grade neuroendocrine tumors, typified by small cell lung cancer (SCLC), which behave aggressively, with rapid tumor growth and early distant dissemination. The biologic behavior of atypical carcinoids is intermediate between typical carcinoids and SCLC. (See "Pathobiology and staging of small cell carcinoma of the lung").

Despite their heterogeneous clinical behavior, lung tumors with neuroendocrine differentiation share certain morphologic and biochemical characteristics. These include:

- The capacity to synthesize neuropeptides
- The presence of submicroscopic cytoplasmic dense core (neuroendocrine) granules, which can be visualized by electron microscopy

WHO classification — Pulmonary neuroendocrine tumors have been the subject of considerable controversy, resulting in multiple competing and confusing classification schemes. In the 2004 World Health Organization (WHO) classification, the spectrum of neuroendocrine tumors of the lung ranges from hyperplastic neuroendocrine cell lesions (carcinoid tumorlets and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia [DIPNECH]) to the high-grade small cell (SCLC) and large cell neuroendocrine tumors ([show table 1](#)). (See "Pathology of lung malignancies").

However, this classification scheme has not been widely adopted in the US, for unclear reasons [[17](#)].

Histology — Typical low-grade carcinoid tumors are composed of cytologically bland cells containing regular round to oval nuclei with finely dispersed chromatin and inconspicuous small nucleoli. The cells are usually polygonal in shape and are arranged in distinct organoid, trabecular, or insular growth patterns with a delicate vascular stroma ([show histology 1A-1B](#)). Mitotic figures are scarce (<2 per 10 high-powered fields [HPF]), and necrosis is not seen.

Peripheral typical carcinoids have a prominent spindle cell growth pattern, and up to 75 percent have foci of neuroendocrine cell hyperplasia (DIPNECH) and/or tumorlets (carcinoid foci smaller than 5 mm in diameter) in the adjacent lung parenchyma. Coexpression of these preinvasive neuroendocrine cell lesions does not seem to affect prognosis, although the number of series with long-term follow-up is limited [[18,19](#)]. (See "Pathology of lung malignancies", section on DIPNECH and carcinoid tumorlets).

Histologic criteria for intermediate-grade atypical carcinoids include the presence of carcinoid morphology and either necrosis ([show histology 2A-2B](#)) or 2 to 10 mitoses per 10 HPF.

Cytologic atypia is also characteristic but insufficiently diagnostic in the absence of these features. However, at the individual patient level, none of these features enables a reliable prediction of clinical outcome [[20](#)].

Detailed discussions of the pathology of neuroendocrine lung tumors are presented separately. (See "Clinical characteristics of primary carcinoid tumors", section on Pathology, and see "Pathology of lung malignancies", section on Non-small cell neuroendocrine tumors).

Atypical carcinoids present more often with hilar or mediastinal nodal metastases (20 to 60 percent versus 4 to 27 percent), and they have a higher recurrence rate compared with typical carcinoids. (See "Prognosis" below).

Histochemistry — Most carcinoids can be tentatively identified on routine light microscopy. Histologic staining patterns for secreted products and certain cytoplasmic proteins provide confirmatory support for the diagnosis.

Historically, one of the most important was silver staining. Like other foregut carcinoids, bronchial carcinoids take up silver but do not reduce it (argyrophilic reaction); other carcinoids both take up and reduce silver (argentaffin reaction) ([show table 2](#)). More recently,

immunohistochemical identification of secreted and cytoplasmic products such as synaptophysin, neuron-specific enolase (NSE) and chromogranin has now replaced silver staining as the most reliable method to confirm neuroendocrine differentiation [21] .

CLINICAL FEATURES

Presenting signs and symptoms — The majority of tumors arise in the proximal airways, and most are symptomatic from an obstructing tumor mass or bleeding due to its hypervascularity. Patients may have a cough or wheeze, hemoptysis, chest pain, or recurrent pneumonia in the same pulmonary segment or lobe due to bronchial obstruction. The diagnosis is often delayed, and patients may receive several courses of antibiotics to treat recurrent pneumonia before the carcinoid is diagnosed.

The one-fourth of patients whose tumors originate peripherally in the lung are usually asymptomatic. These tumors are frequently discovered on a routine chest x-ray.

Fewer than 5 percent exhibit hormonally-related symptoms such as the carcinoid syndrome, reflecting the low incidence of hepatic metastases [21] .

Peptide production and paraneoplastic syndromes — Bronchial carcinoid tumors are thought to arise from a specialized bronchial cell (the Kulchitsky cell) which belongs to a diffuse system of neuroendocrine cells. These cells, which include the enterochromaffin cells of the gastrointestinal tract (the presumed cell of origin for gastrointestinal carcinoids), have the ability to take up and modify amine precursors like L-DOPA or 5-hydroxytryptophan. As a group, tumors that arise from these cells (eg, carcinoids, Merkel cell carcinomas, pheochromocytomas, medullary thyroid carcinomas, and pancreatic neuroendocrine [islet cell] tumors) have been referred to as amine precursor uptake and decarboxylation (APUD) tumors (or apudomas). All of these tumors can synthesize, store, and secrete biologically active neuroamines and neuropeptides.

Not all carcinoids secrete high levels of bioactive peptides. In contrast to midgut tumors, foregut carcinoids (including those arising in the lung) generally have a low serotonin content ([show table 2](#)). This is because foregut carcinoids often lack aromatic amino acid decarboxylase and can't make serotonin and its metabolites ([show figure 1](#)).

Although they can produce a variety of other peptides and hormones within the cell (gastrin releasing peptide [bombesin], 5-hydroxytryptophan, and chromogranins), bronchial carcinoids only occasionally secrete bioactive amines. As a result, elevated plasma or urinary hormone levels are rarely detected.

Serum levels of chromogranin A (CGA) are lower with bronchial carcinoids than they are with other neuroendocrine tumors, and they overlap with those seen in patients who have nonmalignant conditions associated with increased CGA levels (ie, chronic renal failure, proton pump inhibitor therapy, chronic atrophic gastritis) [22] . However, measurement of serum CGA levels can be useful to follow disease activity in the setting of advanced or metastatic disease

[22-25] . (See "Clinical features of the carcinoid syndrome" and see "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Biochemical monitoring).

Carcinoid syndrome — Carcinoid syndrome is caused by systemic release of vasoactive substances such as serotonin. Acute symptoms include cutaneous flushing, diarrhea, and bronchospasm; long-term sequelae of prolonged elevated hormone levels include venous telangiectasias, right-side predominant valvular heart disease, and fibrosis in the retroperitoneum and other sites. (See "Clinical features of the carcinoid syndrome" and see "Carcinoid heart disease").

As noted above, bronchial carcinoids produce lesser quantities of serotonin than do midgut carcinoids, accounting for a lower rate of carcinoid syndrome (1 to 5 percent overall) ([show table 2](#)). In localized disease (the vast majority of cases of typical carcinoid), carcinoid syndrome is encountered only rarely with tumors of large size (>5 cm) [26] . However, it is encountered in over 80 percent of patients with liver metastases from bronchial carcinoid.

When the carcinoid syndrome occurs in the setting of a bronchial carcinoid, symptoms may be atypical, with episodes of flushing and related manifestations that are particularly prolonged and/or severe and accompanied by other symptoms. These include disorientation, anxiety tremor, periorbital edema, lacrimation, salivation, hypotension, tachycardia, diarrhea, dyspnea, asthma, and edema. (See "Clinical features of the carcinoid syndrome", section on Bronchial carcinoid variant syndrome).

For the rare patient in whom carcinoid syndrome is suspected, urinary excretion of 5-HIAA may be elevated [23,24] , but it is not as sensitive a test as it is in patients with midgut carcinoids. Bronchial carcinoids occasionally secrete 5-hydroxytryptophan, but assays for 5-hydroxytryptophan are not available in clinical laboratories in the United States. Measurement of urinary serotonin levels may be of value. It is presumed that DOPA decarboxylase in the renal parenchyma converts the 5-hydroxytryptophan to serotonin in these patients, resulting in high levels of urinary serotonin. (See "Diagnosis of the carcinoid syndrome and tumor localization", section on Biochemical testing for the carcinoid syndrome).

Carcinoid crisis — Rarely, biopsy or manipulation of an actively secreting bronchial carcinoid can induce a carcinoid crisis (acute carcinoid syndrome) due to massive systemic release of bioactive mediators [27,28] . Patients acutely develop flushing, diarrhea, and bronchoconstriction, along with other severe manifestations, which can include acidosis, severe hypertension or hypotension, tachycardia, or myocardial infarction. The outcome may be fatal. (See "Treatment of carcinoid tumors and the carcinoid syndrome", section on Carcinoid crisis).

In contrast to other carcinoids (particularly in the setting of extensive liver metastases), the risk of a carcinoid crisis with pulmonary carcinoids is so low that most clinicians do not recommend prophylactic administration of octreotide prior to tumor manipulation (biopsy or resection). Nevertheless, all clinicians caring for these patients should be aware of the potential for carcinoid crisis with manipulation of an actively secreting tumor and the life-saving benefits of octreotide in this setting. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Prevention and management of carcinoid crisis).

Cushing's syndrome — Both typical and atypical bronchial carcinoids can cause Cushing's syndrome due to ectopic production of adrenocorticotrophic hormone (ACTH) [29-32] . Bronchial carcinoid is the most common cause of ectopic ACTH production; other malignant causes include SCLC and disseminated neuroendocrine tumors of unknown primary site. (See "Overview of the risk factors, pathology, and clinical manifestations of lung cancer" and see "Neuroendocrine carcinoma of unknown primary site").

Symptoms of Cushing's syndrome are seen in 1 to 2 percent of patients with bronchial carcinoid tumors and can be the initial reason for seeking medical attention. The onset is usually acute, and hypokalemia is often present. The diagnosis may be difficult because the production of ACTH by bronchial carcinoids can be suppressed by dexamethasone, unlike other tumors that produce ectopic ACTH [33] . (See "Establishing the cause of Cushing's syndrome" and see "Dexamethasone suppression tests", section on Low-dose dexamethasone suppression tests).

The majority of bronchial carcinoid tumors in patients who present with Cushing's syndrome are small (<2 cm), making it even more difficult to establish the correct diagnosis [34,35] . High-resolution CT with 1 mm sections may be particularly helpful in such cases to identify the primary tumor ([show figure 2](#)). Another option is somatostatin receptor scintigraphy [36] . (See "Other imaging procedures" below).

At least some data suggest that ACTH-producing bronchial carcinoids are more aggressive than hormonally quiescent tumors [37,38] . However, others conclude that outcomes are not worse as long as patients undergo formal anatomic resection with complete mediastinal lymphadenectomy [35] .

Acromegaly — Acromegaly from the ectopic production of growth hormone releasing hormone (GHRH) is a rare manifestation of a bronchial carcinoid [9,39-46] . However, bronchial carcinoid tumors are the most common cause of extrapituitary GHRH secretion. (See "Diagnosis of acromegaly", section on Other causes of acromegaly).

DIAGNOSIS AND STAGING

Radiographic appearance — Approximately 75 percent of bronchial carcinoids have an abnormal chest x-ray. Most tumors appear as round or ovoid opacities that range in size from 2 to 5 cm, and may be associated may be a hilar or perihilar mass ([show figure 2](#)) [47-49] . If a central tumor results in bronchial obstruction, atelectasis and mucoid impaction are the visible features. Cavitation is rare. Pleural effusions are unusual but may occur with postobstructive pneumonia.

The remainder present in the periphery as an asymptomatic solitary pulmonary nodule ([show figure 3](#) and [show figure 4](#)).

CT scan — Compared to a chest x-ray, CT provides better resolution of tumor extent, location, and the presence or absence of mediastinal adenopathy. CT gives an excellent morphologic characterization of peripheral and especially centrally located carcinoids, which may be purely intraluminal (polypoid configuration), exclusively extraluminal, or more frequently, a mixture of intraluminal and extraluminal components (an "iceberg" lesion). CT may also be helpful for

differentiating tumor from postobstructive atelectasis or bronchial obstruction-related mucoid impaction.

Tumors may have lobulated or irregular borders and punctate or eccentric calcification [50,51] . Contrast-enhanced CT scans frequently show marked enhancement due to the vascular nature of the tumors.

Between 5 and 20 percent of typical bronchial carcinoids are associated with hilar or mediastinal adenopathy, but lymphadenopathy may also represent a local inflammatory reaction. While the sensitivity of CT for detecting hilar or mediastinal nodes is high, specificity is as low as 45 percent [24] . The positive predictive value of CT-detected lymphadenopathy as an indication of nodal metastases was only 20 percent in one study [52] .

Bronchoscopy and biopsy — About three-fourths of bronchial carcinoids are centrally located and amenable to biopsy at the time of bronchoscopy. The bronchoscopic appearance is a typically pink to red vascular mass with intact overlying bronchial epithelium. Carcinoids are generally attached to the bronchus by a broad base but can be polypoid and create a ball-valve effect (show picture 1).

The bronchoscopic appearance may be sufficiently characteristic for an experienced bronchoscopist to make a presumptive diagnosis, although it is preferable that brushings or biopsy be performed to confirm the diagnosis.

Cytologic study of bronchial brushings is more sensitive than sputum cytology, but the diagnostic yield of cytology is low overall (4 to 63 percent) [53-55] . The intact bronchial mucosa overlying the carcinoid tumor prevents cells from exfoliating. Furthermore, the cells may be too few in number or benign in cytologic appearance for an accurate diagnosis. The preoperative diagnosis of atypical carcinoid is particularly difficult.

Bronchial carcinoids are vascular, and there has been concern for bleeding in the past, particularly after flexible bronchoscopy with biopsy [56] . However, in many contemporary series, the incidence of serious bleeding complications during bronchoscopic biopsy is very low [5,24,57] . The administration of a diluted epinephrine solution before and after biopsy of a suspected endobronchial carcinoid may have reduced the risk of severe bleeding. (See "Flexible bronchoscopic equipment and procedures").

Peripheral tumors — For peripheral carcinoids that present as solitary pulmonary nodules, CT-guided transthoracic needle aspiration is often the initial diagnostic maneuver. The primary risk with this approach is pneumothorax. Sometimes, patients with a solitary pulmonary nodule proceed directly to surgical excision if the likelihood of malignancy is high. (See "Diagnostic evaluation and initial management of the solitary pulmonary nodule").

Staging system — Pulmonary carcinoids are generally staged using the TNM classification for bronchogenic lung carcinomas (show table 3). Typical carcinoid tumors most commonly present as stage I tumors, while more than one-half of atypical carcinoids are stage II (bronchopulmonary nodal involvement) or III (mediastinal nodal involvement) at presentation.

However, the prognostic relevance of the current TNM staging system is questionable, particularly for typical carcinoids. Larger tumors (eg, T3N0, stage IIB) have a similar prognosis as do stage IA lesions, and 10-year survival is close to 90 percent even with N1 or N2 disease. The proposed modifications for the 7th edition ([show table 4](#) and [show table 5](#)) are better for predicting prognosis for bronchial carcinoids [58], and the International Association for the Study of Lung Cancer (IASLC) has recommended that this version be applied to this set of tumors.

Other imaging procedures — A number of other imaging procedures have a more limited role in patients suspected of having a bronchial carcinoid tumor but are useful in selected patients:

MRI — Preoperative MRI may be needed to differentiate a small contrast-enhancing peripheral carcinoid from pulmonary vessels, or to characterize vascular involvement by a centrally located lesion. The scans characteristically show high signal intensity on T2-weighted images and short T1-inversion-recovery images [59].

Somatostatin receptor scintigraphy — Approximately 80 percent of bronchial carcinoids express somatostatin receptors and can be imaged with radiolabeled octreotide (indium-111 pentetreotide, Octreoscan) [21,52,60-62]. However, specificity is limited because scintigraphy is positive in many other tumors, granulomas, and autoimmune diseases. (See "Localization of pancreatic endocrine tumors (islet-cell tumors)", section on Somatostatin-receptor scintigraphy).

One benefit of somatostatin receptor scintigraphy (SRS) over other modalities is that it can image the whole body and identify metastatic disease, particularly outside the lung [52]. Guidelines from the National Comprehensive Cancer Network (NCCN) suggest "considering" SRS in patients with a bronchial carcinoid. However, due to the rarity of extrathoracic metastatic disease (5 percent in one series of 525 bronchial carcinoids [1]), we do not routinely order preoperative SRS unless there is a suspicion for metastatic disease. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Somatostatin receptor scintigraphy).

PET scans — Positron emission tomography (PET) scanning with fluorodeoxyglucose (FDG) as a means of identifying a solitary pulmonary nodule as a carcinoid has yielded conflicting results, probably related to the small size of these tumors and the fact that they are often hypometabolic [12,63-65]. In a retrospective review of 16 patients with surgically resected bronchial carcinoids, PET detected 12 (75 percent) [63]. (See "Diagnostic evaluation and initial management of the solitary pulmonary nodule").

The use of other tracers, such as 11C-L-DOPA and 11C-5-hydroxytryptophan (11C-5-HT), improves sensitivity for imaging neuroendocrine tumors [66]. In a study of 42 patients (including seven bronchial carcinoids), 11C-5-HT PET scanning detected more tumor lesions than somatostatin receptor scintigraphy or CT. The drawback is the short half-life of 20 minutes of the compound, which necessitates a cyclotron adjacent to the imaging facility. Because of this limitation, neither of these compounds is in routine clinical use.

Liver imaging — The most common metastatic site with all carcinoid tumors is the liver. If metastatic disease is suspected, an abdominal CT scan or somatostatin receptor scintigraphy (SRS) may be ordered to rule out liver metastases. CT scans should be performed both before and after the administration of IV contrast, because carcinoid liver metastases are often hypervascular, becoming isodense relative to the liver parenchyma after contrast administration.

Liver MRI is more sensitive than either CT or SRS for the detection of hepatic metastases. Many authorities now consider MRI to be the imaging study of choice for the detection of metastatic carcinoid. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Magnetic resonance imaging).

None of these studies is recommended preoperatively in patients who are thought to have an isolated bronchial carcinoid. Typical pulmonary carcinoid tumors only rarely metastasize. While atypical carcinoid tumors have a greater tendency to metastasize, the diagnosis is almost never made preoperatively.

TREATMENT AND PROGNOSIS — Surgical resection is the preferred treatment approach for patients whose overall medical condition and pulmonary reserve will tolerate it. For patients whose condition does not permit complete resection and for exceptional cases where the lesion is entirely intraluminal, bronchoscopic resection may be an alternative. (See "Endobronchial management" below).

Surgical resection — Surgery is the treatment of choice for carcinoid tumors and the only therapeutic option offering a real chance of cure. The goal is en bloc resection of the entire neoplasm with preservation of as much functional lung as possible. Attempts to preserve lung parenchyma by the use of bronchoplastic techniques (eg, sleeve, wedge, or flap resection) to avoid lobectomy, bilobectomy, or pneumonectomy are justified and safe [67-69] .

Since carcinoids, unlike bronchogenic carcinomas, tend not to spread submucosally, a surgical margin as small as 5 mm is considered adequate. Intraoperative frozen section analysis is critical to the success of this approach. Although long-term survival has been reported in patients with positive margins [56,68] , wider resections should always be performed if there are positive margins [67,70] .

- Proximal tumors — For polypoid tumors of the main-stem bronchus or bronchus intermedius, a simple bronchotomy with wedge or sleeve resection of the bronchial wall and complete preservation of distal lung parenchyma could be performed [71] . However, such completely parenchyma-sparing procedures are only rarely possible because of the frequency of "iceberg" lesions (in which the tumor appears entirely intraluminal bronchoscopically but has a significant extraluminal component that is evident with high-resolution CT scanning). (See "CT scan" above).

Tumors with more extensive central involvement, those that are associated with severe distal parenchymal disease (ie, nonfunctioning lung parenchyma), and atypical carcinoids require more extensive surgery (eg, lobectomy or pneumonectomy).

- Peripheral tumors — For peripheral lesions, the ideal surgical approach is debated, and there is no consensus. Segmental sleeve resections are associated with a greater risk of postoperative stenosis compared with bronchoplastic procedures in wider bronchial segments. This has led some to advocate lobectomy in the case of a tumor involving the orifice of a segmental bronchus, while others suggest that a more limited resection (eg, wedge resection or segmentectomy) is appropriate for typical carcinoids because of the low likelihood of a local recurrence [72] .
- Lymph node dissection — Between 5 and 20 percent of typical carcinoids, and 30 to 70 percent of atypical carcinoids metastasize to lymph nodes [21] . A complete mediastinal lymph node dissection at the time of initial treatment is indicated, with surgical resection of nodal metastasis whenever feasible. Metastatic involvement of mediastinal lymph nodes does not preclude a full surgical resection or cure.

Prognosis — Typical bronchial carcinoids have an excellent prognosis. Reported five-year survival rates are 87 to 100 percent; the corresponding rates at 10 years are 82 to 87 percent (show table 4) [5,10,21,24,72-78] .

The prognostic impact of nodal involvement for typical bronchial carcinoids is controversial. Some studies show a worse outcome [79,80] , while many do not [18,81,82] . Incomplete resection is the only widely accepted feature associated with negative prognostic significance.

Atypical carcinoids have a greater tendency to metastasize (16 and 23 percent in two large series [78,83]) and to recur locally (3 and 23 percent in the same two series [78,83]). Five-year survival rates range widely from 30 to 95 percent; the corresponding rates at 10 years are 35 to 56 percent (show table 6) [10,11,21,24,74,76,77,80,81,84-86] .

In contrast to typical carcinoids, most series report an adverse influence of nodal metastases on prognosis [73,76,83,84] . This is best illustrated by the experience at the Mayo Clinic [73] . Nineteen of 23 patients with typical bronchial carcinoids and lymph node involvement (83 percent) remained alive and well, while four failed distantly, two of whom died. In contrast, only four of the 11 patients with atypical tumors and lymph node involvement were alive without disease, while seven developed distant metastases and six died.

Adjuvant therapy — The role of adjuvant therapy after complete resection of a bronchial carcinoid is undefined. Due to their favorable long-term outcome even in the presence of mediastinal nodal metastases, most authorities agree that adjuvant therapy is not indicated for completely resected, typical bronchial carcinoids [70] .

In contrast, the worse long-term outcomes among patients with atypical carcinoids and mediastinal (N2) node disease have led some (including the National Comprehensive Cancer Network [NCCN] [87]) to suggest postoperative adjuvant therapy with chemotherapy, radiation therapy (RT), or both [24,88-92] . However, many of the series which purport to show a benefit for adjuvant therapy included patients with large cell neuroendocrine tumors whose outcome is significantly worse than that of patients with atypical carcinoids [76] . The role of chemotherapy and radiation in the setting of small cell and large cell neuroendocrine lung cancers is discussed

elsewhere. (See "Thoracic radiotherapy in the treatment of limited stage small cell lung cancer" and see "First-line chemotherapy for small cell lung cancer").

There are no prospective trials that directly address the benefit of adjuvant therapy for patients with bronchial carcinoids (typical or atypical), and there is only scant experience from a single-institution retrospective series. The following represents the range of findings:

- A report from Sloan Kettering Cancer Center included 25 patients with node-positive disease (12 typical and 13 atypical carcinoids) [82]. Nine of the 15 patients with N2 disease received adjuvant RT. The five-year overall survival rate was 75 percent, and it was not better in those who received adjuvant RT. The use of RT also did not influence the failure pattern; most recurrences were distant and correlated with cell type.
- M D Anderson reported their experience in 73 surgical patients with bronchial carcinoids, seven of whom received adjuvant RT and/or chemotherapy because of positive margins, local invasion, and/or lymph node involvement [92]. Only one of the seven patients who underwent surgery followed by RT was alive without evidence of disease 10 years later.
- In an Italian series of 42 patients with pulmonary carcinoids (26 typical, 16 atypical), RT and/or systemic therapy (four cycles of cisplatin and etoposide) was administered to all seven patients with stage III disease and to one patient who had a T3N1 tumor (show table 3) [24]. Despite the use of adjuvant therapy, five of the seven patients who had received adjuvant therapy recurred and died of their disease, all of whom had atypical histology. Among the four patients who recurred after systemic chemotherapy, all failed with distant disease, none locally.

Summary — Consensus guidelines from the National Comprehensive Cancer Network (NCCN) suggest the use of chemotherapy and radiation therapy for resected stage II or III (show table 3) atypical carcinoids but not for typical carcinoids [93].

However, due to the lack of data and uncertainty as to benefit, we do not routinely recommend adjuvant therapy for completely resected typical or atypical carcinoids, with or without regional nodal involvement. Radiation therapy is a reasonable option for atypical carcinoids if gross residual disease remains after surgery [88], although whether this improves outcomes is unproven.

Endobronchial management — Bronchoscopy is the procedure of choice to obtain a preoperative histologic diagnosis. (See "Bronchoscopy and biopsy" above). In some cases, a polypoid tumor may appear entirely intraluminal and amenable to bronchoscopic resection. However, endobronchial resection with a Nd:YAG laser is not considered curative for the vast majority of patients with central lesions because most tumors extend into or through the wall of the bronchus. Bronchoscopic resection may be considered in the following clinical scenarios:

- For patients with central airway occlusion who are poor surgical candidates, bronchoscopic laser resection is a valuable palliative maneuver [94-96]. (See "Overview of the management of central airway obstruction", section on Laser therapy).

- Laser bronchoscopic removal of an obstructing lesion may be useful for the surgeon to plan the most appropriate surgical procedure [97] . (See "Surgical resection" above).
- Bronchoscopic resection alone may provide prolonged recurrence-free survival for highly selected patients with a polypoid bronchial carcinoid [15,74,80,98] . These are patients who present with a polypoid intraluminal tumor, good visualization of the distal tumor margin, and no evidence of bronchial wall involvement or suspicious lymphadenopathy by high resolution CT.

In the largest series of 72 patients treated with this approach (57 typical and 15 atypical carcinoids), initial bronchoscopic management resulted in complete tumor eradication in 33 (46 percent) [15] . Surgery was required in 37 (including 11 of the 15 atypical carcinoids), two for delayed recurrences at nine and 10 years. At a median follow-up of 65 months, 66 (92 percent) remained alive, and only one of the deaths was tumor-related.

Close posttreatment follow-up is an integral component of bronchoscopic resection. In the series described above, patients underwent high-resolution CT and flexible bronchoscopy with bronchoscopic ultrasonography within six weeks after endobronchial resection and referred for surgery for any evidence of residual disease [15] . Repeat evaluation was performed every six months for two years and annually thereafter.

- The utility of bronchoscopic cryotherapy was addressed in a small series of eighteen isolated endoluminal typical bronchial tumors [99] . There was only a single recurrence seven years after initial treatment, and the procedure was safe and not associated with later development of bronchial stenosis.

Summary — Bronchoscopic resection is not considered standard potentially curative treatment by many clinicians because of the concern about leaving substantial tumor behind either within or beyond the endobronchial lumen. Because of the slow growing nature of carcinoid tumors, it may take years before a recurrence develops. Until more data is available, bronchoscopic treatment is best reserved for selected elderly or debilitated patients.

Locally advanced unresectable disease — Although carcinoid tumors have been considered relatively radiation-resistant, definitive radiation therapy (RT) can provide effective palliation of a locally unresectable primary tumor [88,100] . It is not a curative option, however.

Some recommend that patients with locally advanced unresectable pulmonary carcinoids undergo chemotherapy plus RT, in a manner similar to treatment for intrathoracic small cell lung cancer (SCLC) [101] . However, response rates seem to be lower than are seen with SCLC, and whether this approach is superior to RT alone remains uncertain. (See "Thoracic radiotherapy in the treatment of limited stage small cell lung cancer" and see "First-line chemotherapy for small cell lung cancer").

POSTTREATMENT SURVEILLANCE — Despite their low malignant potential, long-term follow-up of patients with bronchial carcinoids is warranted because local or distant disease recurrence may occur many years after initial treatment.

The optimal posttreatment surveillance strategy is not defined, and there is no consensus on what tests should be ordered. We perform history and physical examination and chest CT annually for patients with resected typical carcinoid and every six months for resected atypical carcinoids for the first two years, then annually. Others perform a chest CT every six months regardless of histology. Guidelines for posttreatment surveillance for bronchial carcinoids are not available from the NCCN [93] .

Although some authors recommend somatostatin receptor scintigraphy in the follow-up of patients with bronchial carcinoid tumors [102] , we do not routinely order SRS unless there is suspicion for metastatic disease. Similarly, measurement of serum levels of chromogranin A (CGA) can be useful to follow disease activity in the setting of advanced or metastatic disease, but we do not routinely monitor CGA levels postoperatively. (See "Other imaging procedures" above and see "Peptide production and paraneoplastic syndromes" above).

MANAGEMENT OF METASTATIC CARCINOID AND THE CARCINOID SYNDROME —

The most frequent site of metastatic disease is the liver; other sites include bone, adrenal glands, and brain. The rarity of bronchial carcinoids has prevented the design of prospective trials, and few data are available regarding treatment for relapsed or advanced disease. In most cases, treatment principles are extrapolated from the experience with the more common gastrointestinal carcinoids.

Liver-directed therapy — The liver is the predominant site of metastatic disease. Hepatic resection is indicated for the treatment of selected patients with isolated, limited volume, metastatic liver disease. Although the majority of cases will not be cured by surgery, symptoms of hormone hypersecretion are effectively palliated, and prolonged survival is often possible, given the slow-growing nature of these tumors. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Hepatic resection).

Other liver-directed therapies for hepatic-predominant disease include hepatic artery embolization and chemoembolization, radiofrequency ablation, and cryoablation. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Nonsurgical liver-directed therapy).

Somatostatin analogs — Control of symptoms caused by secretion of biologically active amines or peptides may be achieved in 60 percent of cases by somatostatin receptor analogs such as octreotide (or where available, lanreotide), with or without interferon-alfa. Although these drugs can also slow tumor growth, radiographic regression of disease is rare. (See "Treatment of carcinoid tumors and the carcinoid syndrome", section on Control of symptoms, and see "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Octreotide and lanreotide).

Radiation therapy — As noted above, carcinoid tumors have been considered relatively radiation-resistant. However, radiation can provide useful pain relief for patients with bone metastases [100,103] .

Chemotherapy — For metastatic carcinoid tumors as a group, multiple cytotoxic drugs have been tried in various combinations, but randomized trials have revealed only minor activity. As a result, there is no standard regimen, and the role of chemotherapy for advanced carcinoid tumors in general continues to be debated. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Combination chemotherapy for carcinoid tumors).

There are some data to suggest that bronchial carcinoids have somewhat different chemotherapy sensitivity compared to carcinoids originating at other sites, although the reasons why this should be so are unclear:

- Patients with metastatic disease from bronchial carcinoid are often treated with regimens that are typically used for SCLC. Although chemotherapy responsiveness is not as predictable as it is with SCLC, objective partial responses have been documented using cisplatin plus etoposide with or without paclitaxel.
- At least some data suggest activity with single agent temozolomide [104]. A study of patients with metastatic or inoperable malignant neuroendocrine tumors included 13 bronchial carcinoids (10 typical and 3 atypical); all received oral temozolomide for five consecutive days every 28 days [104]. Four (31 percent) had a partial response, while four others (31 percent) had stable disease.

This topic is addressed in detail elsewhere. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Single agent therapy).

Novel approaches — The limited efficacy of chemotherapy has prompted investigation of novel therapeutic approaches for patients with advanced carcinoids. These include targeted radiotherapy (eg, therapeutic I-131 MIBG, 177Lu-octreotate), inhibitors of angiogenesis (eg, bevacizumab) and small molecule tyrosine kinase inhibitors (eg, sunitinib). These treatments are all discussed in detail elsewhere. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Novel treatment approaches).

SUMMARY AND RECOMMENDATIONS — Bronchial carcinoid tumors are malignant neoplasms that are characterized by neuroendocrine differentiation and indolent clinical behavior. Typical bronchial carcinoids rarely metastasize and have an excellent prognosis even when regional lymph nodes are involved; atypical carcinoids have a higher likelihood of metastases and a worse prognosis, particularly if mediastinal nodes are involved. (See "Classification, histology, and histochemistry" above and see "Prognosis" above).

- Most patients have a centrally-located tumor and are symptomatic from the tumor mass with coughing, hemoptysis, wheezing, or a recurrent postobstructive pneumonia. Peripheral lesions present most often as an asymptomatic solitary pulmonary nodule. (See "Clinical features" above).
- Computed tomography is the most useful imaging procedure, and the diagnosis is generally confirmed either by bronchoscopic biopsy (for central lesions) or by transthoracic needle biopsy for peripheral lesions. (See "Diagnosis and staging" above).

Additional preoperative staging studies such as somatostatin receptor scintigraphy or hepatic imaging are not indicated unless there is a clinical suspicion for metastatic disease. (See "Other imaging procedures" above).

Localized disease

- For patients with either a typical or atypical bronchial carcinoid whose medical condition and pulmonary reserve will tolerate it, we recommend surgical resection and a complete mediastinal lymph node dissection (**Grade 1B**). The presence of mediastinal lymph node metastases does not preclude cure. (See "Surgical resection" above).

For most patients, endobronchial resection is a suboptimal method of definitive treatment. However, initial bronchoscopic management is a reasonable alternative to immediate surgical resection in patients who present with a polypoid intraluminal tumor, good visualization of the distal tumor margin, and no evidence of bronchial wall involvement or suspicious lymphadenopathy by high resolution CT. Close posttreatment follow-up is an integral component of such treatment. (See "Endobronchial management" above).

- Although others disagree, we suggest not administering postoperative adjuvant therapy for a completely resected bronchial carcinoid of any stage or histology (**Grade 2C**). (See "Adjuvant therapy" above).
- Despite their low malignant potential, long-term follow-up of patients with bronchial carcinoids is warranted. Although the optimal posttreatment surveillance strategy is not defined, we suggest an annual history and physical examination as well as chest CT for typical carcinoids and every six month history and physical examination and chest CT for atypical carcinoids (**Grade 2C**). We reserve postoperative somatostatin receptor scintigraphy for patients who have a clinical suspicion for metastatic disease. (See "Posttreatment surveillance" above).

Locally advanced and metastatic disease

- For patients with surgically unresectable but nonmetastatic disease, options for local control of tumor growth include radiation therapy and palliative endobronchial resection of obstructing tumor. (See "Locally advanced unresectable disease" above and see "Endobronchial management" above).
- For patients who have a limited, potentially resectable liver-isolated metastatic carcinoid, we recommend surgical resection (**Grade 1B**). Although the majority of cases will not be cured by surgery, given the slow-growing nature of the tumor, extended survival is sometimes possible.

Other treatment options for patients with unresectable hepatic-predominant metastatic disease include embolization, chemoembolization, RFA, and cryoablation. (See "Liver-directed therapy" above).

- For patients with more advanced metastatic disease, first-line therapy with a somatostatin analog is reasonable. In progressing cases, a cisplatin-based chemotherapy regimen such as that used for small cell lung cancer or single agent temozolomide are reasonable options. (See "Chemotherapy" above).

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