Primary Carcinoid Tumors of the Lung: A Role for Radiotherapy

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Primary neuroendocrine neoplasms of the lung represent a clinical spectrum of tumors ranging from the relatively benign and slow-growing typical carcinoid to the highly aggressive small-cell lung carcinoma. The rarity of carcinoids has made the role of radiation therapy in their management controversial. This review considers the results of published studies to generate treatment recommendations and identify areas for future research. Surgery remains the standard of care for medically operable disease. Histology plays the most important role in determining the role of adjuvant radiation. Resected typical carcinoids likely do not require adjuvant therapy irrespective of nodal status. Resected atypical carcinoids and large-cell neuroendocrine carcinomas have a significant risk of local failure, for which adjuvant radiation likely improves local control. Definitive radiation is warranted in unresectable disease. Palliative radiation for symptomatic lesions has demonstrated efficacy for all histologies. Collaborative group trials are warranted.

The term carcinoid was first used by Oberndorfer in 1907 to describe tumors more indolent than adenocarcinomas,[1] but earlier reports of bronchial carcinoids[2] described some of their characteristics. Pulmonary carcinoids were originally grouped with adenoid cystic carcinomas under the more general term bronchial adenoma, but this classification was subsequently abandoned.[3] Within the category of carcinoids, a more aggressive atypical carcinoid was first described by Engelbreth-Holm in 1944,[4] but it was not until 1972 that Arrigoni formally separated typical and atypical carcinoids[5] as separate clinicopathologic entities.

Within non-small-cell lung cancer (NSCLC), the large-cell undifferentiated carcinoma with neuroendocrine features was proposed to be a clinically separate entity in 1985, and in 1991 Travis proposed criteria for the large-cell neuroendocrine carcinoma.[5] The current World Health Organization classification of neuroendocrine lung neoplasms recognizes four distinct pathologic entities: the typical carcinoid (TC), atypical carcinoid (AC), large-cell neuroendocrine carcinoma (LCNEC), and small-cell lung cancer (SCLC).[6]

Incidence
The true incidence of pulmonary carcinoids is difficult to estimate. The number of all-site carcinoid cases in the United States has been estimated to be about 4,500 cases per year.[7] Of these, bronchial sites account for 23% to 37%.[7,8] This would imply that the annual number of pulmonary typical and atypical carcinoids is about 1,000 to 1,500. However, lung cancer series estimate carcinoids as 2% of all cases,[9] which would place the number at around 3,400.

By contrast, there were an estimated 35,000 small-cell lung cancers in 2004, indicating that high-grade neuroendocrine neoplasms outnumber carcinoids at the minimum by a factor of 10:1. The incidence of LCNEC is also difficult to estimate, in large part due to its recent definition. In a histologic review of 572 lung cancer patients, 87 were found to be LCNECs, accounting for 9% of NSCLCs and 44% of SCLCs reviewed.[10] It would be inappropriate to try to extrapolate the annual incidence from these data, but they do seem to indicate that the number of LCNECs may be significant.

Patient Characteristics
The median age at diagnosis of neuroendocrine lung neoplasms is about 50 years, with TCs tending to occur in younger patients, and ACs and LCNECs occurring in older patients.[11] For patients younger than age 50, women outnumber men in a ratio of 1.6:1.[12] Cigarette smoking appears to be a risk factor for the development of ACs[12] but not TCs.[13] Smoking is almost certainly associated with LCNECs, with 98% of patients having a history of habitual smoking in one series.[10]

Pathophysiology
The cell of origin is the Kulchitsky cell,[14] a bronchial mucosa cell that can synthesize bioactive amines. Pulmonary carcinoids have stained positive for serotonin, adrenocorticotropic hormone (ACTH), vasoactive intestinal peptide (VIP), bombesin, and leucine enkephalin. Various genetic mutations have been described, with different lesions associated with different histologies. Both 11q deletions and MEN1 mutations are found in TCs and ACs, but not in LCNECs or...
SCLCs, while 10q and 13q deletions are found in ACs, LCNECs, and SCLCs.[12]

Pathologic Criteria
Classically, the gross description of a carcinoid is a vascular-appearing mass with a smooth surface and pink or yellow color, but this is seen more often with TCs than ACs.[15] Under a light microscope, carcinoids have small nuclei, few nucleoli, and ample cytoplasm. They classically stain with silver,[16] although chromogranin, synaptophysin, and neuron-specific enolase are commonly used today to identify neuroendocrine tumors. Using an electron microscope, neurosecretory granules, which contain biogenic amines, are diagnostic.

TCs and ACs are differentiated from one another by the presence of necrosis and the amount of mitoses per high-power field (Table 1).[6] LCNECs and SCLCs both have high mitotic rates and large amounts of necrosis, but can be differentiated based on light microscopy, with LCNECs having cytologic features similar to NSCLCs. LCNECs can be differentiated from NSCLC either by the presence of neurosecretory granules on electron microscopy, or by positive staining of neuroendocrine markers.

Clinical Presentation
Up to 24% of TCs and 7% of ACs are asymptomatic, with their detection only coming at autopsy.[17] Among the rest of neuroendocrine tumors, local symptoms are the common presenting symptoms, including dyspnea, chest discomfort, unilateral wheezing, bronchial obstruction, hemoptysis, cough, or recurrent pulmonary infections.[12]

Pulmonary carcinoids commonly arise from the lobar bronchi (55%) or segmental bronchi (32%), and less commonly, the mainstem bronchi (13%).[18] The right lung is involved in 60% of cases, and the middle and lower lobes may be involved more often than the upper lobe.[19]

Symptomatic clinical syndromes from the production of functional hormones are rare with primary bronchial neuroendocrine tumors, even in those staining positive for bioactive amines.[20] Carcinoid syndrome is found in 1% of patients[18] and is associated with the presence of liver metastases. It is most often caused by the secretion of serotonin, and the classic clinical manifestations include diarrhea, flushing, and palpitations. Less common sequelae include heart dysfunction[12] and coronary valve fibrosis. Rarely, surgical manipulation can cause pulmonary edema or vasomotor collapse, the so-called carcinoid crisis. ACTH production is found in 1% of cases, resulting in Cushing's syndrome, which is clinically manifested by weakness, hypertension, glucose intolerance, hypokalemia, alkalosis, weight loss, anemia, and hyperpigmentation. Growth hormone-releasing factor causing acromegaly has also been rarely described in cases of pulmonary carcinoid tumor.

Diagnosis
The diagnosis of pulmonary carcinoid is commonly made via either bronchoscopy or computed tomography (CT)-guided biopsy. Although significant bleeding at biopsy is relatively rare, it can be difficult to control with a flexible bronchoscope. When a carcinoid is suspected because of its gross appearance, some centers use prophylactic dilute epinephrine solution and only perform a biopsy in an environment where a rigid bronchoscope or Nd:YAG laser is on hand.[21]

Imaging often includes chest x-ray and chest computed tomography. Immunoscintigraphy with somatostatin analogs such as octreotide is increasingly helpful in staging pulmonary carcinoids.[14] In assessing the primary, octreotide scanning has a sensitivity of 97% and specificity of 95%, and for evaluation of metastatic disease, a sensitivity of 93% and specificity of 90%. [14] Nodal disease is
less sensitive (60%) and specific (85%), suggesting that pathologic staging remains standard. Although the use of positron-emission tomography (PET) to stage carcinoids is currently investigational, individual cases of 18F-fluorodeoxyglucose (FDG)-avid TCs and ACs have been reported.[22]

The most common sites of distant metastatic disease are the liver, bone, brain, adrenal glands, and ovary,[23] but imaging of these organs is generally deferred unless clinical symptoms are present. In LCNECs, it is reasonable to routinely order a PET/CT of the abdomen and brain imaging to rule out metastatic disease because these studies are commonly used in the work-up of SCLC and NSCLC. For serotonin-secreting tumors, urine 5-hydroxyindoleacetic acid (5-HIAA) can be useful in monitoring the response to treatment and/or screening for a recurrence.

Surgery
Surgery is the treatment of choice for primary pulmonary carcinoid tumors. TCs are most often managed with a lobectomy, but some surgeons advocate lung-sparing procedures such as a segmentectomy or wedge resection because of the relatively benign nature of the disease.[24] On the other hand, ACs and LCNECs are generally treated with an oncologic resection, and a lobectomy is the smallest acceptable procedure.[11] Mediastinal lymph node sampling should also be performed in these patients, but the role of this procedure in TCs is somewhat controversial. For obstructive lesions, an endobronchial laser resection can provide palliation, although this should not be used definitively,[25] as most lesions spread extraluminally and adequate margins would not be attainable using this approach.

Prognostic Factors
Long-term results from numerous surgical series suggest that the histologic subtype of a bronchial carcinoid is the most important prognostic factor. Tumor-node-metastasis (TNM) stage appears less critical since there seems to be a strong correlation between histology and stage.[26] In a Japanese series of 366 surgically resected neuroendocrine tumors, 3.6% of TCs had nodal disease, compared with 50% of higher-grade lesions.[27] In Fink's series, 10% of TCs were node-positive and 3% had metastatic disease, whereas 57% of ACs were node-positive and 21% had metastatic disease.[18] Tables 2 and 3 summarize survival rates in patients with carcinoid tumors by histology and stage.
Other prognostic factors include completeness of resection, the presence of paraneoplastic...
symptoms, and age.[27] One carcinoid series also shows an association between tobacco use and advanced stage.[19] Gender has been inconsistently reported as a prognostic factor, with two series showing worse outcomes in males,[19,27] and one series of ACs suggesting that women had a worse survival.[23]

Patterns of Failure
TCs with regional metastatic lymph node involvement appear to have similar outcomes compared to those without nodal disease. Thomas et al reported the Mayo experience of 36 patients with regional lymph node disease treated with surgery alone.[4] Of 23 TC patients treated with surgery alone (median follow-up: 84 months), 83% had no evidence of disease recurrence and 9% failed distantly. Schreurs et al reported excellent results in a series of TCs following surgery, including 10% with node-positive disease and 2.1% with positive resection margins. The disease-specific survival rate in this group was 100% through 15 years.[25] In Kaplan's series of 206 patients, stage I TCs that were completely resected had an 8% local failure rate and 7% distant failure rate.[26]

 Failure rates appear to be worse with more aggressive histologies. Kaplan and colleagues reported that for completely resected stage I ACs, 23% failed locally and 23% failed distantly.[26] In the Mayo Clinic series reported by Thomas et al, systemic failure was the dominant site of relapse for 64% of ACs and 100% (2 of 2 patients) of LCNECs. In Gould's series of 87 patients, atypical histology was the only factor associated with an increase in local recurrence-local failure occurred in 17% of ACs and 6% of TCs.[28]

Perkins reported a series of 79 patients from M.D. Anderson with pulmonary carcinoid and no metastatic disease[29]; 49 were TCs and 14 were ACs. A total of 24 had aggressive features, defined as involving regional lymph nodes, carina or vessel invasion, or inoperable disease. The group with aggressive features had a significantly worse 5-year overall survival (51% vs 77%, \( P = .01 \)). Of the eight patients who died of disease with aggressive features, one died of local disease, four died of local and distant disease, and three died of distant disease only. Two patients who died from disease with nonaggressive features had local recurrence and distant disease. Takei reported on failure patterns for a LCNEC series; first recurrences were local in 34% of patients, distant in 57%, and both in 9%.[10]

In summary, bronchial carcinoid patients with aggressive histologies (AC, LCNEC), and possibly high-risk tumor features (positive lymph nodes, invasion of local structures, gross residual disease), have higher rates of failure, both local and systemic.

Radiation Therapy
In the management of neoplasms, the role of radiation therapy (RT) is conventionally defined by its curative (definitive, primary, adjuvant) or palliative intent. With respect to primary neuroendocrine tumors of the lung, the utility of RT has been explored in the postoperative setting—that is, as an adjuvant to surgical interventions.

Adjuvant RT
Pathologic features including lymph node positivity and positive resection margin status have prompted clinicians to consider the use of adjuvant radiotherapy for resected bronchial carcinoids, based on patterns of failure following surgical resection and then modeling treatment approaches after the paradigms employed for resected NSCLC. This approach remains controversial. For example, Cooper et al[30] reported a surgical series of 77 patients including 50 with TCs, 5 with ACs, 9 with LCNECs, 4 with mixed large-small-cell neuroendocrine carcinoma (LSNEC), and 9 with SCLCs. The authors recommended that adjuvant radiotherapy was warranted for lymph node involvement regardless of histology but did not provide supporting postoperative results for this conclusion. Due to the relative rarity of the primary bronchial carcinoids, no randomized studies have addressed the benefits of adjuvant radiotherapy, and therefore, clinical practice has been guided mainly by single-institution retrospective reports.

Carretta described a series of 44 pulmonary neuroendocrine tumors treated initially with resection and lymphadenectomy.[31] One patient received neoadjuvant chemotherapy. A total of 36 were TCs, 3 were ACs, and 5 were LCNECs. Approximately 11% of TCs were node-positive, compared with 25% of ACs/LCNECs. All node-positive patients were treated with adjuvant radiation to a median dose of 56 Gy (range: 45-58 Gy). No local recurrences occurred after RT. Recurrence rates were 8% for TCs and 25% for ACs/LCNECs. The 5-year overall survival rates were 93% for patients with TCs and 70% for those with ACs/LCNECs.

An Italian series described 42 patients with pulmonary carcinoids treated initially with surgical resection[14]; 26 had TCs and 16 had ACs. All patients with stage III disease received radiation and/or systemic therapy. One patient treated with radiation failed in the same lung, but whether this was an in-field recurrence was not recorded. Among the four patients who failed without radiation,
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all failed distantly. Perkins and colleagues from M.D. Anderson reported on 7 of 73 surgical patients who received adjuvant RT and/or chemotherapy based on positive surgical margins, local invasion, and/or lymph node involvement.[29] They were not classified by histologic subtype. One patient who received surgery followed by RT was alive without evidence of disease 10 years after diagnosis. Martini et al at Memorial Sloan-Kettering reported on a series of 25 patients with lymph node-positive disease[9]; 12 had TCs and 13 had ACs. Of 15 patients with N2 disease, 9 received adjuvant radiation. The 5-year overall survival rate for patients with TCs was 92% and for those with ACs, 60%. The authors concluded that most recurrences were distant and correlated with cell type, that no local recurrences were observed in N2 patients, and that the role of adjuvant RT could not be assessed because of the small number of cases treated. Ohta et al reported a case of a patient successfully treated with neoadjuvant chemotherapy and radiation.[32] This patient with a T3, N2, M1 AC of the right superior sulcus and a single brain metastasis was treated with thoracic RT (45 Gy) and concurrent methotrexate, vinblastine, and cisplatin. The patient was restaged and found to be T3, N0, M0, with complete resolution of both the brain metastasis and gross nodal disease. He was then treated with a definitive resection and adjuvant high-dose rate brachytherapy to a dose of 21 Gy to the operative bed. The patient ultimately developed systemic metastases and died but experienced no local recurrences. We have very little data specific to the treatment of LCNECs in the adjuvant setting. However, as many LCNECs were previously classified as NSCLC, it is instructive to review the approach for the latter histology. In NSCLC, the role of adjuvant radiation is controversial for N1 patients based on the postoperative radiation therapy (PORT) meta-analysis, which suggested a survival decrement in patients treated with adjuvant radiation.[33] However, adjuvant mediastinal radiation is indicated in patients with N2 disease, since the modality improves local control in this group with no impact on survival.[34]

In summary, there appears to be little role for adjuvant RT in resected TCs. However, pattern-of-failure findings and suggestions from reported data for AC and LCNECs indicate that adjuvant RT may offer a potential benefit with respect to improved local control in cases with high-risk findings after surgery. Definitive RT for Unresectable Bronchial Carcinoid

The use of definitive RT for medically inoperable or surgically unresectable nonmetastatic pulmonary neuroendocrine tumors has been infrequently reported. Chakravarthy and Abrams from Johns Hopkins reviewed the effectiveness of RT for a broad range of bronchial carcinoids.[35] Of 240 patients reviewed, they described 5 who were treated with RT to the lung or mediastinum for primary localized, unresectable disease. Three were exclusively chest primaries without distant disease. The median RT dose used in treatment to the chest was 51 Gy (range: 39-55.8 Gy). Three of the five patients showed clinical improvement, and one did not respond. Two of the five were alive with in-field disease control at 24 and 48 months. Only one of the five had in-field progression with symptoms.

Wirth et al at the Dana-Farber Cancer Institute reviewed the outcomes of patients with bronchial carcinoids treated with chemotherapy with or without radiotherapy.[36] They identified 18 such patients, with either a TC (n = 8) or an AC (n = 10). Seven of these patients had locally advanced/unresectable disease. Stage IB TC was diagnosed in two patients, one of whom was treated with radiochemotherapy followed by chemotherapy and was alive at 60 months. One patient with stage IIIA TC was treated to a platinum-based chemotherapy alone and had stable disease at 6 months. Two ACs in the series were stage IIIA, and two were stage IIIB. Three of these AC patients were treated with radiochemotherapy; two were alive with stable disease at 8 and 10 months, and the other had a partial response with a survival of 84 months. The other patient with stage IIIA disease was alive at 10 months with stable disease after two forms of chemotherapy. Overall, the authors felt that advanced pulmonary carcinoid disease can respond to treatment mimicking that used for small-cell lung carcinoma (chemotherapy plus radiotherapy), but with far lower response rates. Further study of treatment modalities for unresectable pulmonary carcinoid appears warranted.

Palliative Radiation

Numerous case reports and write-ups of small series have described the utility of RT in the palliative setting. Of interest, these often deal with unusual presentations sometimes seen with metastatic bronchial carcinoid. In general, the efficacy of RT in the palliative setting has been well recognized. Ameer et al notes that RT has a defined palliative role in the treatment of bronchial carcinoids.[37] According to these authors, about 80% of treated patients have a partial or complete response to RT.
Chakravarthy and Abrams described the use of RT for a range of metastatic pulmonary carcinoid lesions including bone, skin, CNS, liver, and prostate metastases.[35] Overall, 87% of 31 treated sites showed clinical improvement with RT and 61% of sites were controlled for greater than 3 months. Schupak and Wallner analyzed the role of RT for 416 patients treated for metastatic or unresectable carcinoid at Memorial Sloan-Kettering.[38] Considering only those with primary lung tumors, three patients with brain metastases showed stable disease without progression after palliative RT, four of six patients with spinal cord compression showed complete responses and two had partial responses following median doses of 30 Gy in 10 fractions, and three of three patients with bone metastases had complete responses after 20 to 24 Gy. RT was overall judged effective at symptomatic palliation in most patients with metastatic carcinoid tumors. In that regard, many authors have noted that RT provides effective pain relief in patients with bone metastases from metastatic carcinoid.[39-41] Many examples in the literature have documented the use of palliative RT in specific clinical cases. Nakamura et al.[42] described a case report involving stereotactic radiosurgery for brain metastases from a pulmonary AC. Three brain metastases showed radiographic evidence of necrosis after radiosurgery, but 1 year later the procedure had to be repeated because of disease progression. The patient died of systemic disease. Pulmonary carcinoids may rarely metastasize to the uvea. Harbour et al.[43] reported the Willis Eye experience of uveal metastases from carcinoid tumors, seven of which were pulmonary carcinoids. Five patients were treated with external-beam irradiation, and four experienced regression. The fifth was salvaged with plaque brachytherapy. Two other patients were treated primarily with plaque brachytherapy, either $^{125}$I or $^{106}$Ru. All seven patients experienced durable local control. Gragoudas and Carroll[44] reported a case of bilateral multiple choroidal lesions 8 years after removal of a bronchial carcinoid tumor. Biopsy confirmed carcinoid metastases. One eye was treated with conventional RT, which produced adverse effects. The other was treated with photocoagulation and proton-beam irradiation without adverse effects. Shimon et al reported an unusual case of metastatic atypical bronchial carcinoid to the anterior pituitary gland in a 47-year-old male who presented with bitemporal hemianopsia and hypopituitarism. The primary bronchial carcinoid had been resected 2 years earlier. Partial removal of the suprasellar mass was performed, and metastatic atypical carcinoid was confirmed. Fractionated radiotherapy to the sella, supplemented with octreotide, was administered postoperatively. The patient's vision returned to normal and the pituitary mass diminished in size.[45] Palliative RT has also been specifically described for LCNECs. Takei and colleagues reported a series of 18 patients treated palliatively with radiation, noting a 28% complete response rate.[10] Systemic Therapy

The indications and forms of systemic therapy for neuroendocrine lung tumors are also controversial and beyond the scope of this review. However, in the context of RT, a novel systemic therapy used to treat metastatic disease involves attaching a radioisotope, such as $^{90}$Y or $^{111}$In, to a somatostatin analog.[46,47] Carcinoid tumors express high levels of somatostatin receptor; therefore, linking a radioactive element with a limited range of activity to the analog permits the delivery of high local doses to tumor while theoretically minimizing normal tissue exposure. Although an interesting concept, systemic radiation in the treatment of carcinoid continues to be investigational.

Treatment Recommendations
Surgical resection remains the standard of care for medically operable localized disease. If gross residual disease is present after surgery, adjuvant radiation is recommended for all histologies. For completely resected TCs, with or without regional nodal involvement, no adjuvant therapy is recommended. Evidence suggests that no adjuvant therapy is indicated for TC with positive margins. For completely resected ACs, adjuvant mediastinal irradiation appears indicated for mediastinal nodal disease but its role in N0/1 disease is uncertain. For completely resected LCNECs, adjuvant mediastinal radiation is recommended in N2/N3 disease but not in N0/N1 cases.

If a patient has localized unresectable disease, definitive radiation is offered, likely with chemotherapy, but the optimal sequence of modalities is unclear. In the metastatic setting, palliative radiation should be considered for symptomatic lesions. Specific dose recommendations are difficult to make considering the range of reported doses used, the heterogeneity of treated sites, and the absence of clear dose-response data. However, common practice has been modeled after the regimens used in similar settings for either non-small-cell or small-cell cancers.

Future Directions
Neuroendocrine neoplasms of the lung continue to offer a challenge to the clinician and investigator alike. Most patients with completely resected TCs have an excellent outcome, but other clinical subsets do not. Improvements in both local and systemic control need to be achieved, and to further
this goal the roles of radiation and systemic agents need to be systematically studied. The best mechanism for proper study of these unusual tumors in their various presentations is through cooperative group trials, which should be encouraged.

Disclosures:
The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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