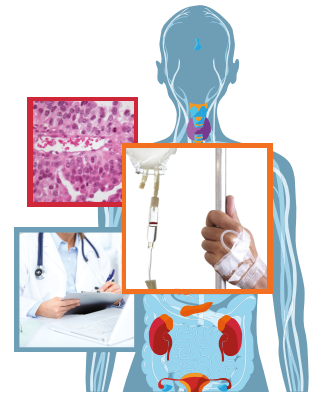
Editorial

For reprint orders, please contact: reprints@futuremedicine.com



International Journal of Endocrine Oncology

Bronchial carcinoids

Dan Granberg*,[1]

[1]Department of Medical Sciences, Division of Endocrine Oncology, Uppsala University Hospital, Uppsala University, Uppsala, Sweden

*Author for correspondence: Tel.: +46 18 611 2732; Fax: +46 18 50 8444; dan.granberg@medsci.uu.se

"External radiotherapy is otherwise used only against brain metastases or for pain relief in patients with bone metastases. There are no studies showing that adjuvant therapy is beneficial after radical surgery."

First draft submitted: 11 April 2017; Accepted for publication: 9 May 2017; Published online: 15 March 2019

Bronchial neuroendocrine tumors are subdivided into typical carcinoids, atypical carcinoids, large cell neuroendocrine carcinomas and small-cell lung carcinomas. Large-cell neuroendocrine carcinomas as well as small-cell lung carcimomas are highly malignant tumors with a poor prognosis. Smoking is a major etiological factor. These patients are principally treated by chemotherapy and radiotherapy. In addition, surgery may have some place in the treatment of large-cell neuroendocrine carcinomas. These two tumor types will not be further discussed in this article, which will focus on typical and atypical carcinoids. In addition, two other entities will be briefly mentioned, namely tumorlets and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, DIPNECH.

Gastroenteropancreatic neuroendocrine tumors are classified according to mitotic count and proliferative rate (Ki67 index) into neuroendocrine tumor grade 1, neuroendocrine tumor grade 2 and neuroendocrine carcinoma grade 3, small and large cell, respectively. The classification of neuroendocrine lung neoplasms, however, is still based on mitotic count. Typical carcinoids have less than two mitoses per 2 mm^2 (ten high-power fields) while atypical carcinoids have between two and ten mitoses per 2 mm^2. Atypical carcinoids may contain necroses, which are always absent in typical carcinoids [1]. Tumorlets have identical morphology as typical carcinoids, but are not larger than 0.5 cm. Diffuse neuroendocrine cell hyperplasia in the airways can be reactive, found in heavy smokers, patients with chronic pulmonary diseases including bronchiectasis and in persons living at high altitudes. DIPNECH means diffuse neuroendocrine cell hyperplasis in the lungs without predisposing conditions. Both DIPNECH and tumorlets may be found in patients with bronchial carcinoids. Symptoms of DIPNECH include coughing, wheezing and dyspnea. The treatment of choice in patients with DIPNECH has not been much studied, but bronchodilators and inhaled corticosteroids may be considered, as well as surgical removal of larger lesions. Somatostatin analogs are also an alternative, and may lead to stabilization of the disease. Metastatic disease may occur.

Pathology

Bronchial carcinoids may be central (60–84%) or peripheral. Central carcinoids may be detectable at bronchoscopy as intrabronchial, polypoid, vascularized tumors, often infiltrating deeply into the bronchial wall and surrounding lung parenchyma. Periferal carcinoids are not accessible by bronchoscopy. The tumor cells are small, growing in regular patterns separated by a fibrovascular stroma (typical carcinoids) or more disorganized architecture (atypical carcinoids). Immunohistochemistry is positive for cytokeratin and the neuroendocrine markers synaptophysin and chromogranin A. In addition, immunoreactivity may be found for several hormones, including serotonin, gastrin-releasing peptide, adrenocorticotropic hormone (ACTH) and pancreatic polypeptide. Positive immunohistochemistry for gastrin-releasing peptide and TTF-1 may aid in differentiating a primary bronchial carcinoid from a lung metastasis from a neuroendocrine tumor with origin in other organs, as well as in finding the primary in case of distant metastases from a neuroendocrine tumor [2]. Ki67 is usually low in typical bronchial carcinoids, but may be higher in atypical carcinoids.

Future Medicine

Clinical symptoms

A substantial proportion, up to 50%, of patients have no symptoms and the tumor is detected on routine chest X-ray or CT scan for other purposes. Frequent-presenting symptoms include cough, hemoptysis, dyspnea, wheezing, recurrent pneumonias, persisting infiltrates on X-ray and chest pain. Some patients may have several years delay in diagnosis, misinterpreted as asthma. Endocrine symptoms, including ectopic Cushing's syndrome and the classical carcinoid syndrome with flush, diarrhea, bronchoconstriction, right-sided valvular heart disease and elevated urinary 5′HIAA, are rare and seen in 2–6% and 2–12%, respectively of patients. An atypical carcinoid syndrome (which should not be confused with atypical carcinoids) caused by secretion of histamine leading to generalized flushing, edema, lacrimation, bronchial constriction and diarrhea, as well as acromegaly, caused by growth-hormone-releasing hormone production, are even less frequent.

Diagnosis

The tumor is detectable on chest X-ray in >60% of patients. CT scan, which is a more sensitive radiological method, should always be performed to delineate the tumor and search for enlarged lymph nodes and tumorlets. Positron emission tomography (PET) with ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE is of value preoperatively to look for distant metastases and find out whether the tumor is somatostatin-receptor positive. PET with FDG is more often positive in atypical than in typical carcinoids and may be used as a prognostic indicator; in one study, median PFS was 26.4 months in patients with FDG PET-negative tumors and 15.3 months in patients with FDG PET-positive tumors [3]. Central tumors are accessible by bronchoscopy, allowing biopsies to be taken, which is usually safe despite the risk of bleeding. Peripheral tumors may be biopsied by computed tomography-guided transthoracic needle biopsy. Misdiagnosis is, however, not infrequent, due to difficulties in differentiating from small-cell lung carcinoma. Staining for Ki67 may aid in solving this problem [4,5]. Plasma chromogranin A should always be analyzed before surgery, but is usually not elevated provided the tumor is confined to the lung. Elevation of chromogranin A in case of normal renal function and absence of treatment with proton pump inhibitors should lead to an intense search for distant metastases.

Treatment

The principal treatment of patients with bronchial carcinoids is surgery, which is the only curative therapy. All patients with disease localized to the thorax should be considered for surgery. The aim is radical removal of the primary tumor and all affected lymph nodes, preserving as much healthy lung parenchyma as possible. This may be performed by bronchotomy with resection of the tumor and bronchoplasty, sleeve resection, segmental resection, lobectomy, bilobectomy and pneumonectomy. In patients with atypical carcinoids, at least a lobectomy should be performed. Since the tumor often grows deeply into the surrounding lung tissue, endoscopic removal of the tumor by yttrium aluminum garnet (YAG)-laser previously has been recommended only in patients at high risk for surgery, as a method to open up the airway in case of obstructive symptoms.

This opinion has later been questioned by two studies that found bronchoscopic laser treatment safe and effective in patients with intrabronchial typical carcinoids. Open surgery was, however, later required in 36–46% of the patients [6,7]. The results were confirmed by a recent report, which found no difference in survival or recurrence rate between the surgical and the endobronchial treatment group of patients [8]. Postoperative radiotherapy may be considered in patients with affection of the resection marigins and/or inomplete tumor resection. External radiotherapy is otherwise used only against brain metastases or for pain relief in patients with bone metastases. There are no studies showing that adjuvant therapy is beneficial after radical surgery.

The treatment of patients with inoperable or metastatic bronchial carcinoids is dependent on the histological type (typical or atypical carcinoid), Ki67 index, expression of somatostatin receptors, extent of disease, bone marrow and renal function, and the patient's general condition. There are no studies comparing the various treatments, and hence no established first-line treatment. Patients whose tumors show high expression of somatostatin receptors may benefit from peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC, which have shown antitumoral activity in uncontrolled studies. In one small study, 5/9 patients receiving ^{177}Lu-DOTATATE obtained radiological response lasting median 31 months [9], and in another study, 24/84 patients receiving ^{90}Y-DOTATOC responded radiologically [10]. In a more recent report, 34 patients, of whom 15 had typical and 19 had atypical carcinoids, were treated with ^{177}Lu-DOTATATE 18.5 or 27.8 GBq in 4 or 5 cycles. Disease control rate was 80% in patients with typical carcinoids (6% complete response, 27% partial response and 47% stable disease), and median progression-free survival (PFS) was 20.1 months. In patients with atypical carcinoids, 47% achieved stable disease,

and median PFS was 15.7 months [3]. In another, comprehensive, retrospective study including 114 patients with advanced bronchopulmonary carcinoids receiving either ^{177}Lu-DOTATATE, ^{90}Y-DOTATOC or ^{90}Y-DOTATOC + ^{177}Lu-DOTATATE, morphological response (partial response + minor response) was obtained in 26.5% of all patients; the highest response rate was seen in those receciving ^{90}Y-DOTATOC + ^{177}Lu-DOTATATE (38.1%), Median overall survival (OS) was 58.8 months and median PFS was 28.0 months. The 5-year OS was similar in the groups treated with ^{177}Lu-DOTATATE and the combination of ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE (64.1%). Median OS was however longer in the ^{177}Lu-DOTATATE group (not reached at 110 months compared to 61.0 months the combination group). In the ^{90}Y-DOTATOC patient group 5-year OS rate was 31.6% [11]. The higher frequency of severe renal side effects in patients receiving ^{90}Y-DOTATOC may favor the use of ^{177}Lu-DOTATATE.

Two randomized placebo-controlled trials have demonstrated antiproliferative effect of somatostatin analogs in patients with neuroendocrine tumors. In the PROMID study [12], 85 patients with metastatic midgut neuroendocrine tumors were randomly assigned to long-acting octreotide (Sandostatin LAR) 30 mg every 4 weeks or placebo. Median PFS was 14.3 months in the treatment arm compared with 6 months in the placebo group. In the CLARINET study [13], 204 patients with well or moderately differentiated nonfunctioning neuroendocrine tumors grade 1 or 2, Ki67 <10%, received either Lanreotide Autogel 120 mg every 4 weeks (n = 101) or placebo (n = 103). PFS was significantly longer in the treatment arm compared with the placebo group (not reached vs 18 months, $p < 0.001$). Most patients were, however, harboring pancreatic (n = 91) or midgut neuroendocrine tumors (n = 73), and none of the patients was reported to have a bronchial carcinoid. The ongoing SPINET trial, randomizing patients harboring metastatic and/or unresectable well-differentiated typical or atypical lung carcinoids to best supportive care plus either Lanreotide Autogel 120 mg every 4 weeks or placebo, will hopefully give the answer whether somatostatin analogs have antitumoral activity also in patients with bronchial carcinoids. The low frequency of serious adverse effects and the antiproliferative activity in other foregut neuroendocrine tumors nevertheless make the use of somatostatin analogs attractive in patients with low proliferative bronchial carcinoids, in addition to those who are suffering from endocrine symptoms.

Several chemotherapy regimens have been tried in patients with metastatic bronchial carcinoids, including carboplatin or cisplatin + etoposide, paclitaxel or docetaxel ± doxorubicin, streptozotocin + 5-fluorouracil or doxorubicin, oxaliplatin + capecitabine, 5-fluorouracil + dacarbazine + epirubicin and 5-fluorouracil + cisplatin + streptozotocin. The success rates have been limited [14–18]. A report from our group, however, confirmed earlier observations that monotherapy with temozolomide may have antitumoral activity in these patients. Radiological partial response was seen in 14% (all harboring atypical carcinoids) and stabilization of progressive disease in 52% (both typical and atypical carcinoids) [19,20]. A combination of temozolomide with other agents, such as capecitabine and/or bevacizumab, may be even more effective, but this has not yet been studied.

The mTOR inhibitor everolimus has shown antitumoral activity in several types of neuroendocrine tumors, including pancreatic neuroendocrine tumors and bronchial carcinoids. In a subanalysis from the randomized, placebo-controlled RADIANT-2 study, patients with lung carcinoids suffering from the carcinoid syndrome were treated with either everolimus + octreotide LAR or placebo + octreotide LAR. PFS was 13.6 months in the everolimus group and 5.6 months in the placebo group, but the difference was not significant. Minor response was obtained in 67% of the patients receiving everolimus and in 27% of the patients receiving placebo [21]. In the RADIANT-4 study, 302 patients with advanced, nonfunctional neuroendocrine tumors of the lung or GI tract were randomized 2:1 to receive everolimus 10 mg daily (n = 205) or placebo (n = 97). Median PFS was 11.0 months in the everolimus group and 3.9 months in the placebo group. In total 90 patients had lung carcinoids, of whom 63 received everolimus and 27 received placebo. A subanalysis showed that everolimus was significantly better than placebo among the lung carcinoid patients [22]. The LUNA study, a randomized three-armed study comparing everolimus, pasireotide and everolimus + pasireotide has closed for recruiting of patients. The results are eagerly awaited. Sunitinib, which inhibits VEGFR, PDGFR and c-kit, prolongs PFS in patients harboring pancreatic endocrine tumors but has not yet been examined in patients with bronchial carcinoids.

The newer PD-1 and PD-L1 inhibitors, including pembrolizumab and nivolumab, which inhibit immune checkpoint proteins, have shown activity in other forms of lung cancer. Studies in patients with bronchial carcinoids would be interesting and will hopefully start within the near future.

Conclusion

Even if the majority of patients with bronchial carcinoids are cured by surgery, the treatment of patients with metastatic disease is still challenging. Possible alternatives include somatostatin analogs, peptide receptor radionu-

clide therapy with ^{177}Lu-DOTATATE, everolimus, temozolomide ± capecitabine and other chemotherapy regimens, but the response rates are moderate. In addition, knowledge about how to sequence and combine current therapies is missing. Studies evaluating newer drugs, possibly targeting the immune system, are urgently desired.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1. *World Health Organization Classification of Tumours. Pathology & Genetics. Tumours of the Lung, Pleura, Thymus and Heart*. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC (Eds). IARCPress, Lyon, France (2004).
2. Granberg D, Skogseid B, Welin S, Örlefors H, Öberg K, Wilander E. Gastrin-releasing-peptide in neuroendorine tumours. *Acta Oncol.* 45(1), 23–27 (2006).
3. Ianniello A, Sansovini M, Severi S *et al.* Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. *Eur. J. Nucl. Med. Mol. Imaging* 43(6), 1040–1046 (2016).
4. Aslan DL, Gulbahce HE, Pambuccian SE, Manivel JC, Jessurun J. Ki-67 immunoreactivity in the differential diagnosis of pulmonary neuroendocrine neoplasms in specimens with extensive crush artifact. *Am. J. Clin. Pathol.* 123(6), 874–878 (2005).
5. Pelosi G, Rodriguez J, Viale G, Rosai J. Typical and atypical pulmonary carcinoid tumor overdiagnosed as small-cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. *Am. J. Surg. Pathol.* 29(2), 179–187 (2005).
6. Brokx HA, Risse EK, Paul MA *et al.* Initial bronchoscopic treatment for patients with intraluminal bronchial carcinoids. *J. Thorac. Cardiovasc. Surg.* 133(4), 973–978 (2007).
7. Neyman K, Sundset A, Naalsund A *et al.* Endoscopic treatment of bronchial carcinoids in comparison to surgical resection: a retrospective study. *J. Bronchology Interv. Pulmonol.* 19(1), 29–34 (2012).
8. Dalar L, Ozdemir C, Abul Y *et al.* Endobronchial treatment of carcinoid tumors of the lung. *Thorac. Cardiovasc. Surg.* 64(2), 166–171 (2016).
9. van Essen M, Krenning EP, Bakker WH, de Herder WW, van Aken MO, Kwekkeboom DJ. Peptide receptor radionuclide therapy with (177)Lu-octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin. *Eur. J. Nucl. Med. Mol. Imaging* 34(8), 1219–1227 (2007).
10. Imhof A, Brunner P, Marincek N *et al.* Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J. Clin. Oncol.* 29(17), 2416–2423 (2011).
11. Rinke A, Müller HH, Schade-Brittinger C *et al.* Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J. Clin. Oncol.* 27(28), 4656–4663 (2009).
12. Caplin ME, Pavel M, Cwikla JB *et al.* Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N. Engl. J. Med.* 371(3), 224–233 (2014).
13. Chong CR, Wirth LJ, Nishino M *et al.* Chemotherapy for locally advanced and metastatic pulmonary carcinoid tumors. *Lung Cancer* 86(2), 241–246 (2014).
14. De Dosso S, Bajetta E, Procopio G *et al.* Pulmonary carcinoid tumours: indolent but not benign. *Oncology* 73(3-4), 162–168 (2007).
15. Granberg D, Eriksson B, Wilander E *et al.* Experience in treatment of metastatic pulmonary carcinoid tumors. *Ann. Oncol.* 12(10), 1383–1391 (2001).
16. Turner NC, Strauss SJ, Sarker D *et al.* Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. *Br. J. Cancer* 102(7), 1106–1112 (2010).
17. Wirth LJ, Carter MR, Jänne PA, Johnson BE. Outcome of patients with pulmonary carcinoid tumors receiving chemotherapy or chemoradiotherapy. *Lung Cancer* 44(2), 213–220 (2004).
18. Crona J, Fanola I, Lindholm DP *et al.* Effect of temozolomide in patients with metastatic bronchial carcinoids. *Neuroendocrinology* 98(2), 151–155 (2013).

19. Ekeblad S, Sundin A, Tiensuu Janson E *et al.* Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. *Clin. Cancer Res.* 13(10), 2986–2991 (2007).

20. Fazio N, Granberg D, Grossman A *et al.* Everolimus plus octreotide long-acting repeatable in patients with advanced lung neuroendocrine tumors: analysis of the Phase III, randomized, placebo-controlled RADIANT-2 study. *Chest* 143(4), 955–962 (2013).

21. Yao JC, Fazio N, Singh S *et al.* Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, Phase III study. *Lancet* 387(10022), 968–977 (2016).