A total of 25% of neuroendocrine tumors originate in the lung. Still, typical and atypical carcinoids of the lung are rare, accounting for only 1–2% of all lung cancers. Distant metastases are infrequent, occurring in 2–14% of cases. The mainstay of treatment of local disease is surgery. In advanced disease there are no antiproliferative agents approved for carcinoids of the lung. None of the currently available drugs provide a cure. There are several treatment options, such as somatostatin analogs, mTOR inhibition, inhibitors of angiogenesis, systemic chemotherapy and radiolabeled somatostatin analogs. Interpretation of the data is complicated, since it mainly consists of small (retrospective) Phase II studies. Fortunately, randomized Phase II and III studies are underway. This article emphasizes the specific features of neuroendocrine tumors in the lung and focuses on the treatment in advanced disease.

Keywords: biomarkers • carcinoid • DIPNECH • lung • neuroendocrine tumors • surgery • systemic treatment • work-up

Background
Lung cancer is by far the most preventable disease in the world. In more than 80% of the cases, smoking is the attributable factor. Unfortunately, there is a relatively small subgroup of lung cancers where the relationship with smoking is not so clear. This class of tumors include neuroendocrine tumors (NETs) and are called typical and atypical carcinoids.

Typical and atypical carcinoids of the lung are rare, accounting for only 1–2% of all lung cancers, and originate from the enterochromaffin cells [1]. These cells are sometimes capable of producing hormones. Substances such as adrenocorticotropic hormone and serotonin, if released into the bloodstream, cause the Cushing and carcinoid syndrome, respectively.

The pathologic classification of NETs in the lung ranges from the low and intermediate grade, typical and atypical carcinoids to aggressive large cell neuroendocrine cancer (LCNEC) and small cell lung cancer (SCLC). This article focuses on the low-grade and intermediate-grade NETs. The course, its prognosis and treatment are distinctly different from the high-grade LCNEC and SCLC. Therefore, it is important that the treating physicians are aware of these special entities.

Incidence
On the basis of the Surveillance, Epidemiology, and End Results database analysis, the incidence of NETs of the lung is 1.35/100.000 per year. Approximately 25% of all NETs are located in the respiratory tract [2]. In this group, small cell and large cell neuroendocrine carcinoma represents approximately 20%, and typical and atypical carcinoids approximately 5%. Other NETs arise in several sites of the body, among the appendix, small intestines, pancreas, colon, rectum, duodenum, stomach and thymus.

Pathology
Typical & atypical carcinoid
In contrast to well-differentiated neuroendocrine neoplasms of other sites, those of the lung are still called ‘carcinoid’. These
carcinoid tumors are divided into two categories based on mitotic rate and the presence of necrosis: typical carcinoid (grade 1) and atypical carcinoid (grade 2) (Table 1). The atypical carcinoid is defined by a lower mitotic rate (2–10 mitosis/mm²), compared with the atypical form of NET by other origin (2–20 mitosis/mm²). Poorly differentiated neuroendocrine neoplasms (grade 3) are known as SCLC and LCNEC (Figure 1) [3,4].

Their bland cytological features recognize carcinoids with uniform round nuclei and coarse chromatin (without nucleoli) and abundant finely granular cytoplasm. Nucleoli are lacking. Nuclear size may vary. They show a ‘neuroendocrine’ growth pattern, either in demarcated nests, trabecular, insular, palisading, ribbon or rosette-like. Their neuroendocrine nature is proven by diffuse positivity with neuroendocrine markers such as synaptophysine, chromogranin or Leu-7 (CD57). CD56, NCAM, an adhesion molecule, is often positive in these tumors, but is not required. To differentiate carcinoid from paraganglioma and other rare tumors with neuroendocrine features, keratin expression is essential. All carcinoid tumors are positive for keratin 8 and 18. In contrast to well-differentiated NETs from other locations, those in the lung are also often positive for keratin 7 and TTF-1. Although quantification of Ki-67 expression (a proliferation marker) is, until now, not mandatory to classify NETs of the lung, this marker can be useful in cases with suboptimal morphology, for example, small crushed biopsies.

Bronchial carcinoid tumorlets & diffuse idiopathic neuroendocrine cell hyperplasia

Distinct features of lung NETs, in contrast to NETs of other origins, are bronchial carcinoid tumorlets and diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH). The real significance of bronchial carcinoid tumorlets is still not completely understood. These tumorlets are clusters of the Kulchitsky cells, the regular neuroendocrine cells in the lung, which extend beyond the basement membrane. They are morphologically identical to typical carcinoids, but have, by definition, a maximal diameter of 0.5 cm. Often the pathologist incidentally discovers them. They can be multifocal and generally do not cause any symptoms nor progress to carcinoid tumors [5].

DIPNECH is considered to be a preinvasive status of carcinoid tumors. The diagnosis DIPNECH is made when patients have widespread neuroendocrine hyperplasia and/or multiple tumorlets in the peripheral airways. Since it is a rare entity, little is known about it. DIPNECH may have distinct clinical features ranging from a form of interstitial lung disease with airway obstruction, probably due to the frequent association with bronchiolar fibrosis, to asymptomatic multiple pulmonary nodules, resembling metastatic malignancies [6]. Most patients are nonsmoking women, with a median age at diagnosis of 58 years (36–76 years). Although seldom, distant metastases have been described. For this reason, one may consider annual radiological follow-up in asymptomatic patients.

Clinical presentation

The median age at diagnosis for lung NETs is 64 years [7]. Characteristic carcinoids present with dyspnea, wheezing, coughing or hemoptysis due to central obstruction of the airway. Carcinoids located in the periphery of the lung are more likely to be asymptomatic and discovered as an incidental radiologic finding.

Typical and atypical carcinoids are also observed in the MEN1 syndrome. This is a genetic disease that is associated with multiple locations of NETs. Approximately 5% of MEN1 patients develop lung NETs [8].

In contrast to gastrointestinal (GI) NET, hormone-producing or functioning tumors are rare in lung NETs. Only 2% of patients with a lung NET present with symptoms caused by hormone production. The most common is the carcinoid syndrome, the result of the production of serotonin and clinically presents with flushes and diarrhea [9]. Another distinct feature in lung NETs is that the carcinoid syndrome can exist without metastasis. This is explained by the direct release of the hormone in the systemic circulation.

Symptoms of the Cushing syndrome, caused by the production of ectopic adrenocorticotropic hormone are also rare in lung NET patients, occurring in only
1–2% of patients [10]. On the other hand, lung NETs is the most common cause of the Cushing syndrome.

**Diagnosis, imaging & staging**

As applies to all tumors, acquiring the right diagnosis and stage of disease is important for prognosis and treatment. This work-up is usually performed by the pulmonologist. Approximately 70% of the carcinoids are located in the central airways, this way they can be reached by (rigid) bronchoscopy. For a correct pathological assessment, large biopsies of the tumor are required. Since carcinoids are quite often highly vascularized, it is advised to be cautious when taking biopsies. Cytology has limited value since it is impossible to determine the mitosis index and should be avoided at the initial diagnosis. To assess the extent of the disease, CT scan should be used. Sometimes a MRI scan can be indicated [10].

In contrast to the high-grade lung cancers, nuclear scans, such as the somatostatin receptor scintigraphy and metaiodobenzylguanidine (MIBG) scan, may be very useful in determining the extent of the disease and will help exploring the treatment options in typical and atypical carcinoids. The $^{111}$In-DTPA0 octreotide scintigraphy will provide information about the metabolic state of the tumor. It shows binding of the indium label to the somatostatin receptors of the tumor. If positive, treatment with the radiolabeled somatostatin analog $^{177}$Lu-DOTATATE or $^{90}$Y-DOTATOC can be considered [11,12]. In the case of uptake of $^{123}$I-MIBG in the tumor, treatment with $^{131}$I-MIBG may be of value [13]. These kind of treatments are only indicated in advanced disease. $^{18}$F-FDG PET is not useful in all carcinoids. It will only show uptake in tumors with high proliferation rates. For typical carcinoids, this is often not the case [14,15].

A solitary pulmonary nodule showing uptake on the somatostatin receptor scintigraphy is very likely a typical carcinoid. Atypical carcinoids are more likely to show uptake on the $^{18}$F-FDG PET scan, although uptake on both scans have been described. In the case of a solitary pulmonary nodule without any uptake on nuclear scans, a hamartoma or granuloma may be considered. For staging purposes, the seventh edition of the International Association for the Study of Lung Cancer TNM staging system is used (Table 2) [16–18].

**Biomarkers**

The circulating tumor marker chromogranin A (CgA) is a 49 kD acidic polypeptide that is present in the granules of neuroendocrine cells. An isolated elevation of serum CgA levels is not sufficient for the diagnosis of a NET. However, combined with a positive somatostatin scintigraphy, the sensitivity of tumor detection increases to 93% [19].

In individual cases, the level of CgA is correlated to tumor burden, making it a suitable marker for the follow-up of patients with advanced disease. As it is elevated in both hormonal active and inactive tumors, it can widely be applied. For typical carcinoids, the sensitivity is 95%, its specificity is 50% and for atypical carcinoids 95 and 73%, respectively [20].

A few considerations have to be made when interpreting elevated CgA levels. The most common mistake is the false-positive value in a patient using proton pump inhibitors. This class of drug causes elevation of circulating CgA levels through indirect stimulation of the enterochromaffin cells of the stomach. For correct interpretation of CgA levels, patients...
should discontinue proton pump inhibitors for at least 2 weeks, before measurement of CgA [21].

Furthermore, somatostatin analogs are known to decrease the blood levels of CgA, therefore serial CgA levels should be measured at the same interval from injection in patients receiving long-acting somatostatin analogs. CgA levels may also be elevated in patients with renal or liver failure.

Another biomarker that can be used is progastrin-releasing peptide. A high (more than twice the upper reference value) level in patients with well-differentiated NETs is a strong indication for a primary tumor in the lung. Progastrin-releasing peptide is a complementary biomarker to CgA, for prognosis and treatment monitoring [22].

Urinary 5-hydroxyindoleacetic acid, the degradation product of serotonin, is tightly linked to the carcinoid syndrome. Since the carcinoid syndrome in lung NETs is rare, the clinical usefulness of urinary 5-hydroxyindoleacetic acid is limited.

**Prognosis**

Both typical and atypical carcinoids are capable of metastasizing to regional lymph nodes and distant sites to liver and bones, albeit seldomly. Patients with typical carcinoids have a very good prognosis, with a 5-year survival rate of 87%. Regional lymph node metastases occur in 10–15% of cases and distant metastases in an additional 2%. Atypical carcinoids are more aggressive, reflecting in a higher frequency of nodal (57%)

<table>
<thead>
<tr>
<th>Description</th>
<th>Definitions</th>
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<tbody>
<tr>
<td>T0</td>
<td>No primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤3 cm, surrounded by lung or visceral pleura, no bronchoscopic evidence of invasion more proximal than the lobar bronchus</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤2 cm</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;2 cm but ≤3 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;3 cm but ≤7 cm or tumor with any of the following: invades visceral pleura, involves main bronchus ≥2 cm distal to the carina, atelectasis/obstructive pneumonia extending to the hilum, but not involving the entire lung</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor &gt;3 cm but ≤5 cm</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor &gt;5 cm but ≤7 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;7 cm or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium; or tumor in the main bronchus &lt;2 cm distal to the carina; or atelectasis/obstructive pneumonia of entire lung; or separate tumor nodules in the same lobe</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodules in a different ipsilateral lobe</td>
</tr>
<tr>
<td>N0</td>
<td>No regional node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral peribronchial and/or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodules in a contralateral lobe; or tumor with pleural nodules or malignant pleural dissemination</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Data taken from [18].
and distant (14%) metastases. The 5-year survival of atypical carcinoid patients is approximately 56% [4,28].

**Surgery**

The mainstay of treatment of locally and locally advanced carcinoids is surgical resection. In patients with a typical carcinoid, a lung-sparing operation is equivalent to a larger resection. Local recurrence and recurrence at distant sites are rare but may occur, even after many years. Atypical carcinoids are more likely to have mediastinal lymph node metastasis at presentation, but even then, surgery is the treatment of choice. Together with resection, a mediastinal lymph node dissection is usually advised, because it was associated with fewer local recurrences in one study [24,25].

There are currently no data to suggest that adjuvant therapy (chemotherapy, radiation or chemoradiation) will prolong a disease-free interval or median survival [10]. Data are lacking to recommend the use of adjuvant therapy after complete resection of locoregional disease. For the follow-up, surveillance for at least 7 years every 6–12 months is recommended, but may be even longer because of the indolent nature of carcinoids. Evaluation should consist of interval history, physical examination and chest roentgenogram. CT-thorax is also advocated. If preoperatively risen, CgA can be used as a biomarker in follow-up.

**Treatment in advanced disease**

At present, there are no antiproliferative agents approved for carcinoids of the lung. None of the currently available drugs provide a cure. The main goal of treatment is stabilization of disease, providing prolongation of progression-free survival (PFS). In general, treatment of lung NET patients does not differ much from NETs of other origin. Important factors that influence the therapeutic decision-making process are the hormone-secreting status of the tumor; expression of the somatostatin receptor present at the octreotide scintigraphy; uptake on the MIBG scan; the grade of the tumor and the amount of tumor burden.

Since some of the carcinoids may have an indolent character, a good strategy may be to classify patients into low- and high-risk groups of estimated growth of the tumor. Parameters for this may be the mitosis index, the absence of growth on a CT scan, the presence of symptoms in any kind, such as pain, weight loss and pulmonary symptoms. Although pulmonary symptoms are not always useful for this purpose, since they can be linked to the obstruction of the bronchus and/or related to infectious disease and may in that case be an indication for local treatment. In the low-risk group an active wait-and-see strategy is allowed. In the high-risk group, some kind of treatment should be considered. Because there is a lack of approved treatments in advanced lung NETs, it is advised to refer this group of patients to a dedicated center with a neuroendocrine multidisciplinary team.

In the following sections, we focus on drugs as somatostatin analogs, IFN-α mTOR inhibitors, inhibitors of angiogenesis and systemic chemotherapy as possible treatment options.

As studies are hard to perform in orphan diseases, the data mainly consist of small (retrospective) Phase II studies. Another complicating factor is that the results of these studies are hard to interpretate since these studies usually have a mixed study population, with differences in grade, site of NET origin and with or without the carcinoid syndrome.

**Somatostatin analogs**

A very well-known treatment is the use of the somatostatin analogs, octreotide and lanreotide. They are the mainstay for the control of the symptoms of the carcinoid syndrome and are approved standard therapies for this indication. They act through interaction with the specific membrane receptors on the responsive cells, leading eventually to the blockade of release of numerous secondary hormones [10]. Although somatostatin analogs have been used as potential antiproliferative agents in carcinoids of other origin [26], there are no prospective data to support this action in lung NETs.

**IFN-α**

IFN-α is also a standard treatment for the control of the carcinoid syndrome, but is mainly used as second-line therapy [10]. Interferon receptors are expressed on the surface of NET cells. Therefore, they were considered a potential target for therapy. Although there is little evidence for the use of interferons as an antineoplastic agent in lung NETs.

A small, retrospective study demonstrated that interferon ± octreotide treatment resulted in stabilized disease in four of 27 (15%) typical lung carcinoid patients, lasting for a median of 15 months. No partial responses were observed [27]. Furthermore, a small randomized Phase III trial comparing 5-fluorouracil and streptozotocin with interferon included only three of 64 patients with carcinoids originating in the lung. The median PFS for chemotherapy was 5.5 versus 14.1 months for interferon, but this was not significant (p = 0.25) [28].

IFN-α has been reported to induce disease stabilisation or partial responses in a small number of patients in NET trials with a mixed study population. Pooling the data of these, unfortunately often from under-powered trials, 37 of 309 (12%) patients had objective tumor responses [29].
mTOR inhibitors

mTOR inhibitors are the most promising drugs at the moment and are currently tested extensively. In a Phase III study (RADIANT-T2), 429 patients with a low- or intermediate-grade NET and a history of the carcinoid syndrome were enrolled. Patients were randomized between the combination of everolimus and octreotide long-acting repeatable (LAR) or placebo and octreotide LAR. The primary end point, median PFS was 16.6 months for the everolimus combination compared with 11.3 months for the placebo combination (hazard ratio: 0.77; 95% CI: 0.59–51.00; p = 0.026) [30]. A retrospective exploratory analysis evaluated the efficacy of all 44 typical and atypical carcinoids of the lung in this study. This showed similar results: the median PFS increased by 8 months from 5.6 months in patients receiving the placebo combination to 13.6 months in patients receiving the everolimus combination. Although this time it was not statistically significant (p = 0.228) [31]. This was probably explained by several limitations of the analysis: a small sample size; imbalanced patient numbers between groups due to the lack of stratification of the primary tumor site and the retrospective nature of the evaluation. These observations supported the continued evaluation of everolimus treatment regimens in patients with lung NETs. Several studies are already underway.

Data about the activity of everolimus in patients with nonfunctioning lung carcinoids are awaited from the RADIANT 4 study, a randomized, placebo controlled, Phase III study testing everolimus in patients with advanced low or intermediate NET of GI or lung origin [32]. This study has completed its enrolment. Another multicenter study that possibly will shed light on the beneficial effect of everolimus (and somatostatin analogs) is the LUNA trial. This three-arm, Phase II trial, evaluates the efficacy of pasireotide LAR or everolimus alone or the combination in patients with well-differentiated neuroendocrine carcinoma (typical or atypical carcinoid) of the lung and thymus [33]. It is recruiting patients at the moment.

Inhibitors of angiogenesis

Inhibitors of angiogenesis have been tested in patients with lung NETs, but were less successful. Based on the high microvessel density in NET tumors, high expectations were set. NETs expresses VEGF and its receptor (VEGFR), where it is a key driver of angiogenesis in pancreatic NETs. This knowledge led to the randomized, placebo controlled, Phase III trial in which the multigatedtyrosine kinase inhibitor sunitinib showed an improved objective response rate, PFS and overall survival in advanced pancreatic NETs over placebo [34].

Sunitinib was tested in a Phase II trial in lung NETs in which 14 of 40 patients with foregut carcinoids (lung and stomach combined) were enrolled. Approximately half of these patients received also stable doses of somatostatin analogs, already started before trial inclusion, for the treatment of the carcinoid syndrome. The objective response rate was low at 2.4% and the median PFS of 10 months was not better than might have been expected with somatostatin analogs alone [35].

Bevacizumab, a monoclonal antibody targeting VEGF has been evaluated in combination with other drugs in several trials. Unfortunately, combinations with temozolomide, 2-methoxyestradiol, capcitabin and oxaliplatin were mostly disappointing and showed no objective responses in lung NET patients [36–38]. Only one Phase II trial of octreotide with either bevacizumab or pegylated interferon showed a higher response in the bevacizumab arm (18 vs 0%) [39], a promising outcome that led to the SWOG Phase III randomized trials in advanced NETs [40].

Systemic chemotherapy

There is a lot of unclarity about the usefulness of chemotherapy in typical and atypical carcinoids of the lung. A generally accepted observation in NETs is that the lower the proliferation rate of the tumor, the less likely chemotherapy results in a beneficial effect. On the other hand, in contrast to carcinoids of the intestines, the natural course of lung NET seems to be more aggressive, as in NETs of the pancreas, granting the use of chemotherapy. According to the available data, (a combination with) temozolomide or oxaliplatin combined with capecitabine seems to be the best choice.

Temozolomide is an oral, alkylating, drug and has shown to be effective in a retrospective series. Thirteen patients with long NETs showed an objective response rate of 31% and 31% had stabilization of disease [41]. The median time to progression was 7 months. Based on these scarce data, temozolomide is considered an option in the treatment of patients with lung NET.

The combination of the oral prodrug of 5-fluorouracil, capcitabine and temozolomide was studied in a recent published retrospective review of 18 patients with low-grade NET metastatic to the liver who had failed previous therapy. Only two patients had a foregut tumor. Results of the whole group showed one complete response (6%; nonsecretory carcinoid of the duodenum), lasting for 25 months. Another ten patients (56%) achieved a partial response. Four patients (22%) had stable disease. Responses occurred after 4–12 cycles of capcitabine/temozolomide, with a median time to response of 6 months, subscribing the
slow kinetics of these tumors. The median PFS of all patients was 14 months [42].

Less noteworthy is the combination of temozolomide and thalidomide, tested in a Phase II study of patients with metastatic NETs; 15 of 28 patients had carcinoids of different sites of origin. In this group, partial response was only 7% [43].

An alternative to temozolomide may be the combination of the platinum oxaliplatin with capecitabine. These drugs were tested in a Phase II study. Five out of 27 patients were patients with low-grade lung NETs. Of these, three patients had a partial response and one patient had stable disease. The median time to progression for the group as a whole was 20 months [44].

The largest study is the one comparing the use of doxorubicin with 5-fluorouracil and streptozocin with 5-fluorouracil. This was a Phase II/III study of 163 patients that ran for 8 years. Approximately a quarter of patients were patients with lung NETs and in both groups objective response rates of 15.9 and 16% were seen, respectively. The PFS was 4.5 and 5.3 months [45]. Unfortunately, other studies could not confirm these response rates [27,28].

Conclusion

In general, lung NETs has a more aggressive course of disease, which is also reflected in the pathological staging. The atypical carcinoid is defined at a lower mitotic rate (2–10 mitosis/mm² compared with other NETs (2–20 mitosis/mm²). Another prominent pathological feature is that low- and intermediate-grade lung NETs are still defined as typical and atypical carcinoids and not as grade 1 and 2 disease. To promote unity in NETs, change in definition is highly recommended.

Special entities in lung NETs, which are not seen in other NETs are bronchial carcinoid tumorlets and DIPHNEC. In contrast to GI NET, in lung NET the carcinoid syndrome may occur in patients that are not metastasized, but this occurs infrequently. For advanced disease, there are many potential treatment options, but because of the lack of reliable data, choices are not straightforward. Fortunately, large randomized Phase II and III studies are underway. Because of the rarity of lung NETs, especially in advanced disease, it is advised to treat patients in dedicated centers with a multidisciplinary neuroendocrine team.

Future perspective

NETs of the lung are an orphan disease with a varying presentation. Low- and intermediate-grade lung NETs is still defined as typical and atypical carcinoids and not as grade 1 and 2 disease. To promote unity in NETs, change in definition is highly recommended.

The mainstay of treatment is surgical resection but other, new and promising treatments are now being tested in the advanced setting. The introduction of somatostatin analogs and availability of oral mTOR inhibitors may now offer patients with metastatic disease better future perspectives. It is of importance that these studies are performed in clinics where a multidisciplinary approach and expertise is available when radical resection is not possible.

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Executive summary

- A total of 25% of neuroendocrine tumors (NETs) originate in the lung.
- The pathological grading system for lung NETs differs from most other NETs.
- Typical and atypical carcinoids of the lung are only in 2% of cases associated with the carcinoid syndrome. The carcinoid syndrome can also occur in lung NET patients in the absence of metastasis.
- Special features in lung NETs are bronchial carcinoid tumorlets and diffuse idiopathic neuroendocrine cell hyperplasia.
- For advanced disease there are many potential treatment options; however, because of the lack of reliable data, choices are not straightforward. Fortunately, large randomized Phase II and III studies are underway.

References

Papers of special note have been highlighted as:

- of interest; •• of considerable interest


• European Society for Medical Oncology clinical practice guideline.
Review Buikhuisen, Tessaear, van Velthuysen, Korse, Taal & Baas


- Article on a series of diffuse idiopathic neuroendocrine cell hyperplasia patients: clinical data, histopathology, management and follow-up.


- More extensive guideline from the North American Neuroendocrine Tumor Society.


- Article on a series of foregut carcinoid tumours treated with 177Lu-octreotate.


- The Spanish experience on a very large series of 661 typical and atypical carcinoids of the lung treated surgically.


- Useful article on the management of the surgical approach to the carcinoid patient of the lung.


28 Dahan L, Bonnetain F, Rougier P et al. Phase III trial of chemotherapy using 5-fluorouracil and streptozotocin compared with interferon alpha for advanced carcinoid
Neuroendocrine tumors of the lung: a comprehensive overview

Review


32 Everolimus plus best supportive care vs placebo plus best supportive care in the treatment of patients with advanced neuroendocrine tumors (GI or lung origin) (RADIANT-4). http://clinicaltrials.gov/show/NCT01524783


40 Octreotide acetate and recombinant interferon alfa-2b or bevacizumab in treating patients with metastatic or locally advanced, high-risk neuroendocrine tumor. http://clinicaltrials.gov/show/NCT00569127


