Ther Adv Med Oncol
2017, Vol. 9(3) 189–199
DOI: 10.1177/1758834016678149

Current understanding and approach to well differentiated lung neuroendocrine tumors: an update on classification and management

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Abstract: Neuroendocrine tumors (NETs) are rare neoplasms that can arise from any tissue. They are classified based on embryonic gut derivative (i.e. foregut, midgut and hindgut) with midgut tumors being the most common (e.g. gastrointestinal NET). The second most common category of NETs is that which arises from the lung. In fact, 25% of primary lung cancers are NETs, including small cell lung cancer (SCLC), which comprises 20% of all lung cancers. The remaining 5% are large cell neuroendocrine cancer (LCNEC, 3%), typical carcinoids (TCs, 1.8%), and atypical carcinoids (ACs, 0.2%). The less common TCs/ACs are well differentiated lung NETs. Their incidence has been increasing in more recent years and although these tumors are slow growing, advanced disease is associated with poor survival. There have been advances in classification of lung NETs that have allowed for more appropriate management upfront. They are cured by surgical resection when disease is limited. However, advanced and metastatic disease requires medical therapy that is ever changing and expanding. In this review, the aim is to summarize the current understanding and classification of well differentiated lung NETs (i.e. TCs and ACs), and focus on recent updates in medical management of advanced disease, along with a brief discussion on potential future discoveries.

Keywords: bronchial carcinoid, neuroendocrine tumor, NET, carcinoid tumor

Introduction

Neuroendocrine tumors (NETs) are epithelial neoplasms with predominant neuroendocrine differentiation that can arise in most body organs and share common pathologic features [Modlin *et al.* 2008]. Studies have focused on classifying NETs based on site of origin and embryonic derivative. Lung NETs arise from bronchial mucosa and are therefore considered foregut derivatives. They are classified along a spectrum of which small cell lung cancer (SCLC) is the most malignant. Low- and intermediate-grade lung NETs, otherwise known as typical and atypical pulmonary carcinoids, respectively, account for the second most common category of NETs (25–30% in studies) [Kulke and Mayer, 1999; Gustafsson *et al.* 2008], but compromise 1–2% of all lung tumors [Bertino *et al.* 2009]. They are more common in women than men and in Whites over other ethnicities. They tend to occur in the fourth-to-sixth decade of life with a one decade difference in mean age for typical carcinoids (TCs) over atypical carcinoids (ACs), 45 years over 55 years, respectively [Hassan *et al.* 2008; Faggiano *et al.* 2012]. Moreover, they represent the most common primary lung neoplasm in children and adolescents [Dishop and Kuruvilla, 2008].

There has been an increase in both prevalence and incidence of TCs/ACs that may be explained by the increased awareness, more liberal use of computed tomography (CT) scans of the chest, and the introduction of low-dose CT scans for lung cancer screening in smokers [Carter *et al.* 2007; Pelosi *et al.* 2008]. The majority of TCs/ACs occur in never or current light smokers [Hassan *et al.* 2008], and the ratio between TCs and ACs is approximately 10:1 [Travis *et al.* 2004]. Although considered to be potentially curable by

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Table 1. WHO classification of neuroendocrine tumors of the lung (2015) [Travis *et al.* 2015].

Differentiation	Grade	Mitotic rate	Diagnosis
Well differentiated	Low grade	<2 mitoses per 2 mm^2 AND no necrosis	TC tumor
	Intermediate grade	2–10 mitoses per 2 mm^2 or foci of necrosis	AC tumor
Poorly differentiated	High grade	⩾11 mitoses per 2 mm^2	SCLC LCNEC

TC, typical carcinoid; AC, atypical carcinoid; SCLC, small cell lung cancer; LCNEC, large cell neuroendocrine cancer.

surgical resection, some patients present with locally advanced or metastatic disease with or without hormone-related syndromes that may prove to be more challenging in management. Furthermore, large-scale clinical trials are limited for this specific patient population due to the overall rarity of the condition. In this review, the aim is to discuss the approach to patients with well differentiated lung NETs with a focus on pathologic description, classification and management of limited and advanced disease.

Classification

Nomenclature

What is widely referred to as a carcinoid tumor is technically a neoplasm of malignant potential. The term 'carcinoid' has been criticized due to the false sense of 'benign' that it conveys. In the most recent World Health Organization (WHO) classification of pulmonary NETs, the term pulmonary 'carcinoid' tumor remains in use when referring to low-grade and intermediate-grade tumors [Travis *et al.* 2004]. Moran and colleagues referred to lung NETs as neuroendocrine carcinomas, which is a more accurate description, but requires grading them pathologically to define their aggressive nature [Moran *et al.* 2009]. The two concepts of grade and differentiation are closely related, but slightly different.

Grade refers to the inherent biologic aggressiveness of the tumor with low-grade referring to an indolent neoplasm and high-grade referring to an extremely aggressive neoplasm. Differentiation refers to the degree of neoplasm resemblance to the non-neoplastic tissue of origin [Klimstra *et al.* 2010]. For example, well differentiated NETs have characteristic arrangements of uniform cells and typically produce abundant neurosecretory granules which allow them to express neuroendocrine markers such as chromogranin A and synaptophysin. Poorly differentiated NETs have a more sheet-like or diffuse architecture, irregular nuclei, and less cytoplasmic granularity, which is why immunoexpression of markers is more limited. In general, well differentiated NETs are considered either low or intermediate grade, while poorly differentiated NETs are considered high grade [Moran *et al.* 2009; Klimstra *et al.* 2010].

The distinction between well differentiated and poorly differentiated NETs is perhaps the most clinically relevant as it directly translates to therapy options and prognosis. The WHO classifies lung NETs based on grade and uses the terms 'typical' and 'atypical' carcinoid for low-grade and intermediate-grade NETs, respectively (Table 1). Referring to low and intermediate-grade NETs as neuroendocrine carcinomas is more accurate and reflects their potential for invasive disease [Klimstra *et al.* 2010].

Grading

The tumor grade is inferred by the degree of proliferation as measured by the mitotic rate, along with features of necrosis (Table 1). The mitotic rate is calculated by counting the number of mitoses per unit area of tumor (expressed as mitoses per 2 mm^2, rather than 10 high-power microscopic fields in the 2015 WHO classification, Table 1) [Klimstra *et al.* 2010; Travis *et al.* 2015]. In tumors that are near the cutoffs of 2 or 10 mitoses per 2 mm^2, at least three sets of 2 mm^2 should be counted and the mean used for determining the mitotic rate, rather than the single highest rate [Travis *et al.* 2015].

Ki-67 is a proliferation marker that can be expressed in neoplastic cells *via* immunolabeling. The index is reported by calculating the percentage of cells that expresses Ki-67. It is used in the classification of gastroenteropancreatic (GEP)-NETs, but has not been fully incorporated into the classification of lung NETs due

to conflicting data regarding its utility in separating TCs from ACs [Walts *et al.* 2012; Caplin *et al.* 2015]. It is typically more useful when the amount of tumor tissue is limited to complete a mitotic rate or when the cells are crushed and possibly, necrotic [Rindi *et al.* 2007; Travis, 2010]. The current role of Ki-67 in lung NETs is mainly to separate the high-grade large cell neuroendocrine carcinoma (LCNEC) and SCLC from the TCs/ACs [Travis *et al.* 2015]. A Ki-67 index $\geqslant$ 50% is seen in high-grade NETs ($\geqslant$80% in SCLC) compared with up to 20% ($\leqslant$5 % in TCs compared with 5–20% in ACs) in TCs/ACs [Pelosi *et al.* 2005; Travis, 2010].

Indeed, there is a large gap in Ki-67 indices between low/intermediate-grade lung NETs and high-grade lung NETs. This underscores the biologic difference between the two entities, which is manifested by unique histopathologic features and a discrete clinical course. There has been no report of progression from TCs/ACs to LCNEC/SCLC and the two ends of the spectrum have distinct epidemiologic characteristics.

It is worthwhile mentioning the entity referred to as diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) which is characterized by widespread hyperplasia of pulmonary neuroendocrine cells and carcinoid tumorlets (nodular proliferations that measure $<$0.5 cm in greatest diameter). It is considered a preinvasive lesion for pulmonary carcinoids (PCs) but is extremely rare and not necessarily required for the development of a well differentiated lung NET [Pelosi *et al.* 2005].

Staging

The American Joint Committee on Cancer TNM system is used for staging TCs/ACs [Edge and Compton, 2010]. The staging criteria rely predominantly on the size of the tumor and the extent of invasion into similar landmarks as used for the staging of non-neuroendocrine carcinomas [Pelosi *et al.* 2005; Klimstra *et al.* 2010]. The utility of this staging system is of concern due to larger cutoff values (e.g. 3 cm and 5 cm) than expected for lung NETs ($<$3 cm) [Volante *et al.* 2015].

Both conventional imaging and scintigraphy should be used for accurate staging. Whole-body somatostatin receptor scintigraphy using 111In-pentetreotide with thorax single-photon emission CT/CT can detect up to 80% of primary tumors preoperatively and can identify the N and M stage [Granberg *et al.* 2003]. Over the past decade, the introduction of positron emission tomography (PET) with the 68Ga-labeled octreotide derivatives DOTATOC and DOTATATE (68Ga-SSA-PET/CT) have demonstrated a sensitivity $>$ 90% and a specificity approaching 100% in the diagnosis of NETs [Yang *et al.* 2014]. The most common sites of metastasis are the liver, bones and mediastinal lymph nodes [Bhosale *et al.* 2013]. Multiphase CT with arterial and portal venous phases with or without MRI, with dynamic acquisition and diffusion-weighted sequences are used for the detection of liver metastases [Sundin *et al.* 2009]. For detection and characterization of bony metastasis, MRI is the test of choice, but SRS has a higher sensitivity [Leboulleux *et al.* 2008].

Treatment

Surgical

Surgical resection is the treatment of choice and the only curative option for TCs/ACs with the aim to remove the tumor and preserve as much normal lung tissue. The approach differs based on tumor stage, invasion, and lymph node status.

Localized disease should be managed with curative intent. The surgical approach depends on the location of the tumor. For patients with peripheral lung tumors, complete anatomic resection with lobectomy and segmentectomy is recommended. For patients with central airway tumors, which are almost exclusively TCs, lung parenchymal-sparing surgery with a bronchial sleeve resection or sleeve lobectomy is recommended. In both cases, systematic nodal dissection should be carried out to designate R0 resections [Detterbeck, 2010]. N2 disease is not an absolute contraindication for operative management in this patient population due to the slow tumor growth [Caplin *et al.* 2015].

On the other hand, surgery for metastatic disease is only carried out on patients with limited sites of disease where radical resection is possible for all sites. For patients with liver metastases, curative intent resection can be considered, or to aid in symptom control with debulking (when $>$90% of tumor can be removed) [Glazer *et al.* 2010]. Current European Neuroendocrine Tumor Society (ENETS) recommendations define

Table 2. Medical therapy options for progressive, advanced/metastatic well differentiated lung neuroendocrine tumors.

Category	Drugs	Indication	Sequence of use*
SSA	Octreotide, lanreotide	TC or AC with strongly positive SSR	First line
mTOR inhibitors	Everolimus	TC or AC of any kind	First line
Temozolomide-based chemotherapy	Temozolomide +/– capecitabine	TC or AC with negative SSR and rapid progression	First or second line
Platinum-based chemotherapy	Cisplatin and etoposide	AC with negative SSR and rapid progression	First or second line
PRRT	177lu-OCTROTATE	TC or AC with strongly positive SSR	Second or third line

SSA, somatostatin analogue; TC, typical carcinoid; AC, atypical carcinoid; mTOR, mammalian target of rapamycin; SSR, somatostatin receptor; PRRT, peptide receptor radionuclide therapy.
*There is no substantial evidence for the preferred regimen or sequence.

curative intent as a resectable TC or low-grade AC; <5% mortality; absence of right heart failure; absence of unresectable lymph node and extra-abdominal metastases; and absence of unresectable peritoneal carcinomatosis [Pavel *et al.* 2012; Caplin *et al.* 2015].

General follow-up recommendations include a reassessment once between 3 and 6 months after complete curative resection, then every 6–12 months for at least 7 years thereafter [Phan *et al.* 2010]. There are no clinical trials evaluating the use of adjuvant chemotherapy in patients with well differentiated lung NETs.

Medical

Medical therapy for well differentiated lung NETs is used in the advanced disease setting. The implementation of adjuvant chemotherapy is an area of controversy among guidelines. The National Comprehensive Cancer Network (NCCN) recommends the use of adjuvant chemotherapy with or without radiation therapy for patients with stage II/III AC [National Comprehensive Cancer Network, 2016]. On the other hand, the ENETS recommends consideration of chemotherapy in patients with ACs with positive lymph nodes [Caplin *et al.* 2015].

In patients with unresectable disease, or with recurrence after resection, effective medical therapy is the only available option. There is a lack of consensus among cooperative groups with regard to the correct order of therapy. Evidence of disease progression within 3–6 months from diagnosis is usually required before initiation of therapy as some tumors might be slow growing and can be managed with an observation strategy. When medical therapy is used, the options include somatostatin analogues (SSAs), mammalian target of rapamycin (mTOR) inhibitors, cytotoxic chemotherapy, and peptide receptor radiotargeted therapy (PRRT) (see Table 2). The goals of medical therapy are to slow tumor growth, and control hormone-related symptoms (in patients with functional tumors).

Somatostatin analogues. Approximately 10% of advanced TCs/ACs are hormone-producing, functional tumors that can impair quality of life (QOL) [Ferolla, 2014]. The most common hormone-related syndrome encountered is carcinoid syndrome, characterized by flushing, diarrhea, shortness of breath and wheezing. These patients benefit greatly from SSAs (e.g. octreotide and lanreotide) with one series reporting 100% symptom control in patients with ACs [Filosso *et al.* 2002].

In patients with refractory carcinoid syndrome while on a SSA, the oral serotonin synthesis inhibitor, teloristat etiprate, [Kulke *et al.* 2014] has shown significant reduction in carcinoid syndrome-induced diarrhea in the phase III TELESTAR trial [Gelhorn *et al.* 2016]. If approved, it can be added to an SSA for symptom management.

In controlling tumor growth for palliation, prospective studies dedicated to TCs/ACs are lacking. However, studies in well differentiated NETs of different sites have reported disease stabilization in 30–70% of patients [Aparicio *et al.* 2001; Faiss *et al.* 2003]. Data on using SSAs for TCs/ACs is extrapolated from two large prospective

randomized controlled trials that demonstrated cytostatic control in GEP-NETs when using SSAs. The first was the PROMID study of octreotide long-acting repeatable (LAR) 30 mg *versus* placebo in 85 patients with midgut NETs that reported a median time to progression for the octreotide group *versus* placebo of 14.3 months *versus* 6 months, respectively [hazard ratio (HR): 0.34; $p < 0.001$] [Rinke *et al.* 2009]. The second was the CLARINET study of lanreotide (120 mg every 28 days) *versus* placebo in 204 patients with nonfunctional GEP-NETs that reported a progression free survival (PFS) at 24 months in the lanreotide group *versus* placebo of 65.1% *versus* 33%, respectively [HR: 0.47; 95% confidence interval (CI): 0.30–0.73; $p < 0.001$] [Caplin *et al.* 2014].

For TCs/ACs with strong expression of somatostatin receptors (SSRs) on imaging, or for functional well differentiated lung NETs, SSAs may be considered as first-line therapy [Pavel *et al.* 2016].

Mammalian target of rapamycin inhibitors. The mTOR pathway involves an intracellular serine/threonine kinase that regulates key cellular functions. The rationale behind targeting the mTOR pathway in the treatment of NETs comes from several observations [Chan and Kulke, 2014]. First, NETs that arise in familial syndromes such as neurofibromatosis type 1 and tuberous sclerosis (TS) have been associated with mutations in genes encoding proteins that lie upstream from mTOR. This results in activation of mTOR and is associated with NETs involving the gastrointestinal tract and pancreas [Starker and Carling, 2009]. Second, sporadic NETs have been associated with somatic mutations in PTEN, TS2, and PIK3CA,especially those that arise from the pancreas [Jiao *et al.* 2011]. Finally, activation of mTOR and its downstream targets has been associated with higher proliferative index and shorter survival [Qian *et al.* 2013].

Everolimus is an inhibitor of the mTOR pathway that is approved for metastatic, progressive, well differentiated lung and GEP-NETs. It was initially approved for pancreatic NETs based on the results of the phase III RADIANT-3 trial [Yao *et al.* 2011]. However, before the RADIANT-3 trial, data existed for the potential benefit of everolimus in lung NETs. In the phase III RADIANT-2 trial, the addition of everolimus to octreotide provided evidence of efficacy in advanced, functional NETs compared with octreotide alone with a PFS of 16.4 *versus* 11.3 months, respectively (HR: 0.77, 95% CI: 0.59–1.00) [Pavel *et al.* 2011; Fazio *et al.* 2013], although the result was not statistically significant. To definitively answer the question, the phase III RADIANT-4 trial was designed to test everolimus in patients with advanced, progressive, nonfunctional NETs of gastrointestinal and lung origin. The study included 302 patients, 90 of which were patients with lung NETs. The results showed a significant improvement in PFS with everolimus compared with placebo (11 months *versus* 3.9 months, respectively, HR: 0.48, $p < 0.001$). Furthermore, an interim overall survival analysis suggested a numeric improvement in favor of everolimus but did not meet statistical significance (HR: 0.64, 95% CI: 0.40–1.05, $p = 0.037$) [Yao *et al.* 2016].

The RADIANT trials culminated in the conclusion that everolimus can be used for patients with advanced NETs of any site, and provided an option for a subpopulation with previously unmet needs. It is currently the only FDA-approved drug for lung NETs and is recommended as a first-line agent by the ENETS [Pavel *et al.* 2016].

Antiangiogenesis agents. Sunitinib is an inhibitor of receptor tyrosine kinases for multiple tumor growth factors [including vascular endothelial growth factor (VEGF)-1, 2, 3 and platelet-derived growth factor receptor (PDGFR)-a and -b], and is currently approved for metastatic, well differentiated pancreatic NETs [Raymond *et al.* 2011]. A large study evaluating the efficacy of sunitinib in patients with advanced NETs included 41 patients with carcinoid tumors (including 14 patients with lung NETs and 27 patients with gastrointestinal NETs) and reported an objective response rate (ORR) of 2.4% and stable disease (SD) in 83%, with no difference in survival compared with pancreatic NETs [Kulke *et al.* 2008].

Although data for its use in lung NETs is lacking, pazopanib was studied in the PAZONET study as a sequencing treatment in progressive metastatic NETs and showed a clinical benefit in 85% of patients including patients with TCs/ACs ($n = 5$) [Grande *et al.* 2012]. However, more recently, another study combining pazopanib and depot octreotide in advanced, well differentiated NETs showed an ORR in pancreatic NETs only [Phan *et al.* 2015].

Another agent is bevacizumab, a VEGF monoclonal antibody that showed efficacy in a phase II study comparing it with pegylated interferon (IFN). Of the 22 patients, 21 demonstrated a partial response (PR) in the bevacizumab group (four of which were TCs/ACs) [Yao *et al.* 2008b]. A larger follow-up study compared IFN plus octreotide *versus* bevacizumab plus octreotide in patients with advanced NETs (including ACs, but not TCs). The results showed no significant difference in PFS between the two arms [Yao *et al.* 2015].

The use of antiangiogenesis agents are not recommended for TCs/ACs outside a clinical trial, due to the lack of data showing efficacy in lung NETs [Pavel *et al.* 2016].

Cytotoxic chemotherapy. The NCCN guidelines recommend systemic cytotoxic chemotherapy for patients with advanced disease only when no other treatment options are available. The ENETS guidelines recommend cytotoxic chemotherapy under specific circumstances including: (1) AC with a Ki-67 in the upper range (15–20%), (2) in rapidly progressive disease within 3–6 months based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1), and possibly (3) in SSR-negative disease [Caplin *et al.* 2015].

Multiple cytotoxic agents have been studied, but the two most commonly used combinations include either a temozolomide or a platinum component.

Data suggest temozolomide-based regimens have efficacy in metastatic well differentiated NETs [Fine *et al.* 2013]. Temozolomide monotherapy was used in a phase II study that included 13 patients with PC (10 with TC and 3 with AC), and showed a PR in 31% and SD in 31% [Ekeblad *et al.* 2007]. Another retrospective study from Sweden included 31 patients with PCs (14 TC, 15 AC, and 2 unclassifiable) and showed a PR in 14% and SD in 52% [Crona *et al.* 2013]. Temozolomide with capecitabine was evaluated in a retrospective study involving 29 patients (8 with PCs) that showed control of tumor growth in 72% of patients [Spada *et al.* 2014].

The standard regimen of cisplatin plus etoposide used for high-grade lung NETs (SCLC and LCNEC) demonstrated low activity for TCs/ACs. However, a subgroup of patients with ACs may benefit from this regimen as shown in a number of studies [Moertel *et al.* 1991; Chong *et al.* 2014]. Current guidelines by the NCCN recommend cisplatin and etoposide for stage II and III ACs with or without radiation therapy [Demetri *et al.* 1996; National Comprehensive Cancer Network, 2016]. The benefit of platinum-based therapy is likely only seen in ACs with a Ki-67 of 15–20% [Caplin *et al.* 2015].

PRRT. Expression of SSRs allows for treatment with SSAs, facilitates imaging with radiolabeled octreotide (e.g. indium-111 SSA scintigraphy or gallium-68 SSA PET scans), and provides the rationale for PRRT. Patients with high uptake of radiolabeled SSAs on imaging may benefit from PRRT to treat metastases of TCs/ACs [Caplin *et al.* 2015].

Studies evaluating PRRT are largely limited to single centers. Early phase II studies of 90yttrium-DOTA octreotide found the response rate to be up to 29% in seven lung NETs [Waldherr *et al.* 2001]. A large retrospective study looking at 1109 metastatic NETs included 84 lung NETs treated with 90yttrium-DOTA octreotide found that 28% of the lung NETs showed a morphological response as estimated by RECIST 1.1 and 38% showed a clinical response with a mean survival of 40 months. Limitations to the use of 90yttrium-DOTA octreotide are due to grade 3 and 4 toxicities seen in 10–33% of patients, including irreversible renal failure seen in 9.2% according to one study [Imhof *et al.* 2011].

177lutetium-DOTA octreotate (DOTATATE) is a combination of the beta-emitting lutetium coupled with octreotate [Kwekkeboom *et al.* 2008]. A study looking at foregut NETs with response to 177lutetium-DOTA octreotate included nine lung NETs, of which five showed a PR and just one had progressive disease [Van Essen *et al.* 2007]. Furthermore, the use of 177lutetium-DOTA octreotate in 265 patients with inoperable or metastasized GEP and lung NETs was associated with significantly improved self-assessed QOL in patients who had suboptimal scores for QOL or symptoms before therapy, and no significant decrease in QOL in patients who had no symptoms before therapy [Khan *et al.* 2011]. More recently, the phase III, randomized controlled NETTER-1 trial evaluated the use of 177lutetium-DOTA octreotate *versus* octreotide LAR in 230 patients with inoperable, progressive, SSR-positive midgut NETs. The study showed a significant increase in PFS in the PRRT arm and

Table 3. Survival by disease stage in patients with well differentiated neuroendocrine tumors (SEER data, 1988–2004) [Yao *et al.* 2008a].

Stage	Median survival (months)	5-year survival	10-year survival
Localized*	Not reached	84%	70%
Regional$	151	72%	56%
Distant§	17	27%	15%

*Localized: invasive neoplasm confined entirely to the organ of origin.
$Regional: invasive neoplasm that extended beyond the limits of the organ of origin directly into surrounding organs/tissues, involved regional lymph nodes, or fulfilled both aforementioned criteria.
§Distant: neoplasm spread to parts of the body remote from the primary tumor.

suggested a survival benefit in patients with advanced midgut NETs [Strosberg *et al.* 2016].

Prospective and randomized trials for lung NETs are warranted before this therapy is widely used.

Prognosis

According to long-term Surveillance, Epidemiology, and End Results (SEER) data of patients diagnosed from 1988 to 2004 in the United States, 73% of patients diagnosed with well differentiated lung NETs with distant metastases die within 5 years [Yao *et al.* 2008a]. TCs are generally less aggressive than ACs, with metastases reported in <15% of cases, while ACs metastasize to mediastinal lymph nodes in 30–50% of cases. After surgical resection, 5-year survival rates for patients with TCs generally exceed 85%; however, even with resection, the 5-year survival rate for ACs is only 44–71% [Kulke, 2007] (see Table 3).

Future directions

Precision oncology is an expanding field that aims to target specific mutations thought to drive tumor growth and disease progression. A recent study examining the mutational profile of lung NETs has shown that the mutational frequency increased with higher-grade lung NETs. TCs had the lowest amount of mutations including SMAD4, IDH, and EGFR. ACs had more mutations including PTEN, KIT, FGFR1, and KRAS. As expected, high-grade lung NETs had the highest amount of somatic mutations including TP53, ALK, NRAS, VHL, and RB1 [Vollbrecht *et al.* 2015].

These mutations are potential targets of existing agents. For example, with regard to activating EGFR mutations, alterations in the TOPO domain were seen in both TCs and ACs. This may lead to activation of the receptor in a similar fashion as seen in non-small cell lung cancer and may be targeted by tyrosine kinase inhibitors (TKIs) such as erlotinib [Vollbrecht *et al.* 2015]. Mechanisms of resistance, however, may develop due to mutations in the PIK3CA gene leading to activation of PI3K signaling which in turn has been associated with failure of TKIs in these patients [Sequist *et al.* 2011]. A combination of erlotinib with everolimus may therefore provide measurable response and prevent resistance. Continued profiling efforts of these tumors may show targets that prove to be of therapeutic benefit.

Harnessing the immune system in treating cancer has shown durable responses in patients with advanced cancers of different subtypes. These promising results are being translated into clinical trials examining the safety and efficacy of anti-PD-L1 and anti-CTLA4 agents for patients with NETs. Furthermore, the use of chimeric antigen receptor T cells, a method that has had dramatic results in hematologic malignancies, is being designed to target neuroendocrine cells. This will pave the way for a potentially curative therapy, if successful.

As efforts are made in the precision oncology and immunotherapy fronts, two large clinical trials are currently examining systemic therapies for TCs/ACs. The first is the SPINET trial [ClinicalTrials.gov identifier: NCT02683941], a two-arm study evaluating the effect of lanreotide, compared with placebo. The primary outcome is PFS. The second is the LUNA trial [ClinicalTrials.gov identifier: NCT01563354], a three-arm study investigating everolimus and pasireotide LAR, alone or in combination, in adults with advanced

TCs/ACs of the lung and possibly the thymus. The primary outcome is the proportion of patients that are progression free at 9 months. The results are expected within the coming year.

Conclusion

Our understanding of the biology of NETs is expanding. As it currently stands, TCs/ACs are managed based on the extent of disease, SSR status, and proliferative index. The approval of the mTOR inhibitor, everolimus, is perhaps the first step towards implementing a molecularly targeted approach in this patient population. Although few prospective trials have been dedicated for lung NETs, data extrapolated from the larger NET population have provided insight into drug efficacy. The next step in the evolution of disease management should be focused on evaluating different drugs for different mutations within the same trial, a so-called umbrella trial design. On the other hand, with the use of immunotherapy, NETs should be included within a trial that is designed to utilize an immune checkpoint inhibitor when the biomarker is present, a so-called basket trial design. Those two strategies should go hand in hand in order to accelerate the drug development process. Efforts that produce novel trial designs will drive much of the future advancements and provide management strategies that can halt disease progression and improve outcomes.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Aparicio, T., Ducreux, M., Baudin, E., Sabourin, J., De Baere, T., Mitry, E. *et al.* (2001) Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. *Eur J Cancer* 37: 1014–1019.

Bertino, E., Confer, P., Colonna, J., Ross, P. and Otterson, G. (2009) Pulmonary neuroendocrine/carcinoid tumors: a review article. *Cancer* 115: 4434–4441.

Bhosale, P., Shah, A., Wei, W., Varadhachary, G., Johnson, V., Shah, V. *et al.* (2013) Carcinoid tumours: predicting the location of the primary neoplasm based on the sites of metastases. *Eur Radiol* 23: 400–407.

Caplin, M., Baudin, E., Ferolla, P., Filosso, P., Garcia-Yuste, M., Lim, E. *et al.* (2015) Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol* 26: 1604–1620.

Caplin, M., Pavel, M., Cwikla, J., Phan, A., Raderer, M., Sedlackova, E. *et al.* (2014) Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 371: 224–233.

Carter, D., Vazquez, M., Flieder, D., Brambilla, E., Gazdar, A., Noguchi, M. *et al.* (2007) Comparison of pathologic findings of baseline and annual repeat cancers diagnosed on CT screening. *Lung Cancer* 56: 193–199.

Chan, J. and Kulke, M. (2014) Targeting the mTOR signaling pathway in neuroendocrine tumors. *Curr Treat Options Oncol* 15: 365–379.

Chong, C., Wirth, L., Nishino, M., Chen, A., Sholl, L., Kulke, M. *et al.* (2014) Chemotherapy for locally advanced and metastatic pulmonary carcinoid tumors. *Lung Cancer* 86: 241–246.

Crona, J., Fanola, I., Lindholm, D., Antonodimitrakis, P., Oberg, K., Eriksson, B. *et al.* (2013) Effect of temozolomide in patients with metastatic bronchial carcinoids. *Neuroendocrinology* 98: 151–155.

Demetri, G., Elias, A., Gershenson, D., Fossella, F., Grecula, J., Mittal, B. *et al.* (1996) NCCN small-cell lung cancer practice guidelines. The National Comprehensive Cancer Network. *Oncology (Williston Park)* 10: 179–194.

Detterbeck, F. (2010) Management of carcinoid tumors. *Ann Thorac Surg* 89: 998–1005.

Dishop, M. and Kuruvilla, S. (2008) Primary and metastatic lung tumors in the pediatric population: a review and 25-year experience at a large children's hospital. *Arch Pathol Lab Med* 132: 1079–1103.

Edge, S. and Compton, C. (2010) The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 17: 1471–1474.

Ekeblad, S., Sundin, A., Janson, E, Welin, S., Granberg, D., Kindmark, H. *et al.* (2007) Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. *Clin Cancer Res* 13: 2986–2991.

Faggiano, A., Ferolla, P., Grimaldi, F., Campana, D., Manzoni, M., Davi, M. *et al.* (2012) Natural

history of gastro-entero-pancreatic and thoracic neuroendocrine tumors. Data from a large prospective and retrospective Italian Epidemiological Study: the NET management study. *J Endocrinol Invest* 35: 817–823.

Faiss, S., Pape, U., Bohmig, M., Dorffel, Y., Mansmann, U., Golder, W. *et al.* (2003) Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors—the International Lanreotide and Interferon Alfa Study Group. *J Clin Oncol* 21: 2689–2696.

Fazio, N., Granberg, D., Grossman, A., Saletan, S., Klimovsky, J., Panneerselvam, A. *et al.* (2013) 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: 955–962.

Ferolla, P. (2014) Medical treatment of advanced thoracic neuroendocrine tumors. *Thorac Surg Clin* 24: 351–355.

Filosso, P., Ruffini, E., Oliaro, A., Papalia, E., Donati, G. and Rena, O. (2002) Long-term survival of atypical bronchial carcinoids with liver metastases, treated with octreotide. *Eur J Cardiothorac Surg* 21: 913–917.

Fine, R., Gulati, A., Krantz, B., Moss, R., Schreibman, S., Tsushima, D. *et al.* (2013) Capecitabine and temozolomide (CAPTEM) for metastatic, well differentiated neuroendocrine cancers: The Pancreas Center at Columbia University experience. *Cancer Chemother Pharmacol* 71: 663–670.

Gelhorn, H., Kulke, M., O'Dorisio, T., Yang, Q., Jackson, J., Jackson, S. *et al.* (2016) Patient-reported symptom experiences in patients with carcinoid syndrome after participation in a study of telotristat etiprate: a qualitative interview approach. *Clin Ther* 38: 759–768.

Glazer, E., Tseng, J., Al-Refaie, W., Solorzano, C., Liu, P., Willborn, K. *et al.* (2010) Long-term survival after surgical management of neuroendocrine hepatic metastases. *HPB (Oxford)* 12: 427–433.

Granberg, D., Sundin, A., Janson, E., Oberg, K., Skogseid, B. and Westlin, J. (2003) Octreoscan in patients with bronchial carcinoid tumours. *Clin Endocrinol (Oxf)* 59: 793–799.

Grande, E., Castellano, D., Garcia-Carbonero, R., Teule, A., Duran, I., Fuster, J. *et al.* (2012) Pazonet: a phase II trial of pazopanib as a sequencing treatment in progressive metastatic neuroendocrine tumors (NETs) patients (pts), on behalf of the Spanish Task Force for NETs (GETNE). *Ann Oncol* 23: 377–377.

Gustafsson, B., Kidd, M., Chan, A., Malfertheiner, M. and Modlin, I. (2008) Bronchopulmonary neuroendocrine tumors. *Cancer* 113: 5–21.

Hassan, M., Phan, A., Li, D., Dagohoy, C., Leary, C. and Yao, J. (2008) Risk factors associated with neuroendocrine tumors: a U.S.-Based Case-Control Study. *Int J Cancer* 123: 867–873.

Imhof, A., Brunner, P., Marincek, N., Briel, M., Schindler, C., Rasch, H. *et al.* (2011) Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol* 29: 2416–2423.

Jiao, Y., Shi, C., Edil, B., De Wilde, R., Klimstra, D., Maitra, A. *et al.* (2011) DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 331: 1199–1203.

Khan, S., Krenning, E., Van Essen, M., Kam, B., Teunissen, J. and Kwekkeboom, D. (2011) Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. *J Nucl Med* 52: 1361–1368.

Klimstra, D., Modlin, I., Coppola, D., Lloyd, R. and Suster, S. (2010) The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 39: 707–712.

Kulke, M. (2007) Clinical presentation and management of carcinoid tumors. *Hematol Oncol Clin North Am* 21: 433–455; vii-viii.

Kulke, M., Lenz, H., Meropol, N., Posey, J., Ryan, D., Picus, J. *et al.* (2008) Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol* 26: 3403–3410.

Kulke, M. and Mayer, R. (1999) Carcinoid tumors. *N Engl J Med* 340: 858–868.

Kulke, M., O'Dorisio, T., Phan, A., Bergsland, E., Law, L., Banks, P. *et al.* (2014) Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide. *Endocr Relat Cancer* 21: 705–714.

Kwekkeboom, D., De Herder, W., Kam, B., Van Eijck, C., Van Essen, Kooij, P. *et al.* (2008) Treatment with the radiolabeled somatostatin analog [177Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 26: 2124–2130.

Leboulleux, S., Dromain, C., Vataire, A., Malka, Auperin, A., Lumbroso, J. *et al.* (2008) Prediction and diagnosis of bone metastases in well differentiated gastro-entero-pancreatic endocrine cancer: a prospective comparison of whole body magnetic resonance imaging and somatostatin receptor scintigraphy. *J Clin Endocrinol Metab* 93: 3021–3028.

Modlin, I., Oberg, K., Chung, D., Jensen, R., De Herder, W., Thakker, R. *et al.* (2008)

Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 9: 61–72.

Moertel, C., Kvols, L., O'Connell, M. and Rubin, J. (1991) Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* 68: 227–232.

Moran, C., Suster, S., Coppola, D. and Wick, M. (2009) Neuroendocrine carcinomas of the lung: a critical analysis. *Am J Clin Pathol* 131: 206–221.

National Comprehensive Cancer Network. (2016) NCCN Clinical Practice Guidelines in Oncology: small cell lung cancer. Version 1.2016., Vol. 2016.

Pavel, M., Baudin, E., Couvelard, A., Krenning, E., Oberg, K., Steinmuller, T. *et al.* (2012) ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 95: 157–176.

Pavel, M., Hainsworth, J., Baudin, E., Peeters, M., Horsch, D., Winkler, R. *et al.* (2011) Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase III study. *Lancet* 378: 2005–2012.

Pavel, M., O'Toole, D., Costa, F., Capdevila, J., Gross, D., Kianmanesh, R. *et al.* (2016) ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 103: 172–185.

Pelosi, G., Rodriguez, J., Viale, G. and Rosai, J. (2005) 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: 179–187.

Pelosi, G., Sonzogni, A., Veronesi, G., De Camilli, E., Maisonneuve, P., Spaggiari, L. *et al.* (2008) Pathologic and molecular features of screening low-dose computed tomography (LDCT)-detected lung cancer: a baseline and 2-year repeat study. *Lung Cancer* 62: 202–214.

Phan, A., Halperin, D., Chan, J., Fogelman, D., Hess, K., Malinowski, P. *et al.* (2015) Pazopanib and depot octreotide in advanced, well differentiated neuroendocrine tumours: a multicentre, single-group, phase II study. *Lancet Oncol* 16: 695–703.

Phan, A., Oberg, K., Choi, J., Harrison, L. Jr., Hassan, M., Strosberg, J. *et al.* (2010) NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well differentiated neuroendocrine tumors of the thorax (includes lung and thymus). *Pancreas* 39: 784–798.

Qian, Z., Ter-Minassian, M., Chan, J., Imamura, Y., Hooshmand, S., Kuchiba, A. *et al.* (2013) Prognostic significance of MTOR pathway component expression in neuroendocrine tumors. *J Clin Oncol* 31: 3418–3425.

Raymond, E., Dahan, L., Raoul, J., Bang, Y., Borbath, I., Lombard-Bohas, C. *et al.* (2011) Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 364: 501–513.

Rindi, G., Kloppel, G., Couvelard, A., Komminoth, P., Korner, M., Lopes, J. *et al.* (2007) TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 451: 757–762.

Rinke, A., Muller, H., Schade-Brittinger, C., Klose, K., Barth, P., Wied, M. *et al.* (2009) 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: 4656–4663.

Sequist, L., Waltman, B., Dias-Santagata, D., Digumarthy, S., Turke, A., Fidias, P. *et al.* (2011) Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 3: 75ra26.

Spada, F., Fumagalli, C., Pisa, E., Antonuzzo, L., Messerini, L., Radice, D. *et al.* (2014) Capecitabine plus temozolomide (CAP-TEM) in patients with advanced neuroendocrine tumors (NETs): an Italian multicenter retrospective analysis. *Pancreas* 43: 505–505.

Starker, L. and Carling, T. (2009) Molecular genetics of gastroenteropancreatic neuroendocrine tumors. *Curr Opin Oncol* 21: 29–33.

Strosberg, J., Wolin, E., Chasen, B., Kulke, M., Bushnell, D., Caplin, M. *et al.* (2016) NETTER-1 phase III: progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-dotatate. *2016 Gastrointestinal Cancers Symposium*. Abstract 194.

Sundin, A., Vullierme, M., Kaltsas, G. and Plockinger, U. (2009) ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations. *Neuroendocrinology* 90: 167–183.

Travis, W. (2010) Advances in neuroendocrine lung tumors. *Ann Oncol* 21: vii65–vii71.

Travis, W., Brambilla, E., Müller-Hermelink, H. and Harris, C. (Eds). (2004) *Pathology and Genetics of*

Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press.

Travis, W., Brambilla, E., Nicholson, A., Yatabe, Y., Austin, J., Beasley, M. *et al.* (2015) The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 10: 1243–1260.

Van Essen, M., Krenning, E., Bakker, W., De Herder, W., Van Aken, M. and Kwekkeboom, D. (2007) Peptide receptor radionuclide therapy with 177Lu-octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin. *Eur J Nucl Med Mol Imaging* 34: 1219–1227.

Volante, M., Gatti, G. and Papotti, M. (2015) Classification of lung neuroendocrine tumors: lights and shadows. *Endocrine* 50: 315–319.

Vollbrecht, C., Werner, R., Walter, R., Christoph, D., Heukamp, L., Peifer, M. *et al.* (2015) Mutational analysis of pulmonary tumours with neuroendocrine features using targeted massive parallel sequencing: a comparison of a neglected tumour group. *Br J Cancer* 113: 1704–1711.

Waldherr, C., Pless, M., Maecke, H., Haldemann, A. and Mueller-Brand, J. (2001) The clinical value of [90y-DOTA]-D-Phe1-Tyr3-octreotide (90y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. *Ann Oncol* 12: 941–945.

Walts, A., Ines, D. and Marchevsky, A. (2012) Limited role of ki-67 proliferative index in predicting overall short-term survival in patients with typical and atypical pulmonary carcinoid tumors. *Mod Pathol* 25: 1258–1264.

Yang, J., Kan, Y., Ge, B., Yuan, L., Li, C. and Zhao, W. (2014) Diagnostic role of gallium-68 DOTATOC and gallium-68 DOTATATE PET in patients with neuroendocrine tumors: a meta-analysis. *Acta Radiol* 55: 389–398.

Yao, J., Fazio, N., Singh, S., Buzzoni, R., Carnaghi, C., Wolin, E. *et al.* (2016) 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: 968–977.

Yao, J., Guthrie, K., Moran, C., Strosberg, J., Kulke, M., Chan, J. *et al.* (2015) Swog S0518: phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis carcinoid patients (NCT00569127). *J Clin Oncol* 33: Abstract 4004.

Yao, J., Hassan, M., Phan, A., Dagohoy, C., Leary, C., Mares, J. *et al.* (2008a) One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 26: 3063–3072.

Yao, J., Phan, A., Hoff, P., Chen, H., Charnsangavej, C., Yeung, S. *et al.* (2008b) Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol* 26: 1316–1323.

Yao, J., Shah, M., Ito, T., Bohas, C., Wolin, E., Van Cutsem, E. *et al.* (2011) Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 364: 514–523.