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REVIEW ARTICLE

Advanced typical and atypical carcinoid tumours of the lung: management recommendations

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ABSTRACT

Background Neuroendocrine tumours (NETs) are classified by site of origin, with lung being the second most common primary site after the gastrointestinal tract. Lung NETs are rare and heterogeneous, with varied pathologic and clinical features. Typical and atypical carcinoid tumours are low-grade lung NETs which, compared with the more common high-grade NETs, are associated with a more favourable prognosis. Still, optimal treatment strategies are lacking.

Methods This review concentrates on classification and treatment strategies for metastatic low-grade lung NETs, considering both typical and atypical carcinoids. The terminology can be confusing, and an attempt is made to simplify it. Promising results from recent trials that included lung NETs are presented and discussed. Finally, guidelines from Europe and North America are discussed, and differences are noted.

Results Even within the group of patients with low-grade NETs, the presentation, the locations of metastasis, and the speed of progression can be very different. The initial work-up and an understanding of the tumour's biology are key in making management decisions. Various treatment options—including somatostatin analogs, peptide receptor radioligand therapy, and biologic systemic therapy, specifically with the mTOR (mechanistic target of rapamycin) inhibitor everolimus—are now available and are presented in a treatment algorithm.

Summary Although lung NETs are rare and evidence supporting optimal treatment strategies is lacking, the recent publication of trials that have included patients with lung NETs advances evidence-based therapy for these tumours. Many variables have to be considered in managing these tumours that have received little attention. Education for treating physicians is needed.

Key Words NETs, carcinoids, atypical carcinoids, neuroendocrine tumours, lung, everolimus, octreotide

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INTRODUCTION

Neuroendocrine tumours (NETs) of the lung are rare and heterogeneous. The tumours derive from neuroendocrine cells, which exist in many organs, and they can therefore initiate in many parts of the body, including the gastrointestinal (GI) tract, lung, thymus, and ovary. The lung is, after the GI tract, the second most common site for NETs, accounting for 25% of all NETs[1,2] and 1%–2% of all lung cancers[1,3,4].

Neuroendocrine tumours are considered to be very rare, and accurate incidence and prevalence data are difficult to obtain. The reported incidence of NETs is increasing, likely because of better diagnostic capabilities[3]. Prevalence rates are high given that patients with NET experience prolonged survival.

Lung NETs demonstrate a variety of pathologic and clinical features, and require varying treatment strategies. A spectrum of cell histology from low-grade carcinoid to high-grade small-cell malignancy are observed. Although it is important for the treating physician to understand the spectrum of lung NETs, the present review focuses primarily on classification and treatment strategies for low-grade, well-differentiated typical and atypical carcinoid lung NETs.

Although NETs are slow growing tumours, advanced disease is associated with poor survival. The primary tumour site has been shown to be a powerful predictor

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of survival duration, with the median survival of patients having metastatic lung NETs being found to be 16 months[1]. In patients with well-differentiated NETs [grade 1 (G1), low grade, or typical carcinoid] and distant metastasis, 73% will die within 5 years[1].

The clinical distinction between functional and nonfunctional NETs is important because the management, approved therapies, and treatment paradigms differ between those two types. The NETs that secrete biologically active amines or peptides are called "functional" and produce a variety of patient symptoms including diarrhea, flushing, abdominal pain, hypotension, and vasospasm. Depending on the source, an estimated 10%–30% of advanced typical and atypical carcinoid NETs are functional[3,5].

Most NETs express somatostatin receptors (SSTRs)[6,7], the presence of which has important implications for both imaging and therapy. Treatment of symptoms in patients with functional lung NETs is essential for management and improvement in quality of life. Appropriate treatment strategies for progression of both functional and nonfunctional tumours are key to prolonging survival. Although these tumours are rare and evidence to support optimal treatment strategies is lacking, the recent publication of trials that have included patients with lung NETs advances evidence-based therapies for affected patients.

CLASSIFYING LUNG NETS BY GRADE

The World Health Organization (WHO) classification of lung NETs was updated in 2015 and organizes the types of lung NETs on a spectrum, shown in Table I[8]. The most important point of differentiation for the treating physician is the dichotomous distinction between tumours that are low-grade (typical carcinoid and atypical carcinoid) and high-grade (large-cell neuroendocrine and small-cell carcinoma). Prognosis and management differ widely between those two groups. Here, the focus is on the low- and intermediate-grade NETs: typical carcinoid and atypical carcinoid.

Typical carcinoid tumours are quite bland in their histology, have fewer than 2 mitoses per 2 mm^2, and lack any evidence of necrosis. Atypical carcinoid tumours can have the same "carcinoid morphology," but the mitotic rate is increased (at 2–10 mitoses per 2 mm^2), and the tumour might be punctuated with necrotic features. The grading of these two tumour types is different: typical carcinoids are G1, and atypical carcinoids are grade 2 (G2).

As their name implies, large-cell neuroendocrine carcinomas have a large cell size, a low nucleus-to-cytoplasm ratio, and frequent nucleoli. The mitotic rate exceeds 10 per 2 mm^2, and necrosis is frequently present. Large-cell neuroendocrine and small-cell carcinomas are both grade 3 (G3).

The G1 NETs (typical carcinoid tumours) account for 2% of thoracic malignancies and have only a 10%–15% chance of distant spread[9]. The G2 NETs (atypical carcinoid tumours) account for 0.2% of thoracic malignancies[4] and have a 20% chance of distant spread[9]. The G3 large-cell NETs have a 3% incidence[4], and the G3 small-cell NETs have the highest incidence at 20%[4]. Both G3 tumour types are considered more aggressive than G1 and G2 tumours.

It is important to note that, despite this classification system, many patients aren't easily placed into a discrete category. Although Ki-67 expression is not validated for use in lung tissue, both the European Neuroendocrine Tumor Society (ENETS) and the WHO recommend measuring Ki-67 to differentiate high-grade large-cell NETs from G1 or G2 NETs when crush biopsies or necrotic cells make the diagnosis difficult[3,8]. The WHO does not recommend using Ki-67 to distinguish typical from atypical carcinoid tumours—a decision that remains controversial[8]. The ENETS has incorporated Ki-67 into their most recent treatment guidelines[10].

The staging of lung NETs follows the TNM staging of non-NET lung cancers, which adheres to the current WHO classification[11]. Given that many lung carcinoids and atypical carcinoids are larger than 3 cm, that staging is not the best for this subset of lung malignancies[12].

WORK-UP PROCEDURES FOR ADVANCED TYPICAL AND ATYPICAL CARCINOIDS IN THE LUNG

Patient History

A detailed patient history is essential to determine whether the tumour is functional and is secreting biologically active amines or peptides. Patients with functional tumours require treatment to manage symptoms and improve quality of life.

Determining the Extent of Tumour Burden

Computed tomography imaging of both chest and abdomen should be obtained at baseline[13]. High-resolution computed tomography can be performed if contrast is contraindicated. According to the U.S. Surveillance, Epidemiology, and End Results program, 12.9% of patients with a NET present with metastasis at diagnosis[14]. Liver, bone, and mediastinal lymph nodes are the most common sites of metastasis[15].

Establish SSTR Status

Most NETs express high-affinity SSTR[6,7]. In all patients with advanced low-grade NETs, SSTR ligand–based imaging should be obtained at baseline to establish SSTR expression levels and to provide information about disease burden.

TABLE I World Health Organization (WHO) classification of neuroendocrine tumours (NETs)[8]

NET type	WHO grade	Histology	Mitosis (per 2 mm^2)	Presence of necrosis
Low-grade (well differentiated)	1	Typical carcinoid	<2	None
Intermediate-grade (well differentiated)	2	Atypical carcinoid	2–10	Present
High-grade (poorly differentiated)	3	Large-cell	>10	Extensive
		Small-cell		High

Expression can be classified as heterogeneous, with only some lesions positive on imaging; homogenous, with all lesions positive on imaging; or strongly positive, with all lesions observed and maximally accentuated on imaging. Imaging with ^{111}In-diethylenetriaminepentaacetic acid–octreotide is an established method[16,17]. Newer imaging technologies also targeting SSTR expression, including ^{18}F–dihydroxyphenylalanine positron-emission tomography or, preferably, ^{68}Ga–DOTATATE positron-emission tomography, are more accurate, permit tumour staging, help to localize disease, and better enable optimal treatment decision-making[18,19]. Immunostained histology specimens can also be helpful for determining the SSTR expression level. Most low-grade (G1 or G2) NETs will be positive on imaging or histology for SSTRs.

Guidelines from the U.S. National Comprehensive Cancer Network (NCCN) recommend that SSTR-based imaging be obtained if treatment with octreotide or lanreotide is being considered[20].

Other Tests

For patients with functional NETs, these tests should also be considered:

- 5-Hydroxyindoleacetic acid (5-HIAA)
  In patients with functional symptoms, a 24-hour urine test for 5-HIAA should be performed at baseline, because high levels of urinary 5-HIAA can correlate with the risk of carcinoid heart disease[21]. The 24-hour 5-HIAA test should be repeated upon disease progression, or when a change is therapy is being considered.
- Echocardiogram
  Because carcinoid complications can occur with time, a baseline echocardiogram should also be performed[22]. Approximately 50%–60% of patients with carcinoid syndrome develop cardiac complications, including tricuspid regurgitation and pulmonary stenosis[23,24]. An echocardiogram should be repeated every 2–3 years in patients with functional tumours[25].

Table II provides recommendations to guide clinical decision-making for patients with advanced low-grade NETs.

TABLE II Recommendations to guide clinical decision-making for patients with advanced low-grade neuroendocrine tumours

1. Baseline history should be performed to determine functional status.
2. Baseline imaging should be conducted to determine whether somatostatin receptors are heterogeneous, homogenous, or strongly positive.
3. Pathology examination should be performed to distinguish between atypical and typical, and to determine mitotic rate and Ki-67 if necessary.
4. Patient follow-up should determine whether the disease is stable, slow-growing, or aggressive.
Based on the outcomes of the foregoing factors, treatment paradigms can be individualized to optimize patient care and survival.

TREATMENT MODALITIES FOR ADVANCED LOW-GRADE NETS

Most of the NET clinical trials conducted to date have focused on gastrointestinal NETs, particularly those of pancreatic (PNET) and midgut origin. Although some of the trial results can be extrapolated, the heterogeneity of lung NETs underscores the need for distinct trials in this area.

A key point in NET management is multidisciplinary consultation. A multidisciplinary approach is in the best interest of patients because individuals with both typical and atypical carcinoid tumours experience prolonged survival, and their treatment spans many disciplines, including surgery, nuclear medicine, and medical and radiation oncology.

Surgery

Surgical treatment for lung NETs might be considered for curative intent or symptom control in patients with advanced or metastatic disease, depending on the individual patient and the site of disease[3]. Resection of the primary tumour and oligometastases could be recommended, depending on the site of metastasis[3].

The NCCN guidelines recommend that resection of recurrent locoregional disease, isolated distant metastases, or a previously unresectable tumour that has regressed be considered in selected patients with adequate performance status[20].

Systemic Chemotherapy for Advanced Low-Grade Lung NETs

Low-grade typical and atypical carcinoid lung NETs might respond to chemotherapy. Multiple cytotoxic drug combinations have shown degrees of activity in lung NETs, although the data are historical, and consensus about standard therapy is lacking. Some studies have shown efficacy with capecitabine–temozolomide (which is a standard chemotherapy choice in GI NETs) in lung NETs[26].

The NCCN NET guidelines recommend cytotoxic chemotherapy for patients with progressive metastases when no other treatment options exist[20]. Temozolomide, cisplatin–etoposide, or carboplatin–etoposide are options. In cases of atypical carcinoids showing aggressive characteristics, negative SSTR expression, and Ki-67 less than 15%, the ENETS recommends chemotherapy (temozolomide-based) as a last line of therapy[10].

Somatostatin Analogs for Advanced Low-Grade NETs

Controlling Symptoms and Slowing Disease Progression

In low-grade lung NETs, SSTRs often show surface overexpression[27]. Somatostatin analogs (SSAs) bind to SSTRs, blocking the release of peptides and amines, and thus helping to control symptoms. The SSAs bind to the 5 known human SSTR subtypes with different affinities. The 2 SSAs currently available in clinical practice for advanced low-grade NETs are octreotide and lanreotide, which bind to SSTR 2 and SSTR 5 with high affinity, and to SSTR 3 with modest affinity. Pasireotide is a second-generation cyclic hexapeptide injectable SSA that binds with high affinity to

4 of 5 SSTRs (SSTRs 1, 2, 3, and 5). Pasireotide is not yet in clinical use, but is currently being tested in the LUNA lung NETs clinical trial[28].

Octreotide is available in both an intermediate-acting subcutaneous formulation and a long-acting release (LAR) formulation that is administered intramuscularly. A 30 mg dose of octreotide LAR can be repeated every 4 weeks and increased in 10 mg increments up to a dose of 60 mg. At the latter dose, most receptors are saturated, and further dose increases have nominal benefit[29]. Lanreotide is administered as a deep subcutaneous injection at a dose of 120 mg every 4 weeks[30]. These somatostatin analogs are both well tolerated, but can lead to increased rates of biliary stones, and so abdominal ultrasonography imaging is recommended every 6 months.

Managing Symptoms

Patients with functional tumours need appropriate treatment to control the symptoms of diarrhea, flushing, abdominal pain, hypotension, and vasospasm. The phase III ELECT trial examined the effect of lanreotide in 115 patients with liver metastases and carcinoid syndrome from GI and pancreatic NETs or NETs of unknown location. Participants were randomized to subcutaneous lanreotide 120 mg every 28 days or to placebo. A short-acting octreotide formulation could be used to rescue patients who were still experiencing symptoms of carcinoid syndrome. To be eligible for the trial, participants had to be SSTR expression–positive on imaging.

The ELECT trial met its primary endpoint. Compared with participants who received placebo, those who received the lanreotide regimen for 16 weeks required octreotide rescue medication to treat the symptoms of carcinoid syndrome for significantly fewer days ($p = 0.0165$)[31].

A carcinoid crisis is very rare, but it can occur when a NET releases a large amount of amines, leading to hypotension and flushing. Such crises can occur in patients with a NET as a secondary effect following from an operative procedure or general anesthesia[32]. To avoid such complications, many surgeons or interventional radiologists require that patients be pre-medicated with a SSA before a procedure.

Slowing Disease Progression

In addition to symptom control, several randomized trials have demonstrated that SSAs slow disease progression. The phase III PROMID trial randomized 86 patients with midgut NETs to receive either octreotide LAR 30 mg or placebo[33]. The primary endpoint, time to progression, was significantly increased in the octreotide arm, at 14.3 months compared with 6 months in the placebo arm [hazard ratio (HR): 0.34; $p = 0.000072$]. Most patients enrolled in the trial (74.1%) were SSTR expression–positive by octreoscan, and 40% had functional tumours. No information is available about octreotide activity or efficacy in patients who are SSTR expression–positive compared with expression–negative.

The phase III CLARINET trial randomized 204 patients with non-functioning well-differentiated or moderately differentiated NETs of the pancreas, midgut, or hindgut to either subcutaneous lanreotide 120 mg or to placebo[34]. All patients had to be SSTR expression–positive by SSTR scintigraphy grade 2 or higher on a scale ranging from 0 (no tumour uptake) to 4 (very intense tumour uptake). The primary endpoint, median progression-free survival (PFS), was significantly increased in patients who received the lanreotide, at an estimated 24 months compared with 18 months in those who received placebo (HR: 0.47; $p < 0.001$). An important limitation of the CLARINET trial is that it did not show an improvement in overall survival or quality of life.

A comparison of the PFS in the placebo arms of PROMID and CLARINET (6 months and 18 months respectively) suggests key differences in the patient populations, making cross-trial comparison impossible. However, both trials illustrated that SSA treatment in patients with a NET provides an antiproliferative effect that improves survival in both nonfunctional and functional pancreatic and other GI NETs. Neither the PROMID nor the CLAIRNET trial included any patients with a lung NET.

The results from the LUNA randomized trial, which was specifically designed for lung and thymic NETs, were recently presented[28]. The LUNA phase II trial randomized 41 patients to intramuscular pasireotide LAR 60 mg monthly, 42 patients to oral everolimus [a TOR (target of rapamycin) inhibitor] 10 mg daily, and 41 patients to pasireotide LAR plus everolimus. The primary endpoint of the trial was the progression-free rate at 9 months (PFR-9). The carcinoid classification was atypical in 68.5% of patients and typical in 31.5%. The primary tumour site was the lung in 93.5% of patients and the thymus in 6.5%. The trial excluded severe functional tumours requiring symptomatic treatment with SSAs. Most patients (77.4%, 96 of 124) had nonfunctional tumours; in the remaining 22.6%, the tumours were functional[35].

The LUNA study endpoint, PFR-9, was achieved by 39.0% of patients taking single-agent pasireotide LAR, 33.3% of patients taking everolimus alone, and 58.5% taking combined everolimus and pasireotide LAR. The best overall response at 9 months was a partial response, which was achieved by 2% of the patients in each treatment arm. Stable disease was attained by 34% of patients taking pasireotide LAR, 31% of those taking everolimus only, and 49% of those taking the combination. Progressive disease occurred in 17% of patients taking pasireotide LAR and in 2% of taking everolimus. None of the patients taking the combined treatment reported progressive disease. Given that the PFR-9 was encouraging in all 3 arms, the LUNA trial supports the use of SSAs as a viable treatment option for controlling symptoms and provide antiproliferative benefit for patients with both functional and nonfunctional lung NETs.

The patients most likely to benefit from the antiproliferative effects of SSAs will likely be those whose tumours are SSTR expression–positive or even strongly positive on imaging. In the PROMID trial, most patients (74.1%) were SSTR expression–positive by octreoscan, and in the CLARINET and ELECT trials, all patients had to be SSTR expression–positive. The recently updated ENETS guidelines state that SSAs can be used in bronchial NETs when the SSTR status is positive (on somatostatin imaging or histology) and if the tumour is slow growing, G1, or G1 with a Ki-67 index less than 10%[10]. The ENETS guidelines also state that SSAs can be considered in an SSTR expression–negative tumour if it is a small-volume lesion and imaging might have provided false-negative information[10].

As was shown in the CLARINET trial, SSTR positivity does not correlate with functionality; all patients in that trial had to be positive for SSTR expression, and yet no tumour was functional.

Peptide Receptor Radioligand Therapy

Peptide receptor radioligand therapy (PRRT) delivers a radiolabelled agent to a specific target, such as SSTRs, which are often overexpressed on the surface of metastatic lung NETs[27]. The first use of PRRT with ^{90}Y-labelled octreotide to treat lung NETs occurred in the early 1990s; that approach has since been used in many centres for decades, despite the lack of phase III trials confirming benefit.

The evidence landscape has now changed with the results of the phase III NETTER-1 trial[36]. That trial enrolled patients whose carcinoid disease was progressing on a standard dose of octreotide LAR 30 mg, randomizing 230 patients with G1–2 metastatic midgut NETs to receive either PRRT ^{177}Lu-DOTATATE (7.4 GBq) every 8 weeks (4 administrations) or octreotide LAR 60 mg every 4 weeks. The primary endpoint of PFS was not reached for ^{177}Lu-DOTATATE; it was 8.4 months for the control group (HR: 0.21; $p < 0.0001$). The objective radiographic response rate was 18% with ^{177}Lu-DOTATATE and 3% with octreotide LAR ($p = 0.0008$). The overall survival analysis, although preliminary, was positive as well (13 deaths in the ^{177}Lu-DOTATATE group and 22 in the control group, $p = 0.019$).

The safety profile of PRRT was favourable. Although the NETTER-1 trial was conducted primarily in patients with midgut NETs, the results could apply to lung NETs that are receptor-positive by nuclear imaging. A retrospective study that included 89 NETs of bronchial origin treated with PRRT revealed a 28% response by the Response Evaluation Criteria in Solid Tumors, supporting this treatment as an option for pulmonary NETs[37].

Although the NETTER-1 trial did not include bronchial NETs, the cumulative experience and data pertaining to PRRT over the last few decades in multiple disease sites supports this therapeutic option in patients whose typical and atypical lung carcinoids that express SSTRs are progressing and for whom systemic therapy is failing.

Systemic Therapy: mTOR Inhibition

Because lung NETs have shown increased activation of the MTOR (mechanistic target of rapamycin) signalling pathway[38], everolimus, an inhibitor of MTOR, is another potential therapy for patients with a lung NET.

The phase III RADIANT-2 trial compared everolimus–octreotide LAR with octreotide LAR alone in advanced NETs with carcinoid syndrome[39]. The trial included patients with lung NETs, but did not stratify them by disease site. Patients treated with the dual agents experienced a nonsignificant improvement in PFS: 16.4 months compared with 11.3 months for those treated with octreotide LAR alone ($p = 0.026$). The predetermined PFS significance rate was 0.0246, and so with a p value of 0.026, RADIANT-2 was a negative trial statistically. In an exploratory subgroup analysis for lung NETs ($n = 44$), a trend toward improved PFS (13.6 months) was observed for the dual treatment compared with 5.6 months for octreotide alone ($p = 0.228$).

An important limitation of the RADIANT-2 trial is that it did not show an improvement in overall survival or quality of life. Given that RADIANT-2 included only small numbers of patients and was not stratified for primary lung site, regulators requested that the trial be repeated to test the effect of everolimus without octreotide (RADIANT-4).

The RADIANT-4 trial randomized patients with nonfunctional NETs of the lung and GI tract to either everolimus or placebo[40]. Functional tumours were excluded because SSAs are needed in that patient population and can affect PFS, as demonstrated in the PROMID trial. In RADIANT-4, the median PFS was significantly prolonged in the everolimus arm compared with the placebo arm (11 months vs. 3.9 months, $p < 0.00001$). That improvement was independent of the site of disease origin: lung, GI tract, or unknown. Everolimus was well-tolerated, with adverse events being mostly grades 1 and 2.

A *post hoc* subgroup analysis looked at the patients with lung NETs ($n = 90$) in RADIANT-4[41]. In the lung subgroup, the PFS with everolimus was 9.2 months compared with 3.6 months for placebo (HR: 0.50; 95% confidence interval: 0.28 to 0.88). The safety profile and adverse events were similar to those in the overall population. Those findings have led to the ENETS recommending everolimus as first-line treatment for metastatic progressive lung NETs[10]. The phase III RADIANT-2 trial (comparing everolimus–octreotide with octreotide alone) included functional tumours of both lung and GI tract, and demonstrated that combination treatment is not only safe, but complementary. However, because the RADIANT-4 trial (comparing everolimus with placebo) excluded functional tumours, the approvals from Health Canada and the U.S. Food and Drug Administration require that, in the treatment of nonfunctional lung NETs, everolimus be used without octreotide.

Finally, the most recently presented LUNA trial again deserves discussion for proof-of-concept with respect to the use of everolimus in lung NETs. As already described, the LUNA trial randomized 41 patients to pasireotide LAR, 42 patients to everolimus, and 41 patients to pasireotide LAR plus everolimus. The study endpoint, PFR-9, was achieved by 39.0% of patients taking single-agent pasireotide LAR, 33.3% of those taking everolimus alone, and 58.5% of those receiving the combination. The best overall response at 9 months was a partial response, which was achieved by 2% of patients in each treatment arm. Stable disease was attained by 34% of patients taking pasireotide LAR, 31% of those taking everolimus, and 49% of those taking the combination. Progressive disease occurred in 17% of patients in the pasireotide LAR arm and in 2% of those in the everolimus arm. No patient receiving combined treatment reported progressive disease. Given that the PFR-9 was encouraging in all 3 arms, the LUNA trial supports the use of SSAs and the use of everolimus in the treatment strategy for low-grade NETs of the lung.

In summary, the phase III RADIANT-4 trial changed the treatment paradigm. Whether typical or atypical, carcinoid that is advanced, nonfunctional, and progressing should be treated with everolimus. Everolimus is currently the only approved targeted therapy in lung NETs.

Other Therapeutic Options

Interferon alfa has been used to treat patients with NETs for many decades; however, the side-effect profile is limiting[42]. The use of interferon alfa with SSAs follows from a surgical

trial in which an improved PFS was associated with the combination of octreotide and interferon alpha compared with octreotide alone[43].

The angiogenesis pathway has also been targeted in patients with NETs, and phase II studies adding bevacizumab to other therapeutics, including octreotide and everolimus, have suggested activity[44,45]. The recent phase III SWOG S0518 trial explored two combinations for superiority: octreotide–bevacizumab or octreotide–interferon alfa[46]. The trial randomized 402 patients with advanced G1 and G2 NETs from multiple sites to those two arms. No significant difference in PFS was observed: 16.6 months for octreotide–bevacizumab and 15.4 months for octreotide–interferon alfa (HR: 0.93; $p = 0.55$). However, octreotide–bevacizumab was better tolerated, with less fatigue, and the combination was associated with a higher response rate (13% vs. 4%, $p = 0.008$). Future trials to further examine inhibition of angiogenesis pathways are ongoing.

TREATMENT RECOMMENDATIONS

The best-practice recommendations for the management of typical and atypical bronchial NETs come from the ENETS[3]. That organization's upgraded guidelines for the management of advanced typical and atypical carcinoid take into account pathology (typical vs. atypical); mitotic rate (Ki-67); SSTR expression; and growth rate, which is classified as slow, progressive, or aggressive (progression within 3–6 months)[10].

In contrast, the U.S. NCCN guidelines (version 2.2017) state that no available data support a specific sequence of regional compared with systemic therapies and that no available data guide the sequencing of systemic therapy options[20].

Figure 1 proposes a treatment algorithm for lung NETs based on mechanism of action.

PATIENT FOLLOW-UP

Patients diagnosed with a low-grade lung NET have to undergo frequent follow-up after surgical resection. For patients with typical carcinoid NETs, conventional computed tomography imaging can be performed at 3 and 6 months, and then annually. For atypical carcinoids, closer monitoring is recommended: first at 3 and 6 months, and then at 6-month intervals[3].

For patients with advanced disease, clear recommendations and guidelines for the type and interval of follow-up for patients with advanced well-differentiated NETs do not exist[1,20,47]. Follow-up and imaging have to be individualized based on the patient's baseline status, new symptoms, and prior treatment, and on whether a change in therapy is contemplated. Chromogranin A measurements can be used to monitor disease progression; however, the frequency and duration of measurement are not articulated. More detailed guidelines that direct the follow-up of patients with these types of tumours are needed.

SUMMARY AND CONCLUSIONS

Lung NETs are unique tumour entities, requiring a multidisciplinary team approach for optimal treatment. A thorough review of patient history can determine whether a tumour is functional. A pathology review is critical to differentiate between low-grade typical and atypical carcinoid NETs and high-grade tumours. Whether the disease is stable, slow-growing, or aggressive must be determined to assist in choosing appropriate management or a change in therapy. A number of treatments are available depending on individual disease factors; however, SSTR-based imaging is necessary to visualize the tumour and to predict both

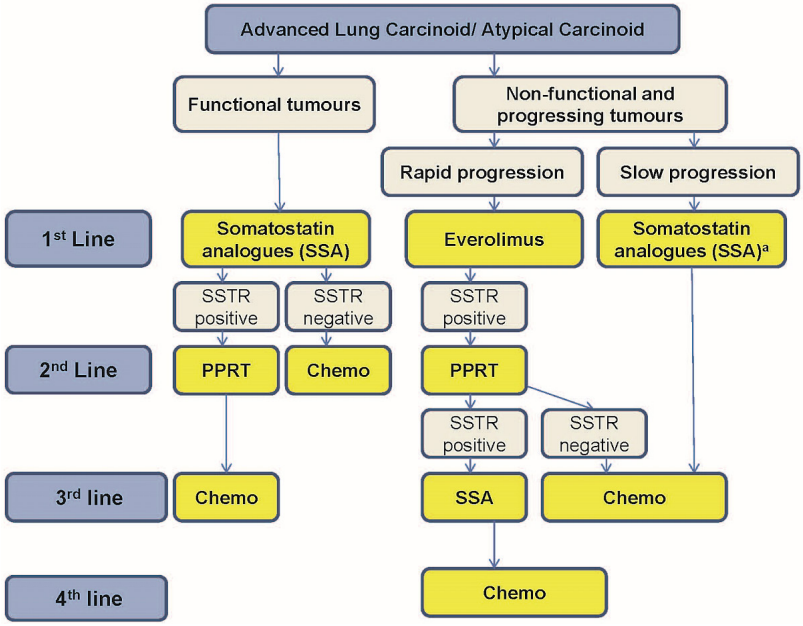

FIGURE 1 Proposed treatment algorithm for typical carcinoid and atypical carcinoid bronchial neuroendocrine tumours. EGFR = epidermal growth factor receptor; TKI = tyrosine kinase receptor; cfDNA = cell-free DNA. [a]For patients with very slow and minimal disease: surgical resection or watchful waiting could be considered. PPRT = peptide receptor radionuclide therapy; chemo = chemotherapy.

the potential efficacy of SSAs and the options for PRRT. Treatment with SSAs can improve carcinoid symptomology in functional tumours and prolong PFS in both functional and nonfunctional disease. Tumours that are SSTR–positive can be treated with PRRT with the goal of improving PFS (now proven in randomized trials). Everolimus, a MTOR inhibitor, has demonstrated efficacy and is now approved for the treatment of advanced nonfunctional lung NETS. Although therapeutic strategies for lung NETS have been extrapolated from clinical trials in GI and pancreatic NETS, new clinical trials that include patients with lung NETS are being reported, and the treatment landscape is changing, with new evidence and new agents. Educating treating physicians about the management of lung NETS is important.

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