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Management of pulmonary neuroendocrine tumors

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Abstract Neuroendocrine tumors (NETs) of the lung are divided into 4 major types: small cell lung cancer (SCLC), large cell neuroendocrine carcinoma (LCNEC), atypical carcinoid (AC) or typical carcinoid (TC). Each classification has distinctly different treatment paradigms, making an accurate initial diagnosis essential. The inconsistent clinical presentation of this disease, however, makes this difficult. The objective of this manuscript is to detail the diagnosis and management of the well differentiated pulmonary carcinoid (PC) tumors. A multidisciplinary approach to work up and treatment should be utilized for each patient. A multimodal radiological work-up is used for diagnosis, with contrast enhanced CT predominantly utilized and functional imaging techniques. A definitive diagnosis is based on tissue findings. Surgical management remains the mainstay of therapy and can be curative. In those with advanced disease, medical treatments consist of somatostatin analog (SSA) therapy, targeted therapy, chemotherapy or peptide receptor radionuclide therapy. SSAs are the standard of care in those with metastatic NETs, using either Octreotide long acting repeatable (LAR) or lanreotide as reasonable options, despite a scarcity of prospective data in PCs. Targeted therapies consist of everolimus which is approved for use in PCs, with various studies showing mixed results with other targeted agents. Additionally, radionuclide therapy may be used and has been shown to increase survival and to reduce symptoms in some studies. Prospective trials are needed to determine other strategies that may be beneficial in PCs as well as sequencing of therapy. Successful diagnosis and optimal treatment relies on a multidisciplinary approach in patients with lung NETs. Clinical trials should be used in appropriate patients.

Keywords Bronchial carcinoid · Neuroendocrine tumor · Lung carcinoid

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1 Introduction

Tumors that arise from neuroendocrine cells can present throughout the body, most commonly in the gastrointestinal tract and pulmonary systems. Neuroendocrine tumors (NETs) of the lung account for about 25% of primary lung cancers, as well as 20–25% of primary NETs [1, 2]. Lung NETs are broken into four separate categories; small cell lung cancer (SCLC), large cell neuroendocrine carcinoma (LCNEC), atypical carcinoid (AC) or typical carcinoid (TC). Pulmonary carcinoid (PC) tumors represent only about 2% of lung NETs and this classification is dependent on morphology [2]. PCs most commonly arise in patients ranging from 40 to 60 years of age and tend to occur in tobacco naive patients or light smokers. This is in contrast to the higher grade lung NETs (SCLC/LCNEC) in patients who generally have a long smoking history [3].

Currently, NETs comprise between 0.5 and 2% of all malignancies [4]. Both the incidence and prevalence of neuroendocrine tumors have increased linearly. Surveillance, Epidemiology, and End Results (SEER) data reports a five-fold increase between the years 1973 to 2004, with the annual

age adjusted incidence of NETS in 1973 being 1.09 per 100,000 and 5.25 per 100,000 in 2004 [1]. The reasons for this are most likely multifactorial; NET knowledge has increased, radiographic technology has become more readily available and lung cancer screening in smokers has become more prevalent [5].

The diagnosis of lung NETs remains challenging due to the variable presentation of patients. Depending on the location of the tumor, patients may be asymptomatic or have symptoms that are very non-specific, making a definitive diagnosis difficult [6]. Centrally located tumors tend to present with obstructive symptoms, while peripheral tumors are commonly found incidentally. Nonspecific symptoms associated with central tumors include cough, hemoptysis, dyspnea, weight loss, chest pain, and recurrent pulmonary infections amongst others. Many of these obstructive symptoms mimic other pathologies, such as COPD and asthma, resulting in a further delay in diagnosis. Often a diagnosis of lung NET is only suspected after initial treatment for these other pathologies fails to show improvement. On occasion, lung NETs can be functional and secrete hormones and peptides resulting in symptoms such as cutaneous flushing, diarrhea, and wheezing [2, 7]. Albeit rare, acromegaly and hypoglycemia have also been demonstrated following the ectopic secretion of growth hormone-releasing hormone (GHRH) and insulin-growth factor 2 (IGF-2) from pulmonary NETs [8–10]. It is important to note that classic carcinoid syndrome is less common in lung NETs than in gastrointestinal NETs [11]. This manuscript will primarily focus on management of the well-differentiated PCs.

2 Initial evaluation

2.1 Radiologic work up

A multimodality approach is required in the evaluation of carcinoid tumors. Single, individual methods are not sensitive and specific enough for evaluation of NETs [12]. Imaging is performed to determine size and location of the primary tumor as well as for staging and evaluation of potential treatment choices. Anatomical imaging with multiphasic contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) as well as functional imaging with 111indium octreotide scintigraphy, ^{123}I–Metaiodobenzylguanidine (MIBG) scintigraphy, gallium 68-tetraazacyclododecane tetraacetic acid-octreotate (^{68}Ga-DOTATATE) positron emission tomography (PET) scan, and ^{18}F–fluorodeoxyglucose PET scan, are used for these purposes [13].

Contrast enhanced CT is predominantly used in the evaluation of pulmonary neuroendocrine proliferations and neoplasms. It is important to know that the histologic variants according to the World Health Organization (WHO) classification system present with different imaging characteristics [14]. In patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), expiratory high resolution CT will show multifocal pulmonary micronodules with or without mosaic attenuation or air trapping [14]. Mosaic attenuation is more commonly seen in symptomatic patients [15]. Bronchiectasis, bronchial wall thickening and atelectasis have also been described [16].

TCs and ACs have similar imaging characteristics. Most occur in the right lung (60%), range in size from 2 to 5 cm with ACs being larger and more peripheral [17]. These tumors may be completely or partially endoluminal (tip of the iceberg morphology) and can be associated with bronchiectasis, mucoid impaction, atelectasis, and air trapping. Calcifications may be present as well [14]. CT is useful for detection of lymphadenopathy and distant metastatic disease to liver, bone or adrenal glands [18].

LCNECs generally present as a large, peripheral mass ranging in size from 1.3 to 9.2 cm and are usually indistinguishable from other lung cancers. Twenty percent can be central and associated with post obstructive effects. Necrosis is commonly seen in larger lesions [19]. CT will also detect associated pleural effusions and hilar and mediastinal lymph node enlargement [20].

SCLC typically manifests as a large central or mediastinal mass involving the hilum in 85% of cases with invasion of the mediastinum in approximately 68% of cases. Post obstructive effects are also expected. Calcifications, pleural effusions, pericardial thickening, pleural nodules and metastases to liver, adrenal glands and bones are also commonly seen [19]. Rarely, SCLC can present as a peripheral lesion without lymphadenopathy [21].

MRI is excellent for detecting metastatic disease in the abdomen, mediastinum and osseous structures [12, 22]. Lesions will be hyperintense on T2 and STIR sequences and demonstrate avid enhancement [23]. MRI has a sensitivity of nearly 100% for detection of bone marrow metastases [24].

Functional imaging depends on expression of somatostatin receptors rather than hormonal hypersecretion. Approximately 80% of lung NET express somatostatin (SST) 2 receptors [25]. One advantage of functional imaging is whole body surveillance, which enables detection of extrapulmonary metastases [26]. Somatostatin receptor scintigraphy has a reported sensitivity of 80–100% [12]. Indium-111 octreotide scan in conjunction with CT aids in preoperative planning by detection and accurate localization of nodal and distant metastases [22]. MIBG scintigraphy is less sensitive than octreotide scan. ^{68}Ga PET/CT scans have shown higher sensitivity and specificity for SST receptor imaging than octreotide scans and are likely to replace it for staging NETs [27]. North American Neuroendocrine Tumor Society (NANETS) guidelines recommend SST receptor scintigraphy to evaluate appropriateness of peptide receptor radionuclide therapy (PRRT) or as part of follow up imaging [28]. Fluorodeoxyglucose (FDG) PET/CT

has been suggested for tumors with Ki-67 greater than 10% [29]. In PCs, a high false negative rate has been reported [17]. However, in both LCNEC and SCLC FDG PET/CT demonstrates increased uptake and is used for staging and restaging. Moreover, a high standard uptake value (SUV) (> 13.7) maybe associated with a shortened survival and worse prognosis [14].

2.2 Diagnosis

Definitive diagnosis is based on tissue diagnosis. Sampling strategies will vary according to the different histologic variants. DIPNECH is usually diagnosed from open lung or thoracoscopic biopsy [15]. Carcinoid tumor definitive tissue diagnosis can be obtained with bronchoscopy, percutaneous image guided biopsy or thoracotomy [30]. Diagnosis of LCNEC may be difficult as it must be differentiated from SCLC, other large cell carcinomas and carcinoid; thus, a surgical biopsy is often needed [11]. Image guided, bronchoscopic or surgical biopsy can be used to diagnose SCLC. Biopsy of suspected metastases may also aid in staging [14].

2.3 Pathology

NETs of the lung can be divided into 4 different categories based on their morphological appearance. The WHO classification of NETs of the lung is seen in Table 1 [31]. Carcinoid tumors are defined as tumors ≥0.5 cm and defined based on the mitotic index and presence or absence of necrosis. TCs have less than 2 mitoses/2 mm2 and absence of necrosis [31]. AC tumors have 2–10 mitoses/2 mm^2 and/or have the presence of necrosis. Higher grade lung NETs include the LCNEC which has prominent nucleoli, extensive necrosis and a mitotic index over 10 (mean 70). SCLC has an absent organoid pattern with extensive necrosis and high mitotic index with a mean of 70 (Table 1).

DIPNECH is a rare condition, which is preneoplastic and can give rise to PCs. DIPNECH is limited to the confines of the respiratory epithelium and characterized by non-invasion of the basement membrane. There are three distinct morphological forms including diffuse proliferation, linear proliferation, and small nodules [31]. DIPNECH can be seen in conjunction with PCs [32]. The role of Ki-67 labeling index has been shown to be useful in NETs of the GI tract and pancreas, however, the role in lung NETs is still evolving [33]. Several studies have shown that Ki-67 may be prognostic in lung NETs, however each used various cut points ranging from 2.5% to 10% [34–36]. Further prospective studies are needed to truly determine the clinical utility.

2.4 Staging

NETs most commonly metastasize to the liver, bones and mediastinal lymph nodes [37]. Various radiographic methods can be utilized during staging. Scintigraphy may be used with 80% detection rate [25], while PET with octreotide derivatives has established a sensitivity and specificity greater than 90% and 99%, respectively [38].

A specific tumor or nodal staging scheme unique to AC or TC is currently not being utilized in the staging of these malignancies. Presently, the Tumor-Node-Metastasis (TNM) staging system for lung cancers included in the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual is used to stage pulmonary NETs, which focuses on the size and invasion of the tumor [39]. The significant flaw in this method is that invasion guidelines are similar to those used in non-NET lung tumors, which are generally bigger and thus have a larger cut off value than projected for NETs [40]. For instance, utilizing cut off values of 3–7 cm are inadequately representative of carcinoid lung tumors, as both AC and TC generally have a diameter that is less than 3 cm [40]. Nodal involvement as a prognostic indicator has been debated in the literature. However, nodal involvement is generally accepted as resulting in poorer outcomes [41–43].

3 Treatment

3.1 Surgical management

Both NANETS and The European Neuroendocrine Tumor Society (ENETS) endorse a multidisciplinary approach for management of pulmonary NETs. Surgical resection is the only

Table 1 WHO Classification of Lung NETs [31]

	Typical Carcinoid	Atypical Carcinoid	Large Cell NE Carcinoma	Small Cell Carcinoma
Cell size	Large	Large	Large	Small
Cytoplasm	Abundant	Abundant	Abundant	Scant
Organoid pattern	Characteristic	Characteristic	Less extensive	Absent
Prominent nucleoli	No	No	Yes	No
Mitoses (×10 HPF)	<2	2–10	>10	Mean 70
Necrosis	Absent	Present	Extensive	Extensive

curative treatment option and is preferred for an early stage disease in a surgically fit patient [44, 45]. Systemic treatment for metastatic or advanced disease will be discussed separately.

Various surgical techniques of resection are in practice. Pneumonectomy or lobectomy are commonly employed due to central location of most carcinoids. Wedge resection or bronchial sleeve surgery can be performed to spare lung parenchyma, especially in TCs due to low potential of locoregional recurrence. This technique is especially employed in the pediatric and young adult population [46–48]. Traditionally, a 5 mm negative margin is considered optimal since submucosal spread is uncommon in carcinoids. Further limited surgical resection has been proposed in low grade well differentiated NET histology without lymph node involvement [49, 50]. Complete mediastinal lymph node resection has been reported to improve outcome in various retrospective series and is considered standard of care at present. [51, 52] Mediastinal metastasis can be present in about 20% of TC patients at presentation whereas this number can be as high as 30–70% in AC [43, 53–55]. In general non-small cell lung carcinoma (NSCLC) resection principles should be followed for AC resection [56]. Table 2 shows distribution of various surgical techniques utilized in management of typical carcinoids per a recently published review of 1109 patients by the European Association of Thoracic Surgeons [57].

3.2 Adjuvant systemic treatment for resectable pulmonary NETs

National Comprehensive Cancer Network (NCCN) guidelines recommend against adjuvant treatment for stage I and II broncho-pulmonary NETs. NCCN guidelines, however do recommend adjuvant treatment for Stage IIIA broncho-pulmonary NETs based on expert opinion. Stage IIIA patients with negative margins and intermediate grade histology, can be offered platinum doublet (carboplatin/cisplatin + etoposide) +/− radiation post operatively. Stage IIIA NETs with low grade histology are recommended to undergo surveillance without adjuvant treatment. Exception to this rule is presence of positive margins. Stage IIIA patients with positive margins, regardless of tumor grade, are recommended to undergo adjuvant chemotherapy +/− radiation. These guidelines are not based on prospective data. They do admit that there is little data of the efficacy of chemoradiation in unresectable stage IIIA or IIIB low grade lung carcinoid tumors [45]. The European Society of Medical Oncology (ESMO) recommends tailoring of adjuvant treatment for ACs with positive lymph nodes on an individual patient basis after a thorough discussion in a multidisciplinary tumor board [44]. NANETS recommends against use of adjuvant systemic treatment, citing a lack of clinical evidence [28].

Table 2 Distribution of various surgical techniques utilized in management of typical carcinoids in 1109 patients by European Association of Thoracic Surgeons. (From Filosso et al. [57])

Type of intervention	n	%
Lobectomy	706	63.7
Wedge resection	130	11.8
Bilobectomy	82	7.4
Segmentectomy	81	7.3
Sleeve resection	77	6.9
Pneumonectomy	29	2.6
Extended resection	1	0.1
Missing data	3	0.2

3.3 Management of advanced disease

3.3.1 Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)

Currently no prospective data exists which can guide management of DIPNECH. The majority of cases are symptomatically managed with close observation and interval imaging (6–12 month CT chest without contrast). A single center experience with somatostatin analogs (SSAs) in patients with DIPNECH yielded favorable results [32]. Symptomatic patients with debilitating cough, wheezing or shortness of breath shall undergo surgical resection if they can tolerate the procedure [58–60]. Anecdotal case reports of use of systemic steroids have been reported but experts largely avoid long term use of steroids due to chronic complications. DIPNECH has the potential to turn malignant and few case reports utilizing lung transplantation have been reported [61, 62] .

3.3.2 Typical and atypical carcinoid tumors

The role of systemic treatment for metastatic disease can be broken into four categories; SSA therapy, targeted therapy, chemotherapy or peptide receptor radionuclide therapy. There can also be combinations of these depending on the patients clinical and radiologic characteristics.

3.3.3 Somatostatin analog therapy

SSAs have been demonstrated to play two roles in patients with NETs. First is for symptom control in those patients with the carcinoid syndrome consisting of diarrhea, flushing and wheezing. Patients with lung NETs experience this uncommonly, about 2% - 10% [11, 63]. Secondly, SSAs have an antiproliferative effect. The role of SSA therapy in NETs of the lung is evolving. Octreotide long acting repeatable (LAR) and lanreotide have demonstrated single agent activity in patients with NETs of the GI tract and pancreas,

however, large prospective trials for lung NETs have not been conducted [64, 65]. The PROMID study examined 85 patients with midgut NETs and randomized them to octreotide LAR 30 mg versus placebo. Octreotide LAR was found to have an increased time to progression (TTP) versus placebo of 14.3 versus 6 months with a hazard ratio (HR) of 0.34; $p < 0.001$) [64]. The CLARINET study included 204 patients with gastroenteropancreatic NETs (GEPNETs) and randomized them to lanreotide 120 mg every 28 days versus placebo [65]. The median progression free survival (PFS) was not yet reached in the lanreotide arm versus 18 months in the placebo arm, $p < 0.001$ with HR of 0.47 (95% CI, 0.30 to 0.73). The 24 month estimated rates of PFS were 65.1% versus 33.3% with lanreotide and placebo respectively.

A small study did examine patients with metastatic lung NETs using first-line SSAs [66]. There were 20 patients on octreotide LAR and 10 patients on lanreotide. The median duration of treatment was 10 months and 86.6% showed stable disease. Five- year survival was 53.0% (95% CI, 15 to 80%) and median PFS was 11.1 months (95% CI, 7.0 to 15.0). Another retrospective trial examining 61 patients with lung NETs demonstrated clinically meaningful PFS benefit in patients on SSAs [67]. This trial population included 41 (67%) AC patients with 77% of overall patients achieving stability of disease with a PFS and overall survival (OS) of 17.4 months (95% CI: 8.7 to 26) and 58.4 months (95% CI: 44.2 to 102.7) respectively. There is currently a phase III clinical trial, NCT02683941, looking to answer the question about SSAs in lung NETs. Despite the lack of prospective data in lung NETs, SSAs are recommended by NANETS, ENETS and NCCN as a consideration [28, 44, 45].

3.3.4 Targeted therapy

Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR) which stimulates cell proliferation, growth and angiogenesis. Everolimus was approved for use in patients with advanced pancreatic NETs based on the RADIANT-3 trial, which demonstrated a median PFS of 11.0 months (95% CI, 8.4 to 13.9) versus placebo at 4.6 months (95% CI, 3.1 to 5.4) with a HR of 0.35; 95% CI, 0.27 to 0.45; $p < 0.001$ [68]. Subsequently, the RADIANT-2 trial was published which examined the use of everolimus plus octreotide LAR in patients with advanced NETs associated with carcinoid syndrome [69]. This study included 429 patients with well differentiated NETs of multiple different sites and randomized them to everolimus 10 mg daily or placebo in conjunction with octreotide LAR 30 mg. The trial showed a trend to improvement in PFS based on central radiology review with the everolimus group having a PFS of 16.4 months (95% CI 13.7 to 21.2) versus 11.3 months (8.4 to 14.6) in the placebo group with a HR of 0.77 (95% CI 0.59 to 1.00) $p = 0.026$. An exploratory subgroup analysis of the 44 patients with lung NETs was performed where 33 patients were randomized to the everolimus arm [70]. This analysis demonstrated a PFS by central radiologic review of 13.63 months (95% CI, 5.55 to 14.29) in the everolimus arm versus 5.59 months (95% CI, 2.79 to 27.76) with a HR of 0.72 (95% CI, 0.31–1.68; $p = 0.228$).

These studies set the stage for the RADIANT-4 trial which randomized patients with advanced, non-functional NETs of the lung or gastrointestinal tract to either everolimus or placebo [71]. This study enrolled 302 patients and met its primary endpoint of PFS with the everolimus group obtaining a PFS of 11.0 months (95% CI, 9.2 to 13.3) compared to 3.9 months (95% CI, 3.6 to 7.4) in the placebo group with a HR of 0.48 (95% CI, 0.35 to 0.67, $p < 0.00001$). The drug was well tolerated compared to placebo with grade 3/4 adverse events including stomatitis (9 vs 0%), diarrhea (7 vs 2%), infections (14 vs 0%), anemia (4 vs 1%), fatigue (3 vs 1%) and hyperglycemia (3 vs 0%). A subgroup analysis of the 90 patients with lung NETs (63 everolimus vs 27 placebo) also showed an improvement in PFS from 3.6 months (95% CI, 1.9 to 5.1) versus 9.2 months (95% CI, 6.8 to 10.9) favoring everolimus [72].

Another phase II trial using everolimus and pasireotide has been reported in lung and thymic NETs. This study randomized patients 1:1:1 to pasireotide, everolimus or the combination [73]. The primary endpoint was the progression free rate at 9 months. There were 124 patients randomized and progression free at 9 months in 39%, 33% and 58.5% with pasireotide, everolimus or the combination respectively. Response rate were 2% in each arm. Together, these trials show that everolimus is a valuable treatment option in patients with lung NETs.

Targeted therapies that inhibit angiogenesis may also play a role in the treatment given the fact that increased vascular endothelial growth factor expression (VEGF) has been demonstrated to confer a poor outcome, however, prospective trials have yet to conclusively demonstrate their benefit [74]. Sunitinib, a multi-kinase inhibitor, plays a role in the treatment of NETs of the pancreas and possibly other low grade NETs [75]. In bronchial carcinoid tumor cell lines, sunitinib was found to be able to inhibit the viability of tumor cells versus control [76]. A phase II study in patients with pancreatic NETs and carcinoid tumors ($n = 41$), including foregut tumors (lung and stomach, $n = 14$) showed that the carcinoid tumor patients had an overall response are (ORR) of 2.4%; however, stability of disease was achieved in 82.9% of patients [77]. It was noted that one foregut patient had a confirmed partial response (PR) and that, overall, 43.9% of carcinoid patients seemed to have some degree of tumor shrinkage. Bevacizumab has been combined with low dose sorafenib

in a phase II study in patients with advanced neuroendocrine tumors (n = 44) with 19 foregut NETs [78]. Overall, PFS was 12.4 months and ORR was 9.4%. There were moderate toxicities observed with this combination and not felt to warrant further development.

3.3.5 Chemotherapy

Chemotherapy for metastatic pulmonary carcinoid tumors is recommended by the NCCN, however, this recommendation is based on small and often retrospective trials. While platinum based chemotherapy is recommended for patients with high grade NETs of the lung, those patients with typical and atypical carcinoid tumors of the lung may not experience similar benefit [45]. Overall, the trials that have been done using platinum based chemotherapy have included a mixed population of NETs with varying responses ranging from 0 to 33% [79–83]. Temozolomide monotherapy has been used in a study in patients with metastatic lung NETs (n = 31) [84]. In this retrospective study, PRs were seen in 14% of patients with stability of disease in 52%. Median PFS was 5.3 months and OS 23.3 months. It was noted that all patients with PRs did have high proliferative activity. In a phase II study temozolomide was combined with bevacizumab in patients with pancreatic NETs and carcinoid tumors (including lung, n = 4) [85]. In the carcinoid tumor arm, there were no PRs but 74% of patients (14/22) achieved stability of disease. Other retrospective studies have examined the role of adding capecitabine to temozolomide (CAPTEM) in patients with metastatic NETs, including lung NETs [86–88]. PRs were reported from 12 to 22% and stable disease 48–53% indicating that this may also be an effective strategy. An interim analysis of a prospective, phase II study using CAPTEM in well differentiated NETs including carcinoids showed PRs in 33% of patients and stability of disease in 58% with a median PFS > 22 months [89]. Lastly, a retrospective study including 45 patients with TC and AC examined the use of oxaliplatin in combination with either 5-fluorouracil or gemcitabine [90]. Patients had received chemotherapy at any line of treatment. PR was achieved in 20% and 64% had stability of disease. Median PFS and OS was 15 and 34 months respectively. There were no significant differences between either regimen. These studies indicate that several different chemotherapy options may be available for patients with PCs.

3.3.6 Radionuclide therapy

In NETs expressing SST receptors radionuclide may present alternative treatments. The goal of therapy is palliative and aimed at prolonging PFS and to reduce symptoms. Likelihood of complete response is approximately 5% while PR according to Response Evaluation Criteria In Solid Tumors (RECIST) may be seen in up to 50% of cases [12]. Uptake in the primary neoplasm as well as metastatic foci should be equivalent or greater than that of the liver [12]. PRRT uses high energy beta emitting radionuclides with either Yttrium-90 (Y-90) or Lutetium-177 (Lu-177) bound to somatostatin analogs to deliver high doses to receptor positive cells [22]. Lu-177 may be more effective for smaller tumors while Y-90 may be more effective for larger tumors due to the difference in range of their beta decay [91].

Multiple analyses have shown the utility of PRRT in patients with NETs, including PCs. In a study examining 1109 patients of various primary sites, including 84 PCs, morphologic response and disease control was found in 34.1% and 39.3% respectively overall [92]. In those patients with PCs morphologic response was seen in 28.6% and clinical response in 38.1%. Another study including 41 mixed tumor types, including 7 PCs showed an overall clinical benefit of 85% with 100% of the PCs showing a complete response, PR or stability of disease [93]. A study of 135 North American patients, including 13.3% PCs undergoing PRRT showed a 32.9 month OS from the 1st PRRT [94]. Additionally, a retrospective study of 114 PCs treated with PRRT showed a morphologic response rate of 26.5% and a median PFS and OS of 28 and 58.8 months, respectively, indicating PRRT is a beneficial therapy with patients with PCs [95].

Similarly, ^{131}I -MIBG may also be a treatment option in patients with ^{123}I–MIBG receptor scintigraphy and avid MIBG accumulation within lesions. In a retrospective study of 6 patients with PCs, 50% were found to have either a PR or stable disease [36]. Prospective trials are needed to determine the number of cycles, doses and best timing for PRRT.

4 Conclusions

Treatment options for patients with lung NETs continue to expand, however, surgery remains the mainstay of therapy, especially in the well-differentiated carcinoids. Figure 1 shows a suggested treatment algorithm. Once disease is progressive, there is still controversy regarding treatment options and misconceptions concerning who to treat, when to treat and what to treat with. Once treatment is decided upon, sequencing treatments are still somewhat debatable. It is important to have a multidisciplinary approach in the management of patients with lung NETs with involvement of a medical oncologist, thoracic surgeon, pulmonologist, nuclear medicine physician, radiologist and pathologist and endocrinologist who have knowledge of the workup and treatment of NETs. Although there are few clinical trials that are exclusive for patients with PCs, several trials listed in Table 3 include these patients [96–103]. Patients

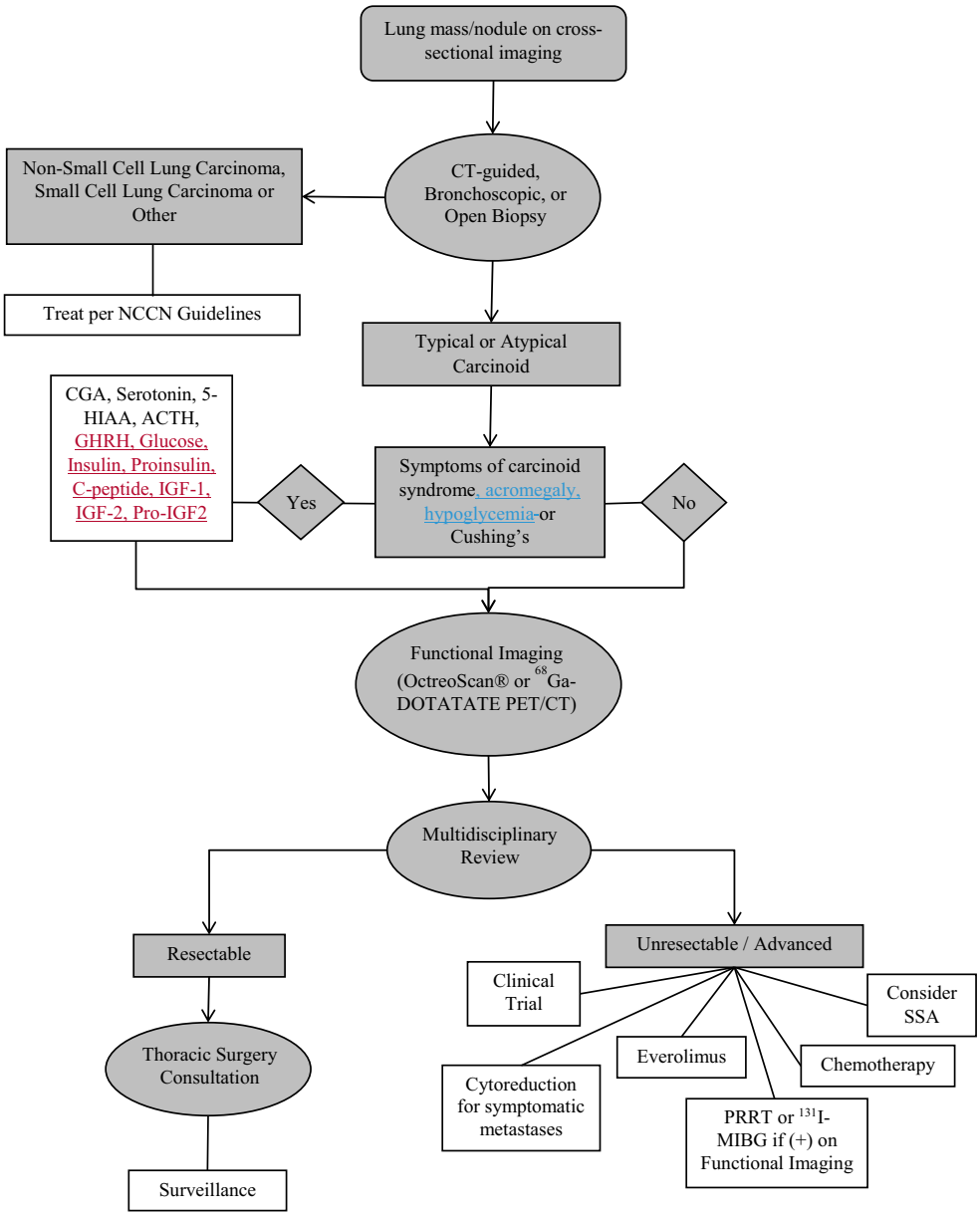

Fig. 1 Suggested treatment algorithm. Abbreviations: NCCN, National Comprehensive Cancer Network; CGA, Chromogranin A; 5-HIAA, 5-Hydroxyindoleacetic Acid; ACTH, Adrenocorticotropic Hormone; PRRT, peptide receptor radionuclide therapy; ^{131}I–MIBG, Iodine-131 metaiodobenzylguanidine; SSA, Somatostatin Analog; ^{68}Ga-DOTATATE PET/CT, Gallium-68-DOTATATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–octreotate) Positron Emission Tomography/Computed Tomography

Table 3 Trials in progress [96–103]

Trial (NCT#)	Indications	Treatment	Phase	Location
NCT02823691	Lung; GI	Lanreotide and Metformin	1	Europe
NCT03095274	Lung; GI; Pancreas	Durvalumab plus Tremelimumab	2	Not Listed
NCT02834013	Lung; Rare Tumors	Nivolumab and Ipilimumab	2	USA
NCT02575300	Lung; Pancreatic	Ibrutinib	2	USA
NCT02683941	Lung	Lanreotide	3	USA Canada Europe
NCT02698410	Lung; Thymus	Lanreotide and Temozolomide	2	Europe
NCT02259725	Lung; GI; Pancreas	Regorafenib	2	USA
NCT02259725	Lung; GI; Pancreas	PDR001	2	USA EUROPE AUSTRALIA ASIA

should be screened for and enrolled in clinical trials whenever possible as there is currently a paucity of data concerning treatment of lung NETs.

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Compliance with ethical standards

Conflict of interest Robert A. Ramirez, DO serves as a consultant for Ipsen Biophamaceuticals Inc. and Bio Theranostics Inc. as well as a speaker for Merck & Co. Inc., Genetech, Astra Zeneca and Ipsen Biopharmaceuticals. No other authors have conflicts of interest to disclose.

Human and animal studies No humans or animals were used in this study.

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