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Baudin E[1], Hayes AR[2], Scoazec JY[3], Filosso PL[4], Lim E[5], Kaltsas G[6], Frilling A[7], Chen J[8], Kos-Kudła B[9], Gorbunova V[10], Wiedenmann B[11], Nieveen van Dijkum E[12], Ćwikła JB[13], Falkerby J[14], Valle JW[15], Kulke M[16], Caplin ME [2*] & The ENETS 2016 Munich Advisory Board Participants

1. Oncologie Endocrinienne et Médecine Nucléaire, Institut Gustave Roussy, Villejuif, France
2. Neuroendocrine Tumour Unit, Royal Free Hospital, London, UK
3. Department of Pathology, University of Lyon, Lyon, France
4. Department of Thoracic Surgery, University of Torino, Torino, Italy
5. Department of Thoracic Surgery, Royal Brompton Hospital, London, UK
6. Department of Pathophysiology, Division of Endocrinology, National University of Athens, Athens, Greece
7. Department of Surgery and Cancer, Imperial College London, London, UK
8. Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510080, China
9. Slaska Akademia Medyczna Klinika Endokrynologii, Zabrze, Poland
10. FSBI "N.N Blokhin Russian Cancer Research Centre", Russian Academy of Medical Sciences, Moscow, Russia
11. Department of Hepatology and Gastroenterology, Campus Charité Mitte and Campus Virchow Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany
12. Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands
13. Department of Radiology, Faculty of Medical Sciences, University of Warmia and Mazury, Olsztyn, Poland
14. Department of Endocrine Oncology, Uppsala University Hospital, Uppsala, Sweden
15. Department of Medical Oncology, The Christie NHS Foundation Trust, University of Manchester/Institute of Cancer Sciences, Manchester, UK
16. Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Running title: Unmet Needs in Pulmonary Carcinoids

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*Corresponding Author: Professor Martyn Caplin, Neuroendocrine Tumour Unit, Royal Free Hospital, Pond Street, London NW3 2QG. Tel: +44 207 830 2867 Fax: +44 207 472 6728 Email: m.caplin@ucl.ac.uk

Abstract

Pulmonary carcinoids (PCs) display the common features of all well-differentiated neuroendocrine neoplasms (NEN) and are classified as low- and intermediate-grade malignant tumours (i.e. typical (TC) and atypical carcinoid (AC), respectively). There is a paucity of randomised studies dedicated to advanced PCs and management principles are drawn from the larger gastroenteropancreatic (GEP) NEN experience. There is growing evidence that NEN anatomic subgroups have different biology and different responses to treatment and, therefore, should be investigated as separate entities in clinical trials. In this review, we discuss the existing evidence and limitations of tumour classification, diagnostics and staging, prognostication and treatment in the setting of PC with focus on unmet medical needs and directions for the future.

Introduction

Pulmonary carcinoids (PCs) are epithelial tumours displaying the common features of all well-differentiated neuroendocrine neoplasms (NENs), namely, a well-conserved endocrine morphology and the expression of the neuroendocrine markers chromogranin A and synaptophysin. They represent 1-2% of pulmonary neoplasms and approximately 25% of all NENs (1-4). Although their characterisation follows similar rules compared to other NENs, the influence of the site of origin justifies specific studies. Among the NEN spectrum, only one phase II clinical trial (5) has been dedicated to thoracic carcinoids highlighting the paucity of prospective evidence. In general, data regarding their

therapeutic management, but also best characterisation, is poor. The WHO classification of pulmonary neuroendocrine tumours (NETs) uses different terminology compared to that of gastroenteropancreatic (GEP) NETs; the terms *typical* and *atypical* carcinoid are used for well-differentiated low and intermediate grade pulmonary NETs respectively, as opposed to neuroendocrine tumour grade 1 and grade 2 used in well-differentiated GEP NETs. As for poorly-differentiated neuroendocrine carcinomas (NECs), the same categories of small cell (SCLC) and large cell neuroendocrine carcinoma (LCNEC) are used for both thoracic and GEP neoplasms, although different mitotic count thresholds differentiate carcinoid from poorly-differentiated tumours or carcinomas in the pulmonary and GEP NET cohorts respectively. Finally, the specific terminology of 'carcinoma' as a synonym of poorly-differentiated neoplasms is only accepted in GEP NETs but not in pulmonary NETs in which the term 'tumour' refers to both well or poorly-differentiated neoplasms. Due to their anatomical site-specific clinical characteristics and molecular alterations, PCs should be evaluated separately from other NETs. Uniform terminology is expected to allow for simplest communication in the NEN field. In this review, we align our terminology with the WHO classification; with pulmonary carcinoids as a whole referring to well-differentiated tumours as opposed to the poorly-differentiated neuroendocrine carcinoma (e.g. SCLC and LCNEC).

CLASSIFICATION AND DIAGNOSTICS

PCs are classified according to the World Health Organisation (WHO) 2015 classification (6) and staged according to the 2017 revision of the *Union Internationale*

Contre le Cancer / American Joint Committee on Cancer (UICC/AJCC) TNM classification (7). In addition, the European Neuroendocrine Tumour Society (ENETS) (8) and North American Neuroendocrine Tumor Society (NANETS) (9) guidelines have provided recommendations for additional pieces of standardisation that encompass biochemical screening for hormonal syndrome, biomarker measurements, imaging for staging including functional imaging, genetic screening and prognostic stratification (Table 1). At diagnosis, the vast majority of PCs are sporadic, non-functioning, typical carcinoids (TC to AC ratio 8-10:1), often diagnosed at an early stage (8, 10).

Among the spectrum of NENs, several distinctive features of PCs, as compared to GEP NETs should be recognised: (i) features of carcinoid syndrome may be atypical due to secretion of histamine metabolites and symptoms can include lacrimation, wheeze and sweating (11). Semiology is typically defined as a purple-red flush, potentially covering the entire body, which can be intense and prolonged in duration as opposed to the more red and patchier flushing seen with midgut NETs which typically does not last as long and predominates on the face and upper trunk (11). Carcinoid syndrome may occur in the absence of liver metastases as vasoactive peptides directly drain into the left heart making mitral and aortic valves first exposed to dysfunction as a consequence (ii) the histopathological WHO classification is based on morphology, mitotic count and the presence or absence of necrosis only. The latest 2015 WHO classification (6) does make reference to the Ki-67 proliferation index, however, only as a tool for the differential diagnosis between carcinoids and high-grade SCLC and LCNEC, especially in small biopsy samples with crushed and/or necrotic tumour cells. (iii) Most PCs are diagnosed at an early stage, typically stage I-II, which makes surgery of the primary a

common first line management strategy in these patients; in addition, a long history of routine lymph node dissection exists in the field of PC, also, (iv) a high diversity of metastatic sites, including higher prevalence of bone and cerebral metastases, require specific screening and treatment.

Several unmet medical needs are cited below that require specific studies to make the characterisation and staging of PCs more precise.

1. Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) is considered a rare, pre-invasive condition of PCs and the natural history is poorly understood (12). The prevalence in PCs is unclear, however, it is likely to be underestimated given the absence of routine reporting of concomitant DIPNECH on histopathology specimens and the often insufficient availability of background lung parenchyma in the setting of lung biopsy. In addition, DIPNECH can also be found in benign conditions associated with chronic cough, such as bronchiectasis and interstitial fibrosis (13-16).
2. Previous studies have defined the different metabolism of serotonin in foregut NETs, compared to midgut NETs, primarily due to the foregut deficiency in the enzyme aromatic L-amino acid decarboxylase (17). A higher diversity of amine and peptidic secretions has also been reported in foregut NETs (17). Carcinoid syndrome is found in less than 5% of PC patients at the time of diagnosis (8) but elevated urinary 5-HIAA levels can be found in reportedly 20% of cases of metastatic PCs, as recently evidenced in the LUNA trial (5). These figures require

further specification in prospective cohorts of patients. In addition, the incidence of carcinoid heart disease in PC is poorly characterised.

3. The WHO 2015 classification (6) recognises two categories of PCs based on morphology, mitotic thresholds and the presence or absence of necrosis; *typical* and *atypical* carcinoids. However, the role of Ki-67 labelling index in the classification of PCs remains unclear, as opposed to GEP NETs where Ki-67 has refined the classification system (18-21). Preliminary studies suggest an overlap in the Ki-67 labelling index between typical and atypical cohorts (8, 22, 23), but also a potential role of Ki-67 to improve the prognostic stratification (23-29) and further data is needed to determine the utility of Ki-67 in PCs. In addition, high mitotic counts above the current WHO threshold of 10 mitoses per 2 mm^2, may still be compatible with well-differentiated morphology; however such cases are currently reported as “high-grade neuroendocrine carcinoma” (30). A distinct WHO category may be defined in the future.
4. Tumour staging for PCs is recommended according to the UICC-TNM system however refinement of descriptive categories is needed. Nodal status (N) and its impact on prognosis has been the most studied and N1 or N2 disease is associated with poorer outcomes (31, 32). The prognostic implications of tumour size (T), pleural invasion and multicentricity remains to be better outlined (31). Most cases of multicentric PC represents synchronous rather than metachronous disease, especially in the setting of DIPNECH, and analysis of Surveillance, Epidemiology and End Results (SEER) and International Association for the Study of Lung Cancer (IASLC) databases confirms favourable outcomes in patients with PC and multiple pulmonary nodules (31). Hence, this subgroup of

PC patients need to be staged differently from non-small cell lung cancer (31). Studies with long-term follow-up, greater than 10 years, are also required to determine the risk of relapse in the setting of R1 resection. Finally, prognostic stratification of both localised and advanced PC are expected.

5. Similar to all NENs, staging is best performed with a combination of conventional and functional imaging. As compared to GEP NETs, PCs are characterised by a higher frequency of bone and cerebral metastases (33, 34), but also a higher diversity of metastatic sites including cutaneous, adrenal, thyroid, ovarian and peritoneum. ENETS guidelines (35) acknowledge the superiority of MRI for imaging of metastases to the brain and bone, however, it remains unclear what imaging should be performed as a matter of routine in the staging and pre-operative assessment of PCs and how that should differ compared to GEP NETs. Somatostatin receptor imaging (SRI) is the pillar of functional imaging and PET dedicated tracers, like ^{68}Ga-labelled somatostatin analogues (i.e. ^{68}Ga-DOTA-TOC/TATE/NOC), have been developed with improved sensitivity (Sn 88-93%) compared to historical somatostatin receptor scintigraphy (Sn 60-80%) (35). Whilst ^{68}Ga-DOTA somatostatin analogue PET/CT generally reveals additional metastases compared to conventional imaging (e.g. CT/MRI) in well-differentiated NET (35), especially of lymph nodes, bone and peritoneum, there are no dedicated studies yet to determine the performance of SRI in the pre or post-operative setting of early-stage PC, namely, for the detection of mediastinal node metastases. A few studies dedicated to advanced PC have provided first evidence that the rate of new sites discovered by SRI is above 10% supporting its routine use (36). ^{18}F-FDG PET/CT is currently recommended in aggressive PC,

but due to its historical role in lung cancer, ^{18}F-FDG PET/CT is frequently performed first (37). FDG avidity has been reported in AC but also in TC, supporting either WHO misclassification or different mechanisms of FDG uptake in these patients which remains to be further explored. A recent systematic review and meta-analysis (38) reported that ^{18}F-FDG PET/CT has poor sensitivity (33%; 95% CI 4-78%) but good specificity (94%; 95% CI 89-97%) to detect the presence of mediastinal lymph node metastases in pulmonary carcinoid tumours (88% typical carcinoid morphology). As the presence of lymph node disease does not preclude selection for surgery, the clinical utility of ^{18}F-FDG PET/CT for preoperative staging of the mediastinal nodes in patients with known carcinoid tumours may be limited.

6. PC is diagnosed in up to 5% of patients with multiple endocrine neoplasia type 1 (MEN1) (39-42). Follow-up of a prospective cohort of MEN1 patients, with primary hyperparathyroidism and negative whole body imaging, is expected to clarify the exact incidence of PCs in patients with MEN1 (NCT03348501). Screening CT or MRI of the chest every 1-2 years is currently recommended in the MEN1 population for detection of pulmonary or thymic carcinoids (43), although the optimum method for screening and the role of SRI has not been established. In addition, it is unclear if MEN1-associated PCs behave more aggressively compared to sporadic tumours.
7. Although rare, PCs are the most frequent source of ectopic Cushing's syndrome (44-46). Historically, ACTH-secreting PCs were considered to behave more aggressively than hormonally-quiescent tumours (47, 48); however, more recent retrospective series suggest localised ACTH-secreting PCs of typical morphology,

especially those amenable to curative surgery, may have prognoses comparable to that of non-ACTH secreting typical PCs (45, 46, 49, 50). Nevertheless, prognosis is determined by underlying tumour morphology, as well as adequate control of hypercortisolaemia, since both affect morbidity and mortality (45, 46). Further studies are required to better characterise the natural history and optimal therapeutic interventions, especially in patients with disseminated disease and/or refractory hormonal syndrome. Patients with functioning PCs should be included in prospective clinical trials.

Prognostication

As for the majority of foregut-derived NETs, WHO histological classification is considered the most powerful prognostic parameter, with UICC-TNM staging the second most important prognostic parameter. Resection (R) status and the specification of node dissection (e.g. number, regions) must be included in surgical and pathological reports.

Both local and distant recurrence have been reported with a frequency of 30 to 70% reflecting heterogeneous populations but also non-standardised modality of staging and follow-up. As a consequence, median recurrence-free survival of localised PC is currently poorly studied, as well as the exact proportion of local versus distant relapse and the precise anatomical locations of relapse. All of these parameters require improved specification in prospective European cohorts with pre-defined modality of follow-up and recurrence-free survival as a primary endpoint.

In metastatic PC, best prognostic stratification remains unknown. The respective value of WHO histological classification and tumour burden is currently unexplored. Preliminary results demonstrate that median overall survival (OS) in patients with metastatic PC is between 5 and 10 years (51) suggesting room for watchful follow-up in the absence of curative options. Poorer OS is observed in the metastatic AC cohort (51).

BIOMARKERS

The role of biomarkers has previously been limited. Serum chromogranin A may be a marker of tumour burden but appears to have poor specificity and sensitivity (52-54). The NETest, a PCR based 51 mRNA marker signature, has recently been suggested to be a more sensitive and specific test for the detection of PCs and for identifying progressive disease (55) but needs to be validated in prospective studies and in a large population of patients.

There is growing understanding of the molecular characterisation of PCs however further studies are needed. Molecular studies have demonstrated frequent alterations in the chromatin remodelling genes, *MEN1, PSIP1* and *ARID1A,* in PCs (56-59) and in inactivating mutations in *TP53* and *RB1*, amplification of *MYC* family members and genetic alterations in the *PI3K/AKT/mTOR* pathway in SCLC (56, 57, 59, 60). Conversely, mutations in chromatin remodelling genes, including those encoding histone

modifiers and members of SWI-SNF complexes, can be found at similar rates in PCs and lung neuroendocrine carcinomas suggesting a major role in lung neuroendocrine tumour pathogenesis (61). The modality of *mTOR* pathway activation in PCs has to be better understood as well as somatostatin receptor and other peptidic receptor activation. Further work is needed to define the role of molecular profiling in the diagnostic and prognostic stratification of PCs as well as the role in potentially guiding treatment.

THERAPEUTICS

Control of hormone-related symptoms

No single study, or subgroup analysis, has explored the efficacy of somatostatin analogue therapy with regard to the control of hormone-related symptoms. Also, the role of locoregional therapy, including liver-directed transarterial embolisation, in the treatment of carcinoid syndrome remains to be evaluated. Better characterisation of carcinoid syndrome in advanced PC patients is considered the primary objective of future studies including both clinical retrospective and prospective studies. The role of telotristat ethyl should be evaluated in those patients with carcinoid syndrome who become resistant to somatostatin analogue therapy. In patients with poorly controlled Cushing's syndrome and advanced PC, the decision to perform bilateral adrenalectomy coincides with the need for active anti-tumour therapy. Such groups of patients could be prospectively investigated to test the risk-benefit ratio in regard to the type of cortisol lowering therapy (medical vs. surgical) and tolerance of anti-tumour agent.

Surgery for localised disease

Surgical treatment of localised PC is extrapolated from surgical principles for localised pulmonary neoplasms with a dedicated focus on lung-sparing surgery. The surgical approach is dependent on size, location and WHO classification of the tumour. For patients with peripheral lung tumours, consensus guidelines (8) recommend complete anatomic resection (e.g. lobectomy, segmentectomy) however there is no prospective data to guide the optimal surgical approach according to the final WHO classification. Peripheral ACs may have an increased risk of local recurrence in the setting of a limited sub-lobar resection (62). Parenchymal-sparing surgery (e.g. sleeve resection, sleeve lobectomy) is favoured over pneumonectomy for patients with central airway TCs with intraoperative frozen section of both bronchial margins (8, 9).

A long history of routine lymph node dissection exists in the field of PC. Consensus guidelines recommend systematic lymphadenectomy since lymph node metastases may be present in up to 25% of cases of TC and >50% in ACs (63, 64) but practice differs across international centres (37) and thus highlighting the importance of lymphadenectomy is an imperative.

Surgery for locoregional recurrence and metastatic disease

Evidence to guide the role of surgery in the management of locoregional recurrence is limited to case reports (65) and consensus guidelines. Surgery for metastatic disease is guided by the management principles of all NETs and is reserved for patients with limited sites of disease where surgery with curative intent is possible for all sites, mainly in the setting of slowly progressive TC. Primary resection and palliative metastasis debulking should also be considered in the setting of an obstructive mass or refractory hormonal syndrome (66). The role of palliative hepatic debulking in asymptomatic patients remains uncertain. Although some retrospective GEP NET series suggest that hepatic debulking is associated with improved survival (67-71), there is a lack of comparative trials with systemic or locoregional therapy in the setting of PC.

Surgery in the setting of multifocal PCs

There is no data to guide optimal surgical management of multicentric PC, especially in the setting of DIPNECH. However, given the rarity of carcinoid syndrome and metastastic spread in this setting, a non-aggressive approach should be adopted in most cases of DIPNECH. The management of multifocal carcinoid tumours needs to be tailored according to the size, number and cell type of tumours, the possibility of achieving complete resection and pre-existing lung function.

Follow-up after surgery

The optimal modality and duration of follow-up of PC after surgery is currently unknown but needs to be guided by type of surgery, underlying tumour WHO classification, stage and R status. Given the continuous decline of survival in PC patients over decades, lifelong follow-up is the expected requirement. Series with median follow-up of 20 years is recommended. Currently, endoscopic, conventional cross-sectional imaging and SRI constitute the recommended procedures for monitoring. Local mediastinal nodes, liver and bone are the most frequent sites of recurrence. Performance of non-irradiating imaging modalities and increasingly lengthened interval of survey require prospective validation.

Endobronchial management

The role of endoscopic treatment in localised PC has not been well-defined but it should be limited to pre-operative disobliteration or for the palliation of patients unfit for surgical intervention. Importantly, nodal involvement may be present in more than 25% of patients and imaging techniques, including ^{68}Ga DOTA somatostatin analogue PET/CT, may not be sufficient to exclude lymph node metastases. Endobronchial therapy (e.g. laser via rigid bronchoscopy) may also act as a bridge to surgery when there is intraluminal tumour causing obstructive pneumonia.

Locoregional therapies

Radiofrequency or cryoablation of the primary tumour are occasionally considered in cases of residual or unresectable disease (8), although data is limited. Liver, bone and

lung metastases also represent potential targets of radiofrequency ablation. Other liver directed therapies for liver predominant disease includes bland particle embolisation (transarterial embolisation, TAE), transarterial chemoembolisation (TACE) or radioembolisation. Radiological response rates with bland or chemoembolisation have been reported between 33 and 73% predominantly in the GEP NET population, however less data is available on the efficacy of these therapies in PC patients. Specifically, the role of locoregional therapy in the therapeutic management of carcinoid syndrome, including bone- and or liver-directed therapies, remains to be evaluated.

Medical therapy in the adjuvant setting

Currently, there is no prospective randomised evidence or consensus on adjuvant therapy in PCs after complete resection and clinical trials are needed in this setting. Patients with atypical carcinoids, with higher incidence of positive regional lymph nodes and disease recurrence, constitute the target subgroup of patients in whom adjuvant therapy could be investigated; however, the feasibility of such a study is questioned due to the long-term survival of these patients and also the relative scarcity of PC.

Medical therapy in the palliative setting

Treatment of advanced PCs is extrapolated from GEP NETs with the somatostatin receptor and the *mTOR* pathway as common targets. To date, four retrospective trials dedicated to PC therapeutic management and one randomised phase II trial, LUNA (5),

have been reported, highlighting the low level of evidence available. In addition, two randomised phase III trials, RADIANT-2 (72) and RADIANT-4 (73) have been published that enrolled 10% and 30% of metastatic PCs, respectively. Currently, everolimus constitutes the only approved drug based on the results of the RADIANT-4 trial. Common to all NETs, there is also little evidence on the best sequencing of therapy including somatostatin analogues, everolimus, cytotoxic chemotherapy and peptide receptor radionuclide therapy.

Cytotoxic chemotherapy has traditionally utilised platinum-etoposide regimens, as per SCLC, although response rates have been reported across diverse regimens in small, retrospective series (74-78). Currently, due to an unfavourable risk-benefit ratio, platinum-based chemotherapy is not recommended in metastatic PC as first line. Response rates with chemotherapy have generally been poor in PCs (<15%) and the interpretation of study results is limited by small patient numbers, mixed populations of primary tumours and the absence of proven disease progression prior to enrolment. Intuitively, one would anticipate that the role for chemotherapy is in the more aggressive atypical carcinoid cohort, especially in those patients with high proliferative indices and/or extensive necrosis. The alkylating agent, temozolomide, has demonstrated some evidence of moderate efficacy in metastatic PC but again only in small, retrospective series (79-81). Given its blood-brain barrier permeability, temozolomide could also be beneficial in cases of PC with brain metastases and analysis of O^6-methylguanine-DNA methyl-transferase (MGMT) expression may help to select responders (80, 82, 83), although prospective validation of this approach is lacking. Prospective studies

assessing the activity and toxicity of temozolomide, as monotherapy or in combination with other therapeutic agents, as well as including MGMT status, is warranted in well-differentiated PCs, especially in the atypical carcinoid cohort with progressive disease. There is currently only one prospective combination temozolomide study in progress dedicated to thoracic carcinoids; the phase II clinical trial, ATLANT (NCT02698410).

Well-differentiated PCs frequently express somatostatin receptor subtype 2 (84-87) and the role of somatostatin analogue therapy, specifically in metastatic or unresectable PCs, is currently being assessed in the phase III clinical trial, SPINET (NCT02683941). Drawing from the GEP NET experience, there would also appear to be a role for peptide receptor radionuclide therapy in the setting of somatostatin-receptor positive metastatic PC, and prospective, randomised studies are needed. Data is currently limited, however, responses in retrospective series of metastatic PC have been reported (88-93).

Tyrosine kinase receptors (e.g. VEGF, c-kit, PDGFRalpha, PDGFRbeta, EGFR) are expressed in a significant number of patients with metastatic PCs (94). However, data on the role of tyrosine kinase inhibitors and antiangiogenic agents in PC is lacking. A phase II study (95) evaluating the efficacy of sunitinib included 41 patients with carcinoid tumours, of whom 14 were of foregut origin, including PC. The objective response rate in patients with carcinoid tumours was 2.4% with stable disease in 83%. Pazopanib was studied in the PAZONET study (96) as a sequencing treatment in progressive metastatic neuroendocrine tumours and included a small cohort (n=5) of PCs. Six per cent and

79% achieved partial response and stable disease respectively. The VEGF monoclonal antibody, bevacizumab, showed efficacy in a phase II study (97) where it was compared with pegylated interferon. Of the 22 patients in the bevacizumab group, that included four patients with PCs, 21 demonstrated a partial response. More studies investigating the activity of tyrosine kinase inhibitors and antiangiogenic agents in metastatic PC are needed.

FUTURE DEVELOPMENTS

Surgical resection is well-recognised as the treatment of choice for PCs, with best chance of cure, especially in localised TC, however disease recurrence, perhaps very delayed, is not uncommon in the PC population. Long term follow-up studies of post-surgical PC patients are expected. Given the paucity of prospective data, the area of most need in PCs relates to the optimal management of recurrent or advanced disease. Response rates with systemic therapy remain modest and novel approaches must be pursued. Data on the efficacy of peptide receptor radionuclide therapy in PC is awaited. Retrospective studies have suggested differing treatment responses, rates of metastatic disease and prognosis in metastatic AC versus TC and their different biology warrant further exploration (51, 98, 99). Advanced technologies incorporating next-generation sequencing, may help identify molecular biomarkers to guide treatment and inform prognosis in the future, however, current supportive evidence in neuroendocrine tumours is limited. Such technologies may also add to the questioning of the current classification of TC and AC. Given the relative scarcity of the disease, individual clinical

trials, based on origin of anatomical primary, are likely to be challenging and future large phase III trials must stratify NETs by primary site. Target-driven trials in phase I or II programs are of great promise in the setting of rare diseases, and the tailoring of new strategies to identified molecular alterations with best driver potential, may help to rapidly identify new promising agents.

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Kaltsas Gregory National University of Athens, Dept. of Pathophysiology, Endocrine Unit Greece

Klöppel Günter Consultation Center for Pancreatic and Endocrine Tumors/Dept of Pathology/TU-Munich Germany

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Kos-Kudła Beata Department of Endocrinology and Neuroendocrine Tumors, Medical University of Silesia Poland

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Lamberts Steven W.Jj Netherlands

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O'Connor Juan Manuel Instituto Fleming Argentina

O'Toole Dermot St. James's and St Vincnt's Univerrsity Hospitals & Trinity College Dublin Ireland

Pape Ulrich-Frank ChariteCampus Mitte/Berlin Germany

Partelli Stefano Pancreatic Surgery Unit, Pancreas Translational & Clinical Research Center, San Raffaele Scientific Institute, "Vita-Salute" University, Milan, Italy.

Pavel Marianne Ellen Universitätsklinikum Erlangen Germany

Peeters Marc Antwerp University Hospital, Department of Oncology Belgium

Ramage John Hampshire Hospitals NHS Trust United Kingdom

Reed Nicholas Simon Beatson Oncology Centre/Gartnavel General Hospital United Kingdom

Rindi Guido Policlinico Universitario A. Gemelli, Rome Italy

Rinke Anja Uniklinikum Gießen und Marburg Germany

Ruszniewski Philippe Department of Gastroenterology-Pancreatology, Beaujon Hospital France

Sorbye Halfdan Haukeland University Hospital, Dept. of Oncology Norway

Sundin Anders Dept. Radiology, Inst. Surgical Sciences, Uppsala University, Akademiska Sjukhuset, SE751 85 Uppsala, Sweden Sweden

Scoazec Jean-Yves Gustave Roussy, Biopathology France

Taal Babs G. Netherlands Cancer Centre Netherlands

Tiensuu Janson Eva Uppsala University Sweden

Toumpanakis Christos Royal Free Hospital, London,UK United Kingdom

Valle Juan University of Manchester / The Christie NHS Foundation Trust United Kingdom

Vullierme Marie-Pierre Hopital Beaujon - Radiologie France

Welin Staffan Endocrine Oncology entrance 78D University hospital, Uppsala 751 85 Uppsala Sweden Sweden

Wiedenmann Bertram Charite Medical School and Hospital (Virchow), Gastroenterology Germany

Table 1. Recommendations for diagnosis and staging of pulmonary carcinoids.

Clinical history • Presence of hormonal syndrome • Family history of MEN1
Pathology • WHO classification • Immunohistochemistry (chromogranin A, synaptophysin, CD56, Ki-67) • Multiple synchronous primaries; DIPNECH features • Specification of node dissection (e.g. number, station) • R status
Biochemistry • Renal function, potassium, calcium, glucose and plasma chromogranin A • 24h u-5HIAA in syndromic patients • (Serum cortisol, ACTH, 24h urine free cortisol, serum GHRH, IGF-1)*
Imaging • TNM staging • Multiphasic contrast-enhanced CT chest and abdomen • Dynamic contrast-enhanced MRI Liver • 111In-DTPA-scintigraphy or preferably ^{68}Ga-DOTA somatostatin analogue PET/CT • Consider ^{18}F-FDG PET/CT in atypical carcinoids or high grade histopathology • Whole spine MRI if symptoms
Bronchoscopy • EBUS in selected cases
If considering surgery perform: • Transthoracic echocardiography • Respiratory function tests
Genetic screening • MEN1 germline testing when suspected

*Clinical symptoms suggestive of Cushing's syndrome or acromegaly

Table 2. Areas of unmet medical needs in pulmonary neuroendocrine tumours

- Common terminology in the NEN field
- WHO classification; role of Ki 67, necrosis as single criteria, relevance of high-grade carcinoid category
- Characterisation and prevalence of carcinoid syndrome
- Characterisation of DIPNECH
- Biomarkers with high sensitivity or specificity
- Performance of SRI in the pre-operative setting and in metastatic PC patients
- Prognostic recurrence free survival stratification for localised PC
- Prognostic overall survival stratification for metastatic PC
- Long-term follow-up of PC patients after surgical resection of primary tumour
- Carcinoid syndrome rate of control with somatostatin analogues, telotristat ethyl or locoregional therapies
- Best therapeutic sequencing in localised and advanced PC complicated by ectopic Cushing's syndrome
- Metastatic PC dedicated prospective clinical trials
- Best therapeutic sequencing in advanced PC
- Active translational research in refractory PC