Editorial, Endocrine.

Diagnosis and Management of Pulmonary Carcinoids.

Zidan, L.

Nuclear Medicine Unit, NEMROCK Center, Faculty of Medicine, Cairo University, Egypt.

INTRODUCTION:

Neuro-Endocrine: Tumours (NETs) are rare slowly growing malignancies that arise from neuroendocrine cells, which can be found anywhere in the human body. Broncho-pulmonary neuroendocrine tumours (bpNETs) represents approximately about 20-30 % of NETs and about 25% of all lung cancers [1, 2]. Recently the prevalence of bpNETs has increased, this may be attributed to early disease detection and/or improved survival [3].

Broncho-pulmonary neuroendocrine tumours are classified according to their degree of differentiation into well and poorly differentiated forms, depends on the mitotic index and presence of necrosis. The well-differentiated pulmonary carcinoid, include the low grade which is the typical carcinoid (TC). While, the intermediate-grade which is the atypical carcinoid (AC). The poorly differentiated group include large cell neuroendocrine carcinomas (LCNEC) and small cell lung cancer (SCLC) [4, 5]. Although there is some similarities between the two groups, the behaviour of pulmonary carcinoids are completely different from that of SCLC and LCNEC [6].

Pulmonary carcinoid tumours are uncommon malignancies, which appeared to be increasing overtime. Diagnosis and management depends on accurate histological classification that also can predict the prognosis. Contrast enhanced CT is the first recommended investigation, 68Ga-dotatate–PET/CT should be done for well differentiated tumours, while FDG PET/CT is useful with tumours of high proliferation index.

Corresponding Author: Zidan, L. **E-mail**: lamiazidan@gmail.com.

Well differentiated NET of the lung, referred to as pulmonary carcinoid, which account approximately about 1-2 % of all primary lung neoplasms. Typical carcinoids are five to six times more common than atypical carcinoids and are less likely to show metastatic spread or relapse post-surgery [6] . Typical carcinoid has an overall better prognosis, with a 5-year survival rate of 87–90%, compared to 44– 78% for AC [7]. The presenting symptoms differ according to the site of the disease. Central bronchial NETs are more likely to be symptomatic, the patient may present with cough, haemoptysis, fever, recurrent respiratory infection, and unilateral wheezing, while peripheral carcinoids are usually incidentally discovered. The carcinoid syndrome is very uncommon in patients with bronchial NETs. However, a carcinoid crisis may occasionally develop following interventions or peptide receptors radiotherapy (PRRT) [8, 9]. Cushing syndrome is a rare presenting symptom (1%–2% of cases) [10]. Diagnosis depends on core biopsy, histologically; TCs have less than 2 mitoses per square millimetre and lack necrosis, whereas ACs have 2 to 10 mitoses per square millimetre and may have focal necrosis [5].

Evaluation of specific neuroendocrine markers, such as chromogranin A is important in initial assessment and during follow-up. Although morphological features and identification of the neuroendocrine phenotype are the gold standard diagnostic method. The proliferation index Ki-67 immuno-staining is a potential meaningful marker to classify bronchial NETs, especially in small biopsies, yet it's not included in the WHO classification criteria [7, 11].

The recommended radiological investigation for detection of pulmonary carcinoids is contrast enhanced computed tomography (CT), the primary lesion mostly appears as a round peripheral lung nodule with smooth or lobulated outline, however, the positive predictive value of CT in assessing hilar and mediastinal metastases is reportedly low (20%–45%) [6].

Approximately 60% to 80% of pulmonary carcinoids express somatisation receptors, particularly low grade tumours; thus, they may benefit from somatisation receptor-based imaging. Gallium-68 ^{68}Ga-dotatate–PET/CT has replaced ^{111}In-pentereotide (Octreoscan) because of its high diagnostic accuracy, shorter scan time and lower radiation dose.

On the other hand ^{18}FDG-PET/CT is useful in patients with high proliferation index (Ki-67) and less somatisation receptor expression. Recent studies showed increase FDG uptake in low grade NETs as well, which in turn can predict prognosis [6, 12].

Surgical resection is the only curative and treatment of choice in patient in respectable bronchial carcinoids [13]. Lobectomy is the most popular surgical technique with low recurrence rate, approximately 5% in TC and 20 % in AC [14].

Inoperable advanced bronchial carcinoids show lack prospective studies, hence most recommended systemic therapy depends on results from studies in gastrointestinal neuroendocrine tumours [15]. Everolimus is currently the only drug approved by the food and drug administration for bronchial carcinoids; it showed improvement in the median progression free survival (PFS) in RADIANT-4 study [16]. Based on that the ENETS guidelines recommended Everolimus as a first –line therapy for metastatic, progressive bronchial NETs, unless a somatisation analogue (SSA) can be considered as first-line therapy [17]. Somatisation Analogue is frequently used in functional well differentiated NETs with low proliferative index and positive SSTR [15]. However, currently it is also recommended for non-functioning NETs, based on its antitumor efficacy which was demonstrated in PROMID trial in small bowel NETs. [18]. The LUNA phase 2 trials stated that long acting pasireotide alone or in combination with Everolimus showed evidence of activity and safety [19]. Nevertheless, the combined action of long-acting pasireotide on SSTR and inhibition of insulin-like growth factor 1 receptor, together with the mTOR inhibitor Everolimus, is presumed to potentially control tumour growth more effectively than either treatment alone [20].

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatisation receptor agonists, using ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE, have been successfully used to target metastatic and inoperable NETs (21). ^{90}Y has long β-particle path length, hence its better used in lager lesions, whereas ^{177}Lu is better suited to smaller lesions and the combination of both has been used in heterogeneous lesions [22].

PRRT is generally well tolerated. The most common side effect is nausea usually occurs during amino acid infusion given for renal protection, reduced with anti-emetic medication. Mild loss of renal function may occur but severe renal damage is extremely rare with the use of good renal protection. Haematological toxicity and provocation of carcinoid syndrome in functional tumours is also rare. Data confirmed lower toxicity with ^{177}Lu compared to ^{90}Y **(22-24)**.

The result of a large cohort study included 114 patients with advanced pulmonary carcinoids treated with PRRT showed a median OS and median PFS of 59 months and 28 months, respectively, patients treated with ^{177}Lu-dotatate had the highest 5-year OS of 61.4% **(24)** . The antitumor activity of ^{177}Lu-DOTATATE was demonstrated in a phase II trial included 34 patients with progressive, metastatic pulmonary typical and atypical carcinoids, with a disease control rates (80% versus 47%) and median PFS (20.1 versus 15.7 months) respectively **(25)**.

Chemotherapy is only considered in rapidly progressive metastatic pulmonary carcinoids and when no other treatment options are available. According to the NCCN guidelines, cisplatin-etoposide is preferred in stage IV AC **(26)**. It has been reported that patients with advanced bronchial carcinoids treated with chemotherapy before PRRT had a shorter OS and PFS, and a higher risk of developing nephrotoxicity **(24)**. Combining radio sensitizing chemotherapy such as capecitabine with or without temozolomide with PRRT has been called peptide receptor chemo- radionuclide therapy (PRCRT), it's a new approach in higher grade NET that still under investigation **(22)**.

Follow-up at least yearly post-surgery is required to detect potential recurrence, and at 3-6 month interval in inoperable metastatic cases to assess therapy response **(7)**. In a recent study included 107 patients with a bronchial NET, third of the patients developed a second tumor during follow-up **(27)**. Based on that careful follow-up of bronchial NET patients is required to detect recurrence, assess therapy response and identify high risk of secondary malignancies.

CONCLUSIONS:

Operable pulmonary carcinoid treated by surgery, where as there is no standard treatment in patient with advanced metastatic pulmonary carcinoids. Somatisation analogue therapy with or without Everolimus is a reasonable first-line treatment. PRRT is safe and effective in progressive metastatic disease. Chemotherapy is considered with PRRT or when no other treatment options are available. Long term careful follow-up is required to detect recurrence or potential risk of secondary malignancy. Finally, a multidisciplinary approach is recommended for each patient with bpNET aiming to improve their management and clinical outcomes as well as large prospective clinical trials to guide clinical decision making as many questions is still open.

REFERENCES

1. ***Klimstra DS, Modlin IR, Coppola D, et al.*** The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 39(6):707-12; 2010.

2. ***Korse CM, Taal BG, Van Velthuysen ML, et al.*** Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. Eur. J. Cancer. 49(8):1975-83; 2013.

3. ***Broder MS, Cai B, Chang E, et al.*** Incidence and prevalence of neuroendocrine tumors of the lung: analysis of a US commercial insurance claims database. BMC. Pulm. Med. 18(1):135; 2018.

4. ***Pelosi G, Sonzogni A, Harari S, A, et al.*** Classification of pulmonary neuroendocrine tumors: new insights. Transl. Lung. Cancer. Res. 6(5):513-29; 2017.

5. ***Travis WD, Brambilla E, Nicholson AG, et al.*** The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J. Thorac. Oncol. 10 (9):1243-60; 2015.

6. ***Hann CL and Forde PM.*** Lung and Thymic Carcinoids. Endocrinol Metab. Clin. North. Am. 47(3):699-709; 2018.

7. ***Oberg K, Hellman P, Ferolla P, et al.*** Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 23 Suppl 7:vii120-3; 2012.

8. ***Travis WD, Rush W, Flieder DB, et al.*** Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am. J. Surg. Pathol. 22(8):934-44; 1998.

9. ***Travis WD.*** Lung tumours with neuroendocrine differentiation. Eur. J. Cancer.45 Suppl. 1:251-66; 2009.

10. ***Limper AH, Carpenter PC, Scheithauer B, et al***. The Cushing syndrome induced by bronchial carcinoid tumors. Ann. Intern. Med. 117(3):209-14; 1992.

11. ***Garg R, Bal A, Das A, et al.*** Proliferation Marker (Ki67) in Sub-Categorization of Neuroendocrine Tumours of the Lung. Turk. Patoloji. Derg; 2018.

12. ***Sundin A, Arnold R, Baudin E, et al***. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine & Hybrid Imaging. Neuroendocrinology. 105(3):212-44; 2017.

13. ***Harpole DH, Feldman JM, Buchanan S, et al.*** Bronchial carcinoid tumors: a retrospective analysis of 126 patients. Ann. Thorac. Surg. 54(1):50-4; discussion 4-5; 1992.

14. ***Detterbeck FC.*** Management of carcinoid tumors. Ann. Thorac. Surg. 89(3):998-1005; 2010.

15. ***Caplin ME, Baudin E, Ferolla P, et al.*** Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann. Oncol. 26(8):1604-20; 2015.

16. ***Fazio N, Buzzoni R, Delle Fave G, et al.*** Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis. Cancer Sci. 109(1):174-81; 2018.

17. ***Pavel M, O'Toole D, Costa F, et al.*** ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 103(2):172-85; 2016.

18. ***Rinke A, Muller HH, Schade-Brittinger C, et al.*** Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J. Clin. Oncol. 27(28):4656-63; 2009.

19. ***Ferolla P, Brizzi MP, Meyer T, et al***. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. Lancet. Oncol. 18(12):1652-64; 2017.

20. ***O'Reilly KE, Rojo F, She QB, et al.*** mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. Cancer Res. 66(3):1500-8; 2006.

21. ***Van Essen M, Krenning EP, De Jong M, et al.*** Peptide Receptor Radionuclide Therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. Acta. Oncol. 46(6):723-34; 2007.

22. ***Hicks RJ, Kwekkeboom DJ, Krenning E, et al***. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. Neuroendocrinology. 105(3):295-309; 2017.

23. ***Pusceddu S, Lo Russo G, Macerelli M, et al.*** Diagnosis and management of typical and atypical lung carcinoids. Crit. Rev. Oncol. Hematol. 100:167-76; 2016.

24. ***Mariniello A, Bodei L, Tinelli C, et al.*** Long-term results of PRRT in advanced bronchopulmonary carcinoid. Eur. J. Nucl. Med. Mol. Imaging. 43(3):441-52; 2016.

25. ***Ianniello A, Sansovini M, Severi S, et al.*** Peptide receptor radionuclide therapy with (177) Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. Eur. J. Nucl. Med. Mol. Imaging. 43(6):1040-6; 2016.

26. ***Ettinger DS, Wood DE, Akerley W, et al.*** NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 4. J. Natl. Compr. Canc. Netw. 14(3):255-64. 7; 2016.

27. ***Agasarova A, Harnett C, Mulligan N, et al.*** Management and Follow-up of Patients with a Bronchial Neuroendocrine Tumor in the Last Twenty Years in Ireland: Expected Inconsistencies and Unexpected Discoveries. Int. J. Endocrinol. 2018:1043287; 2018.