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Characterization, prognosis, and treatment of patients with metastatic lung carcinoid tumors

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Abstract

Introduction: Metastatic lung carcinoids (MLC) remain poorly characterized and no prognostic stratification exists.

Methods: We conducted a retrospective study including patients with MLC in two European expert centers. The aims were to characterize these, identify prognostic factors of survival, and effectiveness of their treatments.

Results: A total of 162 patients with MLC were included: 50% were women, and median age was 61 years. Half of patients had synchronous metastases, mainly located in the liver (75%), bone (42%), and lung (25%). According to WHO classification, MLC were typical (28%), atypical (60%), or unspecified (12%). A functioning syndrome was observed in 43% of cases and an uptake at somatostatin receptor scintigraphy (SRS) in 76% of cases. The 5-year overall survival was 60% and at 10 years this was 25%. In multivariate analysis, ECOG performance status (PS) 0-1 (HR=5.81, 95%CI[2.10;16.11]), uptake on SRS (HR=0.38, 95%CI[0.22;0.66]), low serum chromogranin A (CgA; HR=2.27, 95%CI[1.36;3.81]) and typical carcinoid (HR=1.87, 95%CI[1.26;2.78]) were associated with better survival. According to RECIST 1.0, the highest objective response rates were obtained after radiofrequency ablation of metastases (86%), liver embolization (56%), peptide receptor radionuclide therapy (PRRT; 27%), and oxaliplatin-based chemotherapy (18%).

Conclusions: MLC are characterized by a high frequency of atypical carcinoids, functioning syndrome, and liver/bone metastases. WHO classification, PS, SRS, and CgA were associated with longer survival. Partial response was more frequent with locoregional therapies, PRRT or oxaliplatin-based chemotherapy.

Key words: lung; neuroendocrine tumors; carcinoid; metastatic; prognosis; treatment.

Introduction

Lung carcinoid tumor, the incidence of which is 0.2 to 2 cases per 100,000 inhabitants worldwide, represents 30% of well-differentiated neuroendocrine tumors (NETs) and 2% of all lung cancers.¹⁻³ The 2015 WHO pathological classification⁴ recognizes two subtypes of lung carcinoid tumor, the low-grade typical carcinoids (TC) and the intermediate-grade atypical carcinoids (AC). At diagnosis, most patients (80-95%) present with localized tumor, less than 5% have a carcinoid syndrome and TC represent 80-90% of them.³ However, at the metastatic stage, the proportion of carcinoid syndrome rises to between 15% and 22%,^{5,6} and more AC are reported.^{2,7} Moreover, although little data are available concerning the localization of metastases, preliminary results suggest a higher frequency of bone, cerebral, lung, and skin metastases in metastatic lung carcinoid (MLC) than in digestive NETs.³

The 5-year overall survival of localized carcinoid tumor is 85%.² The most important prognostic factors are WHO classification,^{4,8} TNM stage, and age.^{9,10} However, once the disease is metastatic, the 5-year overall survival is 32% from the SEER database,¹ and then there is little published data on prognostic factors for MLC patients.³ The recommendations for the management of MLC published by the European Neuroendocrine Tumor Society (ENETS),³ European Society for Medical Oncology (ESMO),¹¹ and the North American Neuroendocrine Tumor Society (NANETS)¹² societies are mainly based on small retrospective studies¹³⁻²⁰ and therefore mainly extrapolated from the management of digestive NETs,²¹⁻²³ although a large prospective trial conducted specifically in MLC patients has been recently published.⁵ Somatostatin analogs (SSA), chemotherapy and peptide receptor radionuclide therapy (PRRT) are frequently used in MLC, but everolimus remains the most studied and the only approved agent in this indication based on a significant gain in the median progression free-survival of 5.6 months in the placebo-controlled RADIANT-4 trial in non-functional digestive and thoracic NETs.²⁴

As data on the presentation, prognosis, and treatment of MLC remain scarce, we conducted a retrospective analysis that aimed to characterize MLC, identify prognostic factors of overall survival, and to provide an overview of therapeutic management in a real-life setting.

Material and methods

Population

We retrospectively analyzed the medical records of MLC patients treated at two tertiary referral centers in France (Gustave Roussy Institute – EURACAN center, and Hospices Civil de Lyon – ENETS center of excellence) from November 1995 to June 2017. Consecutive patients with a metastatic disease seen in one of the two centers were included. Inclusion criteria were lung primary location, histologically confirmed carcinoid tumor, and a metastatic stage. Patients with poorly differentiated and mixed tumors were excluded.

The following parameters were collected at the time of first workup for MLC: age, gender, presence of a multiple endocrine neoplasia type 1 (MEN1), disease-free interval, stage at initial diagnosis (TNM classification), primary tumor size, eastern cooperative oncology group (ECOG) performance status (PS, 0-1 or ≥ 2), clinical functioning syndrome (none, carcinoid syndrome - as recorded by the referent physician in medical charts but not necessarily proved by a concomitant high level of 5-hydroxyindoleacetic acid in urine, Cushing syndrome, acromegaly, PTH-rp secretion), carcinoid heart disease, modality of diagnosis (incidental, during monitoring, tumor or hormone-related symptoms, pain, asthenia), metastatic sites (number: 1, 2 or >2 ; location), uptake on somatostatin receptor scintigraphy (SRS) and on fluorodesoxyglucose positron emission tomography (FDG-PET; positive if any uptake of a lesion), serum plasma chromogranin A concentration (CgA; <2 x upper limit of normal – ULN, 2-5 ULN, >5 ULN), WHO classification when the specimen of

the primary tumor was available (TC, AC), mitotic count, and Ki67 index (when reported by the pathologist). The pathological report of the primary tumor with the best quality (surgery and then biopsy) was primarily used. In the absence of primary tumor specimen, the biopsy on a metastasis was used and the tumor was classified as not otherwise specified carcinoid.

Treatment

For each systemic treatment, the following parameters were collected: type of treatment, number of previous lines, time under treatment, number of cycles, reason for discontinuation (progressive disease and death, scheduled, toxicity or unknown), best response (RECIST 1.0 criteria, collected from the radiology reports: objective response rate – ORR, stable disease, progressive disease or unknown), progression-free survival (PFS), and overall survival (OS). For each locoregional treatment, the ~~only~~ parameters collected were the best response according to RECIST and the OS from the first locoregional treatment of each type.

Statistical analysis

Categorical variables are expressed as percentages, and compared using the Chi-square test or the Fisher's exact test when appropriate. Continuous variables are presented as median (range), and were analyzed by the Mann-Whitney U test. OS was calculated from the date of metastatic diagnosis to that of death or last follow-up. Survival curves for OS were estimated using the Kaplan-Meier method. Median and 5-year survival rates were estimated. Comparisons in univariate analyses were performed using the Log-rank test for each variable of interest (Table 1). For continuous parameters, the threshold was defined as the population median. Multivariate analyses using a Cox proportional hazards regression model were performed to identify factors independently associated with prognosis. All significant factors

from the univariate analysis (p-value <0.10 with Log-rank test) were included in the multivariate analyses. A p-value of <0.05 was considered statistically significant. All treatments were included, but when a patient received the same treatment twice, only the first was studied for ORR, PFS, and OS. PFS and OS for each type of treatment were calculated from the date of treatment initiation to the date of first progression or death for PFS and to the date of death or last follow up for OS. All statistical analyses were performed using R package version 3.5.1. The results from the survival analyses are presented with the effect estimates, hazard ratios (HR), and 95% confidence interval (CI).

Results

Patient characteristics at time of metastatic diagnosis

A total of 162 patients with MLC were included: 50% were women, and median age was 61 years. Half of patients had synchronous metastases. Sixty-nine (43%) patients had a functioning tumor, among whom 62 had a carcinoid syndrome. A carcinoid heart disease was described in 8 patients, but this was systematically screened for 41 patients who have carcinoid syndrome. The median number of metastatic sites at diagnosis was 2 (range: 1-5). The main tumor locations were: liver (75%), bone (42%), and lung (25%). SRS was positive in 76% and FDG-PET in 90% of the cases. The median value of CgA was 3.5 ULN. Among the 20 patients with more than 2 metastatic sites, CgA was more often above its median value (14/20, 70%) than below (6/20, 30%, p=0.046). According to the WHO classification, 46 patients (28%) were diagnosed with a TC, 97 (60%) with an AC, and 19 (12%) could not be specified. Seven patients had a tumor with a carcinoid morphology (well differentiated), but with a mitotic count between 11 and 18 /2mm²; they were retained in the AC group (Table 1).

Metachronous metastases were found in 82 (51%) patients (among whom 27 were diagnosed during monitoring); 26 (32%) of these were stage I, 18 (22%) stage II, 20 (24%) stage III disease (the initial stage was not available for 18 patients); these patients without initial metastatic disease had a disease-free interval of 41 months (range: 2-224) after the initial diagnosis of carcinoid tumor. Patient characteristics were not significantly different between synchronous and metachronous disease except for the symptoms at diagnosis: patients with synchronous disease had more frequently symptomatic pain (34% versus 12%, $p=0.004$).

Prognostic factors of overall survival

The median follow-up was 56 months (range: 3-277), and 92 (57%) patients died during this time. The median OS for the total population was 80.9 months (95%CI [62; 99]; Figure 1A), the OS at 5 was 60.2% and at 10 years it was 24.5%. In univariate analysis, an ECOG PS 0-1, a low number of metastatic sites (median: 2), the absence of bone or distant node metastasis, a positive uptake at SRS, a low serum plasma level of CgA (median: 3.5x ULN), and TC subtype were significantly associated with better OS. A lower Ki67 index was also found to be significantly associated with better OS in univariate analysis but it was not included in the multivariate analysis owing to the number of missing data. In multivariate analysis, the ECOG PS (HR=5.81, 95%CI [2.10; 16.11]; $p<0.001$), the uptake of SRS (HR=0.38, 95%CI [0.22; 0.66]; $p<0.001$), the serum CgA level (HR=2.27, 95%CI [1.36; 3.81]; $p=0.002$), and the WHO classification subtype (HR=1.87, 95%CI [1.26; 2.78]; $p=0.002$) were significantly associated with OS (Figure 1B-E and Table 2). Patients with 0-1 unfavorable prognostic factors had a significantly better survival (median OS=105.3 months, 95%CI [98.7-152.5]), than those with 2 (median OS=55.4 months, 95%CI [46.2-88.3]) and 3-4 unfavorable factors (OS=32.9 months, 95%CI [22.0-not reached], Supplementary figure 1). Among patients with

only one metastatic site (liver, lung, or other) there was a non-significant ($p=0.09$) trend towards better survival for patients with only lung metastases at diagnosis (5-year OS=85%) compared to those with liver (5-year OS=72%) or other metastatic sites (5-year OS=75%; Supplementary figure 2).

Treatment

Median time from the metastatic diagnosis to the first treatment was 67 days (range: 0-7595). Most patients (57%) underwent resection of the primary tumor; among the 80 patients with synchronous metastases 21 (26%) patients did so. Patients received a median of 1 (range: 0-4) locoregional and 3 (range: 0-8) systemic treatments; 106 patients (65%) received at least one locoregional treatment (Table 3). ORR was 28/50 (56%) for liver embolization, and 12/14 (86%) for radiofrequency ablation. Median OS [95%CI] was 81.9 months [63.5-not reached] after surgery of metastases, 79.2 months [75.0-not reached] after radiofrequency ablation, and 68.8 months [53.2-101.4] after liver embolization. The most frequent first-line systemic treatment was SSA (83 patients; 14 of these received SSA in association with another anti-tumoral treatment). In total during the course of metastatic disease, 438 systemic treatments were analyzed and the three main systemic treatments given were chemotherapy (143 patients), SSA (131 patients in total, among whom 110 received SSA monotherapy) and everolimus (68 patients, Table 3). The main reason for discontinuation was progressive disease for Tem-based, SSA, interferon and everolimus; it was most frequently scheduled for parenteral chemotherapy and PRRT. Among systemic treatments, the highest ORR was obtained for PRRT (27%), followed by chemotherapy (between 8% and 22%), interferon (6%), everolimus (4%) and SSA (3%). The longest median PFS was obtained for PRRT (9.5 months), oxaliplatin-based chemotherapy (9.3 months) and everolimus (9.0 months; Tables 4

and 5). Among platinum-based chemotherapies, ORR and median PFS were respectively 8% and 7.1 months with cisplatin or carboplatin/etoposide regimens, and respectively 18% and 9.3 months for oxaliplatin-based chemotherapy (Table 4).

Discussion

The present study highlights several characteristics of MLC that deserve attention. The first is that patients are in good general condition, as reflected by ECOG PS, which supports the low aggressiveness of these lung cancers. Furthermore, MLC patients have a surprisingly high prevalence of carcinoid syndrome, which was at least half more frequent as that reported in series of localized tumor (5-15%).^{7,9,25,26} This may be explained by the definition of carcinoid syndrome used herein and the study population: all patients had tumor at metastatic stage; all consecutive patients with MLC were included without exclusion of patients with uncontrolled carcinoid syndrome, as it was the case in the LUNA study in which the prevalence of carcinoid syndrome was 23%.⁵ Furthermore, it is of note that carcinoid heart disease should be systematically screened for in patients who have carcinoid syndrome,^{3,27} yet this was assessed in only around two-thirds of such patients herein. Interestingly, just under two-thirds of MLC herein were AC, almost as many as that found in the LUNA study (69%).⁵ As the frequency of TC is five-to-ten times higher than AC at the localized stage (80-90% of LC),³ this strongly suggests that AC are more likely to become metastatic than TC. Regarding the modality of tumor spread, both herein and in the LUNA study,⁵ the main metastatic site was the liver, as has been reported for digestive NETs,²⁸ however the frequency of bone and lung sites was much higher in MLC patients. It is also of note that uptake on FDG PET was more frequent herein than in digestive NETs,^{3,29} yet bias cannot be excluded since only half the patients underwent this exam which may be prescribed for more aggressive disease (this was not reported in the LUNA study⁵).

The median OS herein was close to that found for metastatic ileum NETs as reported in the PROMID study.³⁰ It was also longer in the present study than in previous reports for MLC from registry data (for example OS of 24 months for grade 1-2 MLC in the most recent report using the SEER database¹). This discrepancy between population-based studies and single or multicenter studies is well known; it may be explained by selection bias, as herein patients were seen in tertiary referral centers that allowed a precise pathological diagnosis according to the WHO classification (for example, some poorly differentiated carcinoma may be coded as MLC in the SEER database) and by adapted delivery of therapy. Regarding prognostic factors, similarly to that found for digestive NETs,^{29,31} poor ECOG PS, higher tumor grade (atypical subtype according to the WHO classification), high tumor burden (high CgA levels which is reported to be correlated with tumor burden³²), and absence of uptake on SRS were significantly associated with poor survival. Interestingly, WHO classification is currently based on primary tumor analysis and its relevance at the metastatic stage has yet to be established; herein, however, we found that WHO classification remained a strong prognostic factor at the metastatic stage. In contrast with the digestive WHO classification,³³ Ki67 is not required in the lung WHO classification.⁴ This information was available for two-thirds of the patients and was therefore not included in the multivariate analysis, but as it was associated with OS in univariate analysis it may be of prognostic interest as proposed elsewhere.³⁴ These results suggest that, in addition to WHO classification, the biology of the tumor captured by the CgA levels and somatostatin receptor expression are more relevant than the number of metastatic sites or their location to stratify MLC patient prognosis. We herein show that the CgA level is correlated with the number of metastatic sites, and therefore may be seen as a surrogate marker of tumor bulk in some patients. This may also indicate that tumor burden as described by the number and location of metastases is insufficient, and that more precise information is required as to the volume of each metastatic lesion which is currently not

routinely performed. Moreover, the relevance of lung metastases in MLC has to be clarified, as it is difficult to distinguish isolated lung metastases from diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) but also idiopathic multiple primaries. This is supported by the trend towards better prognosis in patients with isolated lung metastases in comparison with isolated liver or other isolated metastases.

The treatments received by the study population provides a good overview of the real-life clinical practice of the two expert centers. In contrast with other lung cancers, locoregional treatments are frequently used. This standard of care is derived from the digestive NET guidelines for low progressive and functional tumors with liver metastases,³ and led to the highest ORR (33-73% in digestive NET,^{3,35} 56-100% in the present study). Moreover, surgery of the primary tumor may be considered, in particular for patients with symptomatic tumors but also in selected patients with low aggressive disease and limited metastatic disease.³ However, its impact on OS has not been studied and we cannot conclude from the present study the benefit.

The most frequently used systemic treatment was SSA. The median PFS under SSA was shorter than in metastatic digestive NETs^{23,30} as well as in two other retrospective studies on MLC,^{18,36} but similar to that found in the pasireotide arm in the LUNA trial (7.7 months).⁵ However, randomized studies such as the SPINET trial are mandatory to demonstrate the efficacy of SSA in MLC.³⁷ The best PFS were herein obtained with everolimus, oxaliplatin-based chemotherapy and PRRT, but the heterogeneity of patients and treatment strategies precludes direct comparison. Moreover, therapeutic options have changed over the recruitment period of the present study; for instance, access to PRRT was difficult in France and most patients were treated abroad, suggesting a selection bias. Furthermore, the positioning of cytotoxic chemotherapy is debated in MLC.³ The ORR for these chemotherapy drugs herein is lower than that obtained in poorly differentiated carcinoma (69%)³⁸ and

pancreatic NETs (33%),³⁹ which are recommended indications; it is, however, higher than that reported for intestinal NETs (<10%).⁴⁰ This may also be dependent on the choice of drug; the two most frequently used chemotherapies herein were oxaliplatin-based and temozolomide-based regimens. These have demonstrated their activity in small retrospective cohorts of MLC,^{15,16,19,20} and an ongoing randomized trial will help to determine the best option (NCT03217097). Among platinum-based chemotherapies, oxaliplatin must be preferred to cisplatin or carboplatin (which are still too frequently used in lung NET, probably because these are used to treat small cell lung carcinoma), as the latter are known to be poorly tolerated and we report herein a lower effectiveness. Everolimus is the most studied agent in MLC, within RADIANT-2, RADIANT-4 and LUNA trials.^{5,21,24,41} In the present study, its effectiveness was similar to the efficacy found in trials (median PFS: 9 to 13 months month in LUNA study and subgroup analysis of the RADIANT 2 and 4 trials). However, tolerance remains an issue since more than a third of patients discontinued because of adverse events herein.

The study does also have some limitations. For instance it is a retrospective cohort, and the patients treated in this study were diagnosed over a period of 22 years. This long recruitment period was necessary to collect a sufficient number of patients with this rare disease but also to explore the longitudinal management of MLC patients. During this period, the baseline work-up and the treatment options changed. Moreover, part of the work-up and the initial treatments could have been done outside of the reference center. Furthermore, we were not able to retrospectively explore spontaneous tumor growth which is an important prognostic factor in metastatic digestive NET.^{29,31}

In summary, MLC are characterized by a high frequency of AC subtypes, functioning syndrome, and liver/bone metastases. WHO classification, PS, SRS, and CgA were associated with longer survival, and partial response was more frequent with locoregional therapies,

PRRT or oxaliplatin-based chemotherapy. Further studies are required to define the therapeutic strategy that would most benefit patients.

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Figure legends

Figure 1. Overall survival of patients according in the total population (A), and according to the WHO classification (B), the ECOG performance status (C), the chromogranin A levels (D), and the uptake on somatostatin receptor scintigraphy (E). The p-values are presented for Log-rank tests.

ECOG, eastern cooperative oncology group; OS, Overall Survival.

Supplementary figure 1. Overall survival of patients according to the number of unfavorable prognostic factors. The p-values are presented for Log-rank tests.

Supplementary figure 2. Overall survival of patients with only one metastatic site at diagnosis (n=80), according to the localization of metastatic sites: liver (n=51), lung (n=16), and other (n=13: bone (n=5), thyroid (n=2), subcutaneous tissue (n=2), brain (n=1), breast (n=1), distant node (n=1), adrenal glands (n=1)). The p-value is presented for Log-rank test.

References

1. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;3(10):1335-1342.
2. Rekhtman N. Neuroendocrine tumors of the lung: an update. *Arch Pathol Lab Med.* 2010;134(11):1628-1638.
3. 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.* 2015;26(8):1604-1620.
4. 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.* 2015;10(9):1243-1260.
5. 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.* 2017;18(12):1652-1664.
6. Halperin DM, Shen C, Dasari A, et al. The frequency of carcinoid syndrome at neuroendocrine tumor diagnosis: A large population-based study using SEER-Medicare data. *Lancet Oncol.* 2017;18(4):525-534.

7. Fink G, Krelbaum T, Yellin A, et al. Pulmonary carcinoid: presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. *Chest*. 2001;119(6):1647-1651.
8. Asamura H, Kameya T, Matsuno Y, et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. *J Clin Oncol*. 2006;24(1):70-76.
9. García-Yuste M, Matilla JM, Cueto A, et al. Typical and atypical carcinoid tumours: analysis of the experience of the Spanish Multi-centric Study of Neuroendocrine Tumours of the Lung. *Eur J Cardio-Thorac Surg*. 2007;31(2):192-197.
10. Ramirez RA, Beyer DT, Diebold AE, et al. Prognostic Factors in Typical and Atypical Pulmonary Carcinoids. *Ochsner J*. 2017;17(4):335-340.
11. Öberg K, Hellman P, Ferolla P, Papotti M, ESMO Guidelines Working Group. Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23 Suppl 7:vii120-123.
12. Phan AT, Oberg K, Choi J, et al. NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the thorax (includes lung and thymus). *Pancreas*. 2010;39(6):784-798.
13. Mariniello A, Bodei L, Tinelli C, et al. Long-term results of PRRT in advanced bronchopulmonary carcinoid. *Eur J Nucl Med Mol Imaging*. 2016;43(3):441-452.
14. 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*. 2016;43(6):1040-1046.

15. Crona J, Fanola I, Lindholm DP, et al. Effect of temozolomide in patients with metastatic bronchial carcinoids. *Neuroendocrinology*. 2013;98(2):151-155.
16. Walter T, Planchard D, Bouledrak K, et al. Evaluation of the combination of oxaliplatin and 5-fluorouracil or gemcitabine in patients with sporadic metastatic pulmonary carcinoid tumors. *Lung Cancer*. 2016;96:68-73.
17. Filosso PL, Ruffini E, Oliaro A, Papalia E, Donati G, Rena O. Long-term survival of atypical bronchial carcinoids with liver metastases, treated with octreotide. *Eur J Cardio-Thorac Surg*. 2002;21(5):913-917.
18. Bongiovanni A, Recine F, Riva N, et al. Outcome Analysis of First-line Somatostatin Analog Treatment in Metastatic Pulmonary Neuroendocrine Tumors and Prognostic Significance of 18FDG-PET/CT. *Clin Lung Cancer*. 2017;18(4):415-420.
19. Granberg D, Eriksson B, Wilander E, et al. Experience in treatment of metastatic pulmonary carcinoid tumors. *Ann Oncol*. 2001;12(10):1383-1391.
20. Chong CR, Wirth LJ, Nishino M, et al. Chemotherapy for locally advanced and metastatic pulmonary carcinoid tumors. *Lung Cancer*. 2014;86(2):241-246.
21. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977.
22. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol*. 2011;29(17):2416-2423.

23. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.
24. 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*. October 2017.
25. Detterbeck FC. Clinical presentation and evaluation of neuroendocrine tumors of the lung. *Thorac Surg Clin*. 2014;24(3):267-276.
26. Lim E, Goldstraw P, Nicholson AG, et al. Proceedings of the IASLC International Workshop on Advances in Pulmonary Neuroendocrine Tumors 2007. *J Thorac Oncol*. 2008;3(10):1194-1201.
27. De Jesus T, Luis SA, Ryu JH, et al. Carcinoid Heart Disease in Patients With Bronchopulmonary Carcinoid. *J Thorac Oncol*. 2018;13(10):1602-1605.
28. Kos-Kudła B, O'Toole D, Falconi M, et al. ENETS consensus guidelines for the management of bone and lung metastases from neuroendocrine tumors. *Neuroendocrinology*. 2010;91(4):341-350.
29. Foulfoin M, Graillot E, Adham M, et al. Treatment of metastatic pancreatic neuroendocrine tumors: relevance of ENETS 2016 guidelines. *Endocr Relat Cancer*. 2017;24(2):71-81.
30. Rinke A, Müller H-H, 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*. 2009;27(28):4656-4663.

31. Durante C, Boukheris H, Dromain C, et al. Prognostic factors influencing survival from metastatic (stage IV) gastroenteropancreatic well-differentiated endocrine carcinoma. *Endocr Relat Cancer*. 2009;16(2):585-597.
32. Nehar D, Lombard-Bohas C, Olivieri S, et al. Interest of Chromogranin A for diagnosis and follow-up of endocrine tumours. *Clin Endocrinol*. 2004;60(5):644-652.
33. FT B, F C, RH H, ND T. *WHO Classification of Tumours of the Digestive System*. <http://publications.iarc.fr/Book-And-Report-Series/Who-Iarc-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Digestive-System-2010>.
34. Pelosi G, Rindi G, Travis WD, Papotti M. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practice. *J Thorac Oncol*. 2014;9(3):273-284.
35. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology*. 2012;95(2):157-176.
36. Sullivan I, Le Teuff G, Guigay J, et al. Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids. *Eur J Cancer* 1990. 2017;75:259-267.
37. Efficacy and Safety of Lanreotide Autogel/ Depot 120 mg vs. Placebo in Subjects With Lung Neuroendocrine Tumors - ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02683941>.

38. Pujol JL, Carestia L, Daurès JP. Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. *Br J Cancer*. 2000;83(1):8-15.
39. Kunz PL, Catalano PJ, Nimeiri H, et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol*. 2018;36(15_suppl):4004-4004.
40. Dahan L, Bonnetain F, Rougier P, et al. Phase III trial of chemotherapy using 5-fluorouracil and streptozotocin compared with interferon alpha for advanced carcinoid tumors: FNCLCC-FFCD 9710. *Endocr Relat Cancer*. 2009;16(4):1351-1361.
41. Fazio N, Granberg D, Grossman A, et al. Everolimus plus octreotide long-acting repeatable in patients with advanced lung neuroendocrine tumors: analysis of the phase 3, randomized, placebo-controlled RADIANT-2 study. *Chest*. 2013;143(4):955-962.

Table 1. Patient characteristics at time of metastasis diagnosis of lung carcinoid tumors

| | Total population, n=162 |
|---|--|
| Median age, years (range) | 61 (20-87) |
| Female sex, n (%) | 81 (50%) |
| MEN1 syndrome 1, n (%) | 3 (1%) |
| Metachronous, n (%) | 82 (51%) |
| Stage at initial diagnosis, n (%) | |
| I | 26 (16%) |
| II | 18 (11%) |
| III | 20 (12%) |
| IV | 80 (49%) |
| NA | 18 (11%) |
| Median primary tumor size, mm (range) | 30 (5-120) |
| ECOG performance status, n (%) | |
| 0-1 | 145 (90%) |
| ≥2 | 10 (6%) |
| NA | 7 (4%) |
| Functioning tumors, n (%) | |
| Non functioning | 92 (57%) |
| Carcinoid syndrome | 62 (38%) |
| Cushing syndrome | 4 (2%) |
| Acromegaly | 1 (1%) |
| PTH-rp | 2 (1%) |
| Carcinoid heart disease, n (%) | 8 (5%) |
| Presentation at metastatic diagnosis, n (%) | |
| Pulmonary symptoms | 39 (24%) |
| Functioning symptoms | 14 (9%) |
| Pain | 39 (24%) |
| Asthenia | 9 (6%) |
| Follow-up | 27 (17%) |
| Incidental | 24 (15%) |
| Other or NA | 7 (4%) |
| Median number of metastatic sites (range) | 2 (1-5) |
| Number of metastatic sites, n (%) | |
| 1 | 80 (49%) |
| 2 | 57 (35%) |
| >2 | 25 (15%) |
| Location of metastatic sites, n (%) | |
| Liver | 121 (75%) |
| Bone | 68 (42%) |
| Lung | 40 (25%) |
| Other# | 46 (28%) |
| Uptake on SRS, n/N (% of patients with SRS) | 108/143 (76%) |
| Uptake on FDG-PET, n/N (% of patients with FDG PET) | 72/80 (90%) |
| Median xULN chromogranin A (range) | 3.5 (0.2-800.9) |
| Chromogranin A, n (%) | |
| <2 ULN | 56 (35%) |
| Between 2 and 5 ULN | 25 (15%) |

| | |
|--|----------|
| >5 ULN | 61 (38%) |
| NA | 20 (12%) |
| WHO classification, n (%) | |
| Typical carcinoid | 46 (28%) |
| Atypical carcinoid | 97 (60%) |
| Not otherwise specified carcinoid (only metastatic sample available) | 19 (12%) |
| Median % Ki67 (range) – 109 patients with available data | 8 (0-68) |
| Median number of mitoses (range) – 138 patients with available data | 2 (0-18) |

Other metastatic sites were distant nodes (n=12), pancreas (n=6), adrenal gland (n=6), subcutaneous tissue (n=6), breast (n=5), brain (n=3), peritoneum (n=2), thyroid (n=2), ovary (n=2), choroid (n=1) and kidney (n=1).

ECOG, Eastern Cooperative Oncology Group; SRS, somatostatin receptor scintigraphy; FDG-PET, positron emission tomography fluorodesoxyglucose; ULN, Upper limit of normal; MEN1, multiple endocrine neoplasia type 1; NA, not available; WHO, World Health Organization; PTH, Parathyroid hormone related protein; CI, confidence interval

Table 2. Prognostic factors of overall survival after univariate and multivariate analysis

| | <i>n</i> | Median OS [95% CI] | 5-year OS | p value univariate (log rank) | HR OS multivariate [95% CI] | p value multivariate |
|---|----------|-----------------------|--------------|-------------------------------------|-----------------------------------|-------------------------|
| Age | 162 | | | 0.3 | | |
| < median | | 80.9 [60.2; 107.8] | 61% | | | |
| ≥ median | | 82.9 [60.0-98.8] | 59% | | | |
| Sex | 162 | | | 0.5 | | |
| Female | | 83.4 [62.2-105.3] | 63% | | | |
| Male | | 79.2 [56.9-98.8] | 57% | | | |
| ECOG PS | 155 | | | <0.001 | 5.81 [2.10; 16.11] | <0.001 |
| 0-1 | | 82.9 [68.0-99.8] | 62% | | | |
| ≥2 | | 33.5 [15.4-NR] | 0% | | | |
| Metachronous vs synchronous metastases | 162 | | | 0.3 | | |
| Metachronous | | 84.3 [76.6-106.6] | 69% | | | |
| Synchronous | | 60.2 [54.0-92.2] | 52% | | | |
| Functioning tumors | 162 | | | 1 | | |
| No | | 80.9 [62.2-105.0] | 61% | | | |
| Yes | | 79.2 [60.0-105.0] | 59% | | | |
| Number of metastatic sites | 162 | | | 0.003 | 1.16 [0.50; 2.71] | 0.727 |
| ≤ median (≤2) | | 84.3 [72.9-105.0) | 65% | | | |
| > median (>2) | | 41.0 [30.2-NR) | 28% | | | |
| Location of metastatic sites | | | | | | |
| Liver | 162 | | | 0.3 | | |
| No | | 72.9 [43.5-NR] | 58% | | | |
| Yes | | 80.9 [60.8-95.4] | 61% | | | |
| Bone | 162 | | | <0.001 | 1.49 [0.89; 2.53] | 0.129 |
| No | | 98.7 [82.9-108.0] | 73% | | | |
| Yes | | 42.0 [37.0-80.9] | 41% | | | |
| Lung | 162 | | | 0.3 | | |
| No | | 80.9 [60.8-98.7] | 61% | | | |
| Yes | | 76.6 [55.6-NR] | 58% | | | |
| Distant node | 162 | | | 0.005 | 1.91 [0.63; 5.78] | 0.251 |
| No | | 83.4 [68.0-98.8] | 62% | | | |
| Yes | | 38.6 [35.5-NR] | 31% | | | |
| Other | 162 | | | 0.3 | | |
| No | | 84.3 [68.0-99.8] | 63% | | | |
| Yes | | 46.2 [42.0-NR] | 41% | | | |
| Uptake on SRS | 143 | | | 0.007 | 0.38 [0.22; 0.66] | <0.001 |
| No | | 46.2 [37.6-NR) | 41% | | | |
| Yes | | 88.3 [69.2-105.0] | 67% | | | |
| Uptake on FDG-PET | 80 | | | 0.8 | | |
| No | | 82.9 [62.2-105.0] | 64% | | | |
| Yes | | 79.0 [55.6-128.0] | 55% | | | |
| Chromogranin A | 142 | | | 0.005 | 2.27 [1.36; 3.81] | 0.002 |
| < median | | 98.7 [83.4-152.5] | 70% | | | |
| ≥ median | | 60.8 [46.2-84.6] | 53% | | | |

| | | | | | | |
|-----------------------------------|-----|--------------------|-----|------|------------------|-------|
| WHO classification | 162 | | | 0.04 | 1.87 [1.26-2.78] | 0.002 |
| Typical carcinoid | | 104.6 [84.6-152.0] | 83% | | | |
| Atypical carcinoid | | 65.1 [54.0-92.2] | 53% | | | |
| Not otherwise specified carcinoid | | 55.4 [42.4-NR] | 47% | | | |
| Ki67 (%) | 109 | | | 0.03 | | |
| < median | | 88.3 [55.6-123.0] | 58% | | | |
| ≥ median | | 57.1 [32.9-105.0] | 44% | | | |

OS, Overall Survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDG-PET, positron emission tomography fluorodesoxyglucose; WHO, World Health Organization; NR, not reached; SRS, somatostatin receptor scintigraphy

Table 3. Treatments received by patients with metastatic lung carcinoid tumors

| | Total population, n=162 |
|--|--|
| Primary tumor resection, n (%) | 93 (57%) |
| Metachronous metastases, n | 72 |
| Synchronous metastases, n | 21 |
| Median time from metastases to the first treatment, days (range) | 67 (0-7595) |
| Median number of locoregional treatments during the course of metastatic disease (range) | 1 (0-4) |
| ≥1 locoregional treatment during the course of the metastatic disease, n (%) | 106 (65%) |
| Type of locoregional treatment, n (%) | |
| Surgery of metastases | 49 (30%) |
| Radiofrequency ablation | 14 (9%) |
| Liver embolization | 50 (31%) |
| External radiotherapy | 50 (31%) |
| Median number of systemic treatments during the course of the metastatic disease (range) | 3 (0-8) |
| Type of systemic treatments, n (%) | |
| Somatostatin analogs | 131 (81%) |
| Interferon alpha | 16 (10%) |
| Cytotoxic chemotherapy | 143 (88%) |
| Oxaliplatin-based chemotherapy | 84 (52%) |
| Temozolomide-based chemotherapy | 58 (36%) |
| Dacarbazine-based chemotherapy | 27 (17%) |
| Streptozotocin-based chemotherapy | 29 (18%) |
| Platin-etoposide chemotherapy | 24 (15%) |
| Other cytotoxic chemotherapy | 19 (12%) |
| Everolimus | 68 (42%) |
| Sunitinib | 13 (8%) |
| Other targeted therapy | 7 (4%) |
| Peptide receptor radionuclide therapy | 22 (14%) |

Table 4. Effectiveness of the main systemic cytotoxic chemotherapy treatments

| | Platin/Etoposide, n=24 | Oxaliplatin- based, n=84 | Tem-based, n=58 | Dacar-based, n=27 | Strept-based, n=29 |
|--|-----------------------------------|-------------------------------------|----------------------------|------------------------------|-------------------------------|
| Median time between metastatic diagnosis and treatment start, months (range) | 2 (0.1-38.5) | 18.8 (0.2-122.7) | 28.5 (0.3-144.6) | 15.8 (0.9-117.9) | 19.8 (2.0-63.6) |
| Number of prior systemic lines, n (%) | | | | | |
| 0 | 18 (75%) | 22 (26%) | 1 (2%) | 4 (15%) | 4 (14%) |
| 1 | 5 (21%) | 27 (32%) | 16 (28%) | 3 (11%) | 12 (41%) |
| 2 | 0 (0%) | 14 (17%) | 20 (34%) | 12 (44%) | 7 (24%) |
| ≥3 | 1 (4%) | 21 (25%) | 21 (36%) | 8 (30%) | 6 (21%) |
| Median time under treatment, months (range) | 2 (0.1-5.2) | 3.2 (0.2-29.9) | 3 (0.1-12.7) | 3.6 (0.1-10.6) | 3.9 (0.1-15.2) |
| Median number of cycles (range) | 4 (1-6) | 8 (1-24) | 3 (1-14) | 5 (1-9) | 4 (1-14) |
| Reason for discontinuation, n (%) | | | | | |
| Progressive disease and death | 8 (33%) | 24 (29%) | 38 (66%) | 9 (33%) | 10 (34%) |
| Scheduled | 10 (42%) | 35 (42%) | 6 (16%) | 10 (37%) | 11 (38%) |
| Toxicity | 4 (17%) | 22 (26%) | 5 (9%) | 5 (19%) | 7 (24%) |
| Unknown | 2 (8%) | 1 (1%) | 1 (2%) | 2 (7%) | 1 (3%) |
| Best response, n (%) | | | | | |
| Objective response | 2 (8%) | 15 (18%) | 6 (10%) | 6 (22%) | 3 (10%) |
| Stable disease | 13 (54%) | 52 (62%) | 22 (38%) | 14 (52%) | 15 (52%) |
| Progressive disease | 7 (29%) | 13 (15%) | 23 (40%) | 3 (11%) | 8 (28%) |
| Unknown | 2 (8%) | 4 (5%) | 7 (12%) | 4 (15%) | 3 (10%) |
| Median PFS, months [95% CI] | 7.1 [3.9-10.8] | 9.3 [7.2-12.7] | 4.6 [3.0-5.7] | 5.8 [4.6-12.0] | 8.0 [6.0-18.2] |
| Median overall survival, months [95% CI] | 44.0 [33.2-NR] | 37.8 [29.6-45.2] | 25.0 [14.8-40.2] | 26.2 [17.4-67.7] | 49.2 [35.5-80.9] |

SSA, Somatostatin analogues; Tem-based, Temozolomide-based chemotherapy; Dacar-based, Dacarbazine-based chemotherapy; Strept-based, Streptozocin-based chemotherapy; PFS, progression-free survival; CI, confidence interval; NR, not reached.

Table 5. Effectiveness of the main systemic treatments

| | SSA, n=110* | Interferon, n=16 | Everolimus, n=68 | PRRT, n=22 |
|--|--------------------|-------------------------|-------------------------|-------------------|
| Median time between metastatic diagnosis and treatment start, months (range) | 6.7 (0-249) | 16 (0.8-75.1) | 30.5 (2.5-137.4) | 38.6 (19.7-104.3) |
| Number of prior systemic lines, n (%) | | | | |
| 0 | 81 (74%) | 5 (31%) | 3 (4%) | 0 (0%) |
| 1 | 16 (15%) | 5 (31%) | 23 (34%) | 1 (5%) |
| 2 | 4 (4%) | 3 (19%) | 19 (28%) | 9 (41%) |
| ≥3 | 8 (7%) | 3 (19%) | 23 (34%) | 12 (55%) |
| Median time under treatment, months (range) | 10.8 (0.2-193.4) | 3.4 (1.5-21.6) | 4.3 (0.1-33.7) | 4.6 (1.4-8) |
| Median number of cycles (range) | - | - | - | 3 (2-4) |
| Reason for discontinuation, n (%) | | | | |
| Progressive disease and death | 70 (64%) | 11 (69%) | 37 (54%) | 3 (14%) |
| Scheduled | 6 (6%) | 1 (3%) | 3 (4%) | 19 (86%) |
| Toxicity | 3 (3%) | 3 (19%) | 27 (40%) | 0 (0%) |
| Unknown | 16 (15%) | 1 (6%) | 0 (0%) | 0 (0%) |
| Best response, n (%) | | | | |
| Objective response | 3 (3%) | 1 (6%) | 3 (4%) | 6 (27%) |
| Stable disease | 55 (50%) | 8 (50%) | 44 (65%) | 11 (50%) |
| Progressive disease | 40 (37%) | 7 (44%) | 16 (24%) | 5 (23%) |
| Unknown | 11 (10%) | 0 (0%) | 5 (7%) | 0 (0%) |
| Median progression-free survival, months [95% CI] | 6.9 [6.2-8.9] | 4.9 [3.4-9.4] | 9.0 [6.5-9.3] | 9.5 [8.3-19.3] |
| Median overall survival, months [95% CI] | 75.4 [53.7-95.7] | 48.6 [28.7-NR] | 28.5 [19.4-43.0] | 30.6 [27.1-NR] |

SSA, somatostatin analogs, PRRT, Peptide Receptor Radionuclide Therapy; CI, confidence interval; NR, not reached.

* Patients for whom SSA was introduced in association with another treatment were excluded of this analysis (n=21)

