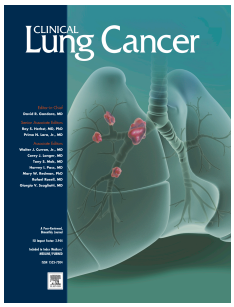
Accepted Manuscript



Outcome Analysis of First-Line Somatostatin Analog Treatment in Metastatic Pulmonary Neuroendocrine Tumors and Prognostic Significance of ^{18}FDG-PET/CT

Alberto Bongiovanni, MD, Federica Recine, MD, Nada Riva, MD, Flavia Foca, MStat, Chiara Liverani, PhD, Laura Mercatali, PhD, Silvia Nicolini, MD, Federica Pieri, MD, Dino Amadori, MD, Toni Ibrahim, MD

PII: S1525-7304(16)30358-8

DOI: 10.1016/j.cllc.2016.11.004

Reference: CLLC 558

To appear in: *Clinical Lung Cancer*

Received Date: 12 July 2016

Revised Date: 8 November 2016

Accepted Date: 8 November 2016

Please cite this article as: Bongiovanni A, Recine F, Riva N, Foca F, Liverani C, Mercatali L, Nicolini S, Pieri F, Amadori D, Ibrahim T, Outcome Analysis of First-Line Somatostatin Analog Treatment in Metastatic Pulmonary Neuroendocrine Tumors and Prognostic Significance of ^{18}FDG-PET/CT, *Clinical Lung Cancer* (2016), doi: 10.1016/j.cllc.2016.11.004.

ORIGINAL ARTICLE

Outcome Analysis of First-Line Somatostatin Analog Treatment in Metastatic Pulmonary Neuroendocrine Tumors and Prognostic Significance of ^{18}FDG-PET/CT

Alberto Bongiovanni, MD,[a,*] Federica Recine, MD,[a] Nada Riva, MD,[a] Flavia Foca, MStat,[b] Chiara Liverani, PhD, [a] Laura Mercatali, PhD,[a] Silvia Nicolini, MD,[c] Federica Pieri, MD,[d] Dino Amadori, MD,[a] Toni Ibrahim, MD,[a]

[a]Osteoncology and Rare Tumors Center, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

[b]Unit of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

[c] Nuclear Medicine Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

[d]Pathology Unit, Morgagni-Pierantoni Hospital, Forlì, Italy

*Corresponding author.

Address for correspondence: Alberto Bongiovanni, MD, Osteoncology and Rare Tumors Center, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via P. Maroncelli 40, 47014 Meldola, Italy.

E- mail : alberto.bongiovanni@irst.emr.it

MicroAbstract

The purpose of the present study was to investigate the efficacy of Somatostatin Analogs (SSAs) as first- line treatment of metastatic non-functioning Neuroendocrine Pulmonary Carcinoids.

Our results showed that both Lanreotide and Octreotide improved tumor control with very few side-effects in progressive metastatic lung neuroendocrine carcinoids patients . Moreover, ^{18}FDG-PET/CT positivity was an independent prognostic factor of progression-free survival identifying more aggressive tumors that may only marginally benefit from SSA treatment alone.

ABSTRACT

Introduction: Pulmonary carcinoids (PCs) are classed according to the WHO 2004 classification as typical (TC) or atypical carcinoids (AC). Due to their rarity, no dedicated clinical trials with somatostatin analogs (SSAs) have been carried out on primary PCs.

Methods: From January 2007 to December 2015, 30 patients with metastatic PCs underwent first-line SSA treatment (20 with octreotide LAR 30 mg and 10 with lanreotide 120 mg every 28 days). Eight (23.3%) patients had TC and 23 (76.7%) had AC.

Results: Median age was 65.5 years (range 47-82). All patients (23 males and 7 females) were ^{68}Ga-DOTA-TOC-PET/CT-positive (29 patients) or Octreoscan-positive (one patient). Of the 20 patients who performed ^{18}FDG-PET/CT, 14 (70.0%) were positive and 6 negative (30.0%). Median treatment duration was 10 months (range 2-59). One patient achieved a partial response (3.3%) and 26 (86.6%) showed stable disease. One patient interrupted SSA treatment due to symptomatic cholelithiasis. Five-year survival was 53.0% (95% CI: 15.0-80.0). Median PFS (mPFS) was 11.1 months (95%CI: 7.0-15.0). Negative ^{18}FDG-PET/ CT patients had an mPFS of 15.2 months (95% CI: 7.6-not reached) compared to 7.0 months (95% CI: 4.0-10.1) for ^{18}FDG-PET/CT -positive patients. No differences in mPFS were found in relation to TTF1-value, histological subtype, and presence of extrahepatic metastases.

Conclusion SSAs showed antitumor activity in terms of disease control rate and PFS and proved safe, even in patients with poor ECOG status. ^{18}FDG-PET/CT would appear to be a prognostic factor.

Keywords: Pulmonary carcinoids; Lung neuroendocrine tumors; Octreotide; Lanreotide; Somatostatin analogs

Introduction

Neuroendocrine tumors (NETs) are rare tumors arising from endocrine cells in various anatomic sites of both the gastrointestinal and pulmonary systems.[1]

Bronchopulmonary NETs represent approximately 25% of primary lung tumors and 20%-25% of all neuroendocrine neoplasms[2] and have increased in prevalence over the past 30 years as a consequence of improved technological and immunohistochemical diagnostic procedures.[3]

World Health Organization (WHO) 2004 criteria classify lung NETs into 4 histologic variants: typical carcinoid (TC) and atypical carcinoid (AC), defined jointly as pulmonary carcinoids (PCs), and poorly differentiated neuroendocrine carcinomas subdivided into large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (SCLC) according to cell morphology.[4] Although a new grading system for lung NETs including Ki-67, mitotic rate and necrosis was recently proposed, further validation studies are urgently needed.[5]

Prognosis is poor in advanced and progressive disease and there is still no standard therapeutic algorithm available.[6,7] The clinical management of advanced PCs requires a multidisciplinary approach. Furthermore, very few agents have been evaluated in randomized clinical trials and there are still no standard therapies for metastatic diseases. [8]

Recent prospective clinical trials investigated the role of different therapies in metastatic PCs. In the Radiant-4 trial, Yao et al. reported durable tumor control with everolimus in non-functioning lung or gastrointestinal NETs.[9] Peptide receptor radionuclide therapy with 177Lu-DOTATATE showed good activity in 34 consecutive patients with metastatic PCs, with a mPFS of 20.1 months in patients with TC and 15.7 months in those with AC.[10]

Somatostatin analogs (SSAs) induce stabilization in 30-70% of patients with well differentiated NETs, as demonstrated in multiple prospective and retrospective studies,[11] and are often used as first-line treatment of metastatic lung NETs.

Octreotide acetate, developed as a pharmacologically stable, long-acting repeatable (LAR) analog of the hormone somatostatin octreotide, has also proven to be an effective agent because of its antiproliferative effect. Lanreotide is a synthetic analog of somatostatin. Mimicking the actions of somatostatin, SSAs were initially for their antisecretory effects.[12] In a paper by Srirajaskanthan et al., SSAs were administered to 7 patients with inoperable TC and to 5 with AC, both syndromic, to obtain an anti-tumor effect or symptom control. Six patients receiving first-line SSA treatment showed a time-to-progression (TTP) of 10.5 months.[13] In another work, 7 AC patients with liver metastases underwent SSA treatment, obtaining complete control of carcinoid crisis and carcinoid syndrome, with a partial response (PR) in 2 (28.5%) patients and a complete response (CR) in one (14.2%) patient.[14]

The use of SSAs is more controversial in non-functioning tumors, but in the wake of the promising results from the PROMID and CLARINET trials on gastroenteropancreatic (GEP-)NETs, octreotide and lanreotide are now more widely used for non-functioning tumors of other origin. Conversely, clinical trials on the use of SSAs in PCs are lacking.[15,16]

The objective of this paper was to retrospectively evaluate the efficacy of SSAs as first- line treatment of metastatic non-functioning PCs. We also aimed to identify prognostic factors and to assess their potential to improve the therapeutic management of these patients.

Methods

Patients

Patients ≥18 years old were required to have histologically confirmed measurable metastatic TC or AC according to the WHO 2004 classification. All patients were required to have a positive ^{68}Ga-DOTA-TOC-PET/CT (29 patients) or Octreoscan (one patient) . All ^{68}Ga-PET/CTs were performed at our institute. Poorly differentiated tumors were excluded from this analysis. The majority of patients had extrahepatic disease at diagnosis. Histology referrals of patients from other institutes were reviewed by our pathologist, as per our internal guidelines. Median follow-up was 40 months (range 1-88 months).

Clinical data were retrieved from the Rare Tumor Database and the project was reviewed and approved by the Medical Scientific Committee and Ethics Committee of Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS. All patients had previously consented to treatment and had signed a consent form authorizing the processing of their personal data for research purposes.

Staging procedures performed before the start of treatment included physical examination, biochemical profile and brain-chest-abdominal CT scan or liver and brain MRI and chest CT scan. Treatment was discontinued in the event of worsening clinical conditions, unacceptable toxicity or disease progression. Patients were evaluated every three months or if disease progression was suspected, and those without radiological restaging were defined as non evaluable. Response to treatment was evaluated using response evaluation criteria in solid tumor (RECIST) parameters.[14] Toxicity was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Treatment

All patients who received at least one administration of octreotide LAR or lanreotide were considered eligible for the study. Lanreotide was given at a dose of 120 mg via deep subcutaneous injection every 28 days. Octreotide LAR was administered at dose of 30 mg by deep intramuscular injection at 4-week intervals after a 15-day induction period with octreotide 0.1 mg three times daily by subcutaneous injection.

Statistical Analysis

Categorical variables were presented as frequency and percentage, while continuous variables as median and range. Overall survival (OS) was calculated from the date of the start of the first-line regimen to the date of death or last contact. Progression-free survival (PFS) was measured from the date of the start of the first-line regimen to the date of the first documented disease progression, the date of the start of second-line treatment or the date of death due to any cause, whichever came first. OS and PFS were estimated by the Kaplan-Meier method and 95% confidence interval (95%CI) were computed. OS and PFS were reported as median values while the proportion of patients who were alive after 5 years was also shown for OS. Differences between groups were analyzed using the logrank test.

Results

From January 2007 to December 2015, 30 patients with metastatic PC received first-line SSA treatment (20 with octreotide LAR 30 mg and 10 with lanreotide 120 mg every 28 days). No prior treatments for either metastatic or localized disease were permitted. Seven (23.3%) patients had TC and 23 (76.7%) had AC. The Ki67 value was ≤ 5% in 9 (30%) patients and between 6% and 20% in 16 (53%).

Median age was 65.5 years (range 47-82) and ECOG performance status at diagnosis was 0 in 14 (46.7%) patients, 1 in 11 (36.7%) patients and 2 (16.6%) in 5 patients. At diagnosis, 16 (53.3%) patients had undergone surgery for localized disease while 14 patients (46.6%) presented with locally advanced or metastatic cancer. Ninety percent of patients had extrahepatic metastatic disease and 20 showed a high liver tumor burden. The most common sites of metastasis were the liver and bone. All patients were ^{68}Ga-PET/CT- or Octreoscan- positive. All 30 patients underwent second-line treatment, 6 with chemotherapy and 23 with peptide receptor radionuclide therapy (PRRT) and 12 (40 %) received also a third-line therapy. Patient characteristics are listed in Table 1.

Median treatment duration was 10.0 months (range 2.0-59.0). The minimum follow up was 3 months. One patient progressed after only one month. One (3.3%) patient achieved a partial response and 26 (86.6%) showed stable disease, both statuses maintained for a median of 12 months. Fourteen (46.6%) patients experienced steatorrhea and 8 (26.6%) had grade 1 diarrhea, treated with symptomatic drugs. One (3.3%) patient interrupted SSA due to grade 3 symptomatic cholelithiasis. No deaths occurred from toxicity.

The 5-year overall survival rate was 53.0% (95% CI: 15.0-80.9) (Fig. 1) . Median PFS was 11.1 months (95% CI: 7.0-15.0) (Fig. 2). No significant differences in median PFS

were found in relation to age, sex, performance status, TTF1 value, Ki67 value, histological subtype, liver tumor burden or presence of extrahepatic metastases (Table 2). No differences in median PFS (mPFS) or 5-year OS were seen between the lanreotide and octreotide groups (PFS 10.1 months vs. 11.1 months, respectively: 5-year OS 87.5% vs. 65.6%) (Fig. 3).

^{18}FDG-PET/CT evaluation

Of the 20 patients who performed ^{18}FDG-PET/CT, 14 (70.0%) were positive and 6 negative (30.0%). Patients with negative ^{18}FDG-PET/CT had a median PFS of 15.2 months (95% CI: 7.6-not reached), while those with ^{18}FDG-PET/CT positivity had a median PFS of 7.0 months (95% CI: 4.0-10.1). This difference was statistically significant (p = 0.0169) (Fig. 4). The median ^{18}FDG-PET maximum standardized uptake value (SUVmax) was 3.5 (range 0-7.7). The mPFS was greater in patients with ^{18}FDG-PET/CT SUV max $\leq$ 3.5 (mPFS: 12 months, 95% CI: 1.6-25.3) than in those with SUV max >3.5 (mPFS: 7 months, 95% CI: 3.0-12.9) (p=0.0497) (Fig. 5.) No differences in terms of mOS were observed between ^{18}FDG-PET-positive (mOS: 42 months) and -negative patients (mOS not reached) (p=0.8747)

Discussion

PCs are rare tumors with an incidence of 5-10/1,000,000 person-years and an estimated 5-year OS of 61-88% for resected ACs, 90% for resected TCs and about 27% (median OS of 17 months) in the metastatic setting.[6]

In metastatic disease, the role of cytotoxic agents, *e.g.* cisplatin, streptozocin, capecitabine, dacarbazine, 5-fluorouracil, temozolomide and interferon, is unclear.[17]

Recently, everolimus, a targeted m-TOR inhibitor, showed positive results in a prospective clinical trial involving patients with progressive lung NETs.[9] According to recently published guidelines, SSAs can be considered for the first-line systemic treatment of patients with advanced PCs with a low proliferation index and a positive Octreoscan. However, these recommendations were based on the results of GEP-NET clinical trials and on the safety profile of these drugs.[8] No dedicated trials have been carried out on non-secreting PCs and caution should thus be exercised in administering SSAs to patients with a high tumor burden, high mitotic index or rapidly progressing disease.

In our study, patients with non-secreting PCs had an mPFS of 11 months. Although a direct comparison with the mPFS of the PROMID and CLARINET trials is not feasible, we confirmed that SSAs (both octreotide and lanreotide) obtained long-term tumor control and showed very few side-effects in progressive metastatic lung NETs. Our results also suggest that PCs have a variable prognosis and appear to be more aggressive than GEP-NETs. In our case this could be because of the high percentage of patients with ACs (76.7%), which are more aggressive than TCs but also by the high number of patients with extrahepatic disease and a high liver tumor burden. However, histology cannot be the only factor to guide the choice of medical treatment but more clinical and pathological information is needed to distinguish between patients with a good prognosis and those with a bad one.

It is widely accepted that somatostatin receptor scintigraphy and ^{68}Ga-DOTATATE/TOC PET/CT are useful in the diagnosis of well differentiated lung NETs given that about 80% of these tumors express somatostatin receptors, with a high

prevalence of subtype 2.[18] ^{18}FDG PET/CT is also a helpful tool in the identification of mediastinal lymph node disease in ACs.

In a retrospective study by Kaira et al., the amount of ^{18} FDG uptake in early stage lung NETs was determined by markers of glucose metabolism, hypoxia and angiogenesis and increased in pancreatic NETs as tumor progressed from low- to high-grade from low-grade to high-grade pancreatic NETs.[19] In our study, patients with a positive ^{18}FDG PET/CT had a shorter PFS than those who showed ^{18}FDG-PET/CT negativity and this difference was statistically significant (p = 0.0154). This suggests that information obtained from ^{18}FDG-PET/CT could help to identify more aggressive tumors that may only marginally benefit from SSA treatment alone and could be included in the treatment decision algorithm for metastatic disease.

Our study has a number of limitations, the most important being the small number of patients evaluated due to the rarity of this subgroup of tumors. In addition, although octreotide LAR and lanreotide would seem to be equally effective in controlling the disease, a comparison between subgroups was not possible because of the retrospective nature of the study. For the same reason, safety information may have been underestimated. There was also no central review of the images, and patient follow up was performed on the basis of local institutional guidelines.

Despite the above limitations, our findings confirm the activity and safety profile of both octreotide and lanreotide in non-functioning PCs and provide valuable information on the prognostic significance of ^{18}FDG-PET/CT . These data could be taken into consideration when designing prospective clinical studies on pulmonary carcinoids. Prospective clinical and biological studies specifically focusing on PCs are needed to

better understand the natural history of these tumors, which seems to differ from that of GEP-NETs, and to guide physicians in their choice of treatment.

Clinical Practice Points

- Pulmonary carcinoids are rare tumors including different histological subtypes with different clinical outcomes.
- PCs are divided in “functioning” and “not-functioning” tumors depending on hormone secretion capability
- Few dedicated clinical studies are available and the clinical management of PCs requires a multidisciplinary approach.
- Our study shows that SSAs improve tumor control in patients with non - functioning metastatic PCs with a median PFS of 11.1 months and a 5-year overall survival rate of 53.0% .
- Clinical factors including age, sex, performance status, TTF1 value, histological subtype, liver tumor burden or presence of extrahepatic metastasis are not correlated to mPFS

- Moreover, ^{18}FDG-PET/CT could help to identify more aggressive tumors and should be included in the treatment decision algorithm for metastatic disease.

Acknowledgements

The authors thank Cristiano Verna for editorial assistance.

Conflict of interests

The authors declare no conflicts of interests.

Authors' contributions

Alberto Bongiovanni and Toni Ibrahim conceived the idea for this study. Nada Riva, Federica Pieri and Silvia Nicolini reviewed the literature and advised on the clinical classification of pulmonary neurondocrine tumors . Laura Mercatali and Chiara Liverani collected the data. Flavia Foca performed the biostatistical analysis. Alberto Bongiovanni, Toni Ibrahim and Federica Recine co-drafted the manuscript. Dino

Amadori critically reviewed the manuscript for important intellectual content. All authors read and approved the final version of the paper.

References

1. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003;97: 934-959.
2. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26: 3063-3072.
3. Carter D, Vazquez M, Flieder DB, et al. Comparison of pathologic findings of baseline and annual repeat cancers diagnosed on CT screening. *Lung Cancer*. 2007;56:193- 199.
4. Travis W, Brambilla E, Muller-Hermelink H, et al. Tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2004.
5. Rindi G, Klersy C, Inzani F, et al. Grading the neuroendocrine tumors of the lung: an evidence-based proposal. *Endocr Relat Cancer*. 2013;21:1-16.

6. Travis WD. Advances in neuroendocrine lung tumors. *Ann Oncol*. 2010;21 Suppl 7:vii65-71.
7. Pusceddu S, Lo Russo G, Macerelli M, et al. Diagnosis and management of typical and atypical lung carcinoids. *Crit Rev Oncol Hematol*. 2016;100:167-176.
8. 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*. 201526:1604-1620.
9. 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;387:968-977.
10. 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;43:1040-1046.
11. Filosso PL, Ferolla P, Guerrera F, et al. Multidisciplinary management of advanced lung neuroendocrine tumors. *J Thorac Dis*. 2015; 7 Suppl 2: S163–S171.
12. Edward M. Wolinthe expanding role of somatostatin analogs in the management of neuroendocrine tumors gastrointest. *Cancer Res*. 2012; 5:161-168.
13. Srirajaskanthan R, Toumpanakis C, Karpathakis A, et al. Surgical management and palliative treatment in bronchial neuroendocrine tumours: a clinical study of 45 patients. *Lung Cancer*. 2009;65:68-73.

14. 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 Cardiothorac Surg*. 2002; 21:913-917.

15. Rinke A, Müller 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*. 2009;27:4656-4663.

16. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371:224-233.

17. Eads JR, Meropol NJ. A new era for the systemic therapy of neuroendocrine tumors. The Oncologist. 2012;17:326-338.

18. Righi L, Volante M, Tavaglione V, et al. Somatostatin receptor tissue distribution in lung neuroendocrine tumours: a clinicopathologic and immunohistochemical study of 218 'clinically aggressive' cases. *Ann Oncol*. 2010;21:548-555.

19. Kaira K, Murakami H, Endo M, et al. Biological correlation of ^{18}F-FDG uptake on PET in pulmonary neuroendocrine tumors. *Anticancer Res*. 2013;33:4219-4228.

Figure legends

Figure 1. Overall survival (OS) in the entire population.

Figure 2. Progression-free survival (PFS) in the entire population.

Figure. 3 PFS according to ^{18}FDG-PET/CT scan.

Figure. 4 Median PFS (mPFS) (a) and 5-year OS (b) according to the type of somatostatin analog used.

Figure 5. Progression-free survival as a function of ^{18}FDG-PET/CT SUV.

Table 1. Patient characteristics

Variable	No. (%)
Sex	
Male	23 (76.7)
Female	7 (23.3)
Median age, years (range)	65.5 (47-82)
ECOG Performance Status	
0	14 (46.7)
1	11 (36.7)
2	5 (16.6)
WHO Classification	
Typical carcinoid	7 (23.3)
Atypical carcinoid	23 (76.7)
Ki67%	
≤ 5%	9 (36%)
6-20%	16 (64%)
Unknown	*5*
TFF1	
Negative	12 (80.0)
Positive	3 (20.0)
Missing	*15*
Ga68-PET/CT or Octreoscan	
Negative	0 (0.0)
Positive	30 (100.0)
FDG-PET/CT	
Negative	6 (30.0)
Positive	14 (70.0)
Not performed	*10*
Somatostatin analog	
Lanreotide	10 (33.3)
Octreotide	20 (66.7)
Site of Metastasis	
Liver	27 (90.0)
Bone	22 (73.3)
Lymph node	19 (63.3)
Lung	18 (60.0)
Liver tumor burden	
One hepatic lesion	2 (7.4)
2-6	5 (18.5)
>6	20 (74.1)
Extra hepatic metastasis	
Yes	27 (90.0)
No	3 (10.0)

Variable	No. (%)
Second-line treatment	
Chemotherapy	6 (20.0)
PRRT	23 (76.7)
Other	1 (3.3)
Third-line treatment	
Chemotherapy	6 (50.0)
PRRT	4 (33.3)
Other	2 (16.7)
Missing	*18*

PRRT, peptide receptor radionuclide therapy

Table 2. Prognostic factors

Variables	No. patients (%)	No. events	5-year survival rate (95%CI)
Total	24	8	53 (23.7-77.1)
Pet result			
FDG-PET/CT negative	5	1	80.0 (20.4-96.9)
FDG-PET/CT positive	12	4	48.9 (7.3-82.2)
WHO Classification			
Typical carcinoid	6	3	60.0 (12.6-88.2)
Atypical carcinoid	18	5	41.2 (6.4-75.1)
TFF1			
Negative	9	1	87.5 (38.7-98.1)
Positive	3	1	-
KI67% value			
≤5%	6	2	65.6 (15.7-90.9)
6-20%	8	4	47.7 (8.6-80.0)
Somatostatin analog			
Lanreotide	9	3	87.5 (38.7-98.1)
Octreotide	15	5	65.7 (29.4-86.6)
Liver tumor burden			
One hepatic lesion	1	0	-
2-6	4	2	-
>6	16	5	72.2 (40.8-88.9)

Fig. 1

Variables	No. pts (%)	No. events	Median OS (95%CI)	5-years survival (95%CI)
Total	24	8	74.0 (39.0-Not estimate)	53 (23.7-77.1)

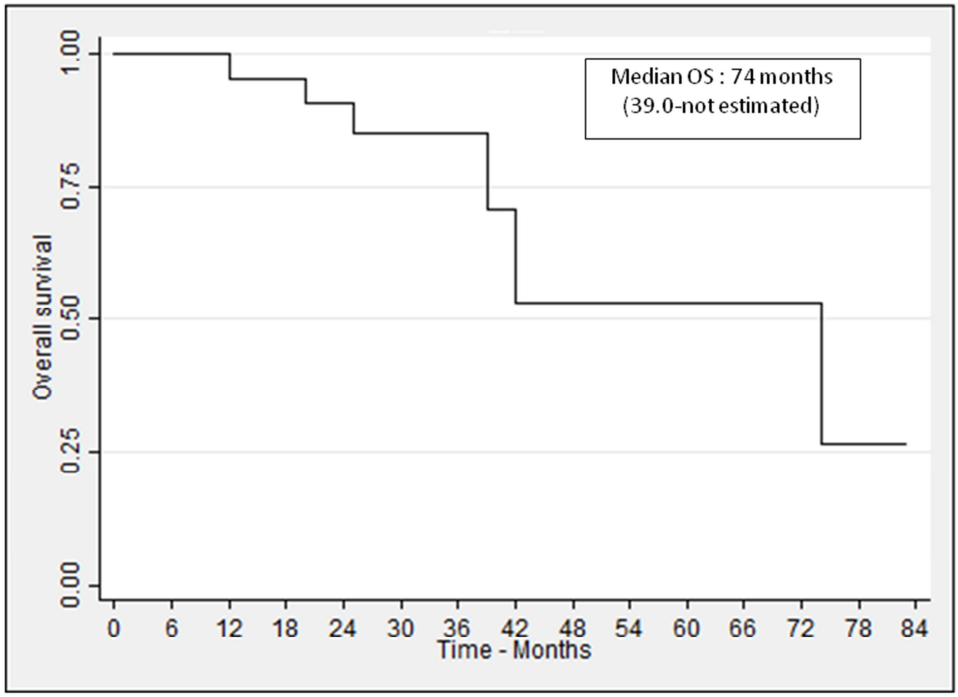


Fig. 2

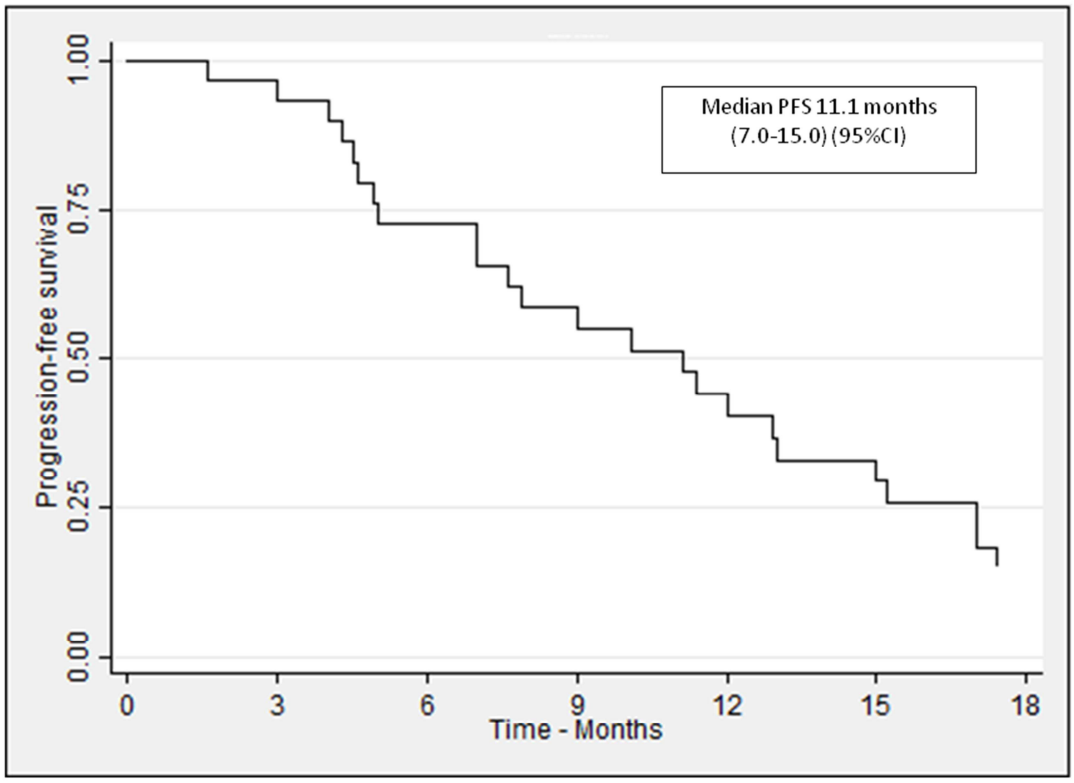


Fig. 3

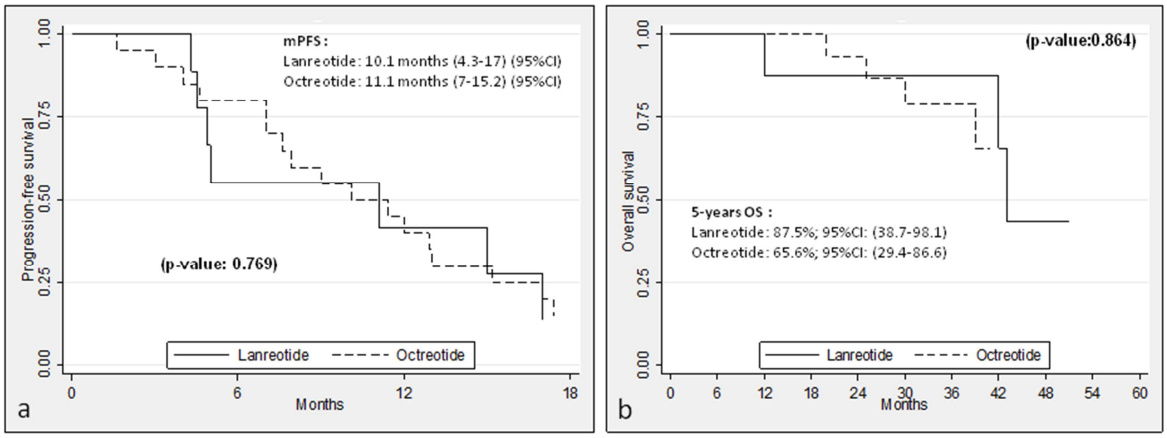


Fig. 4

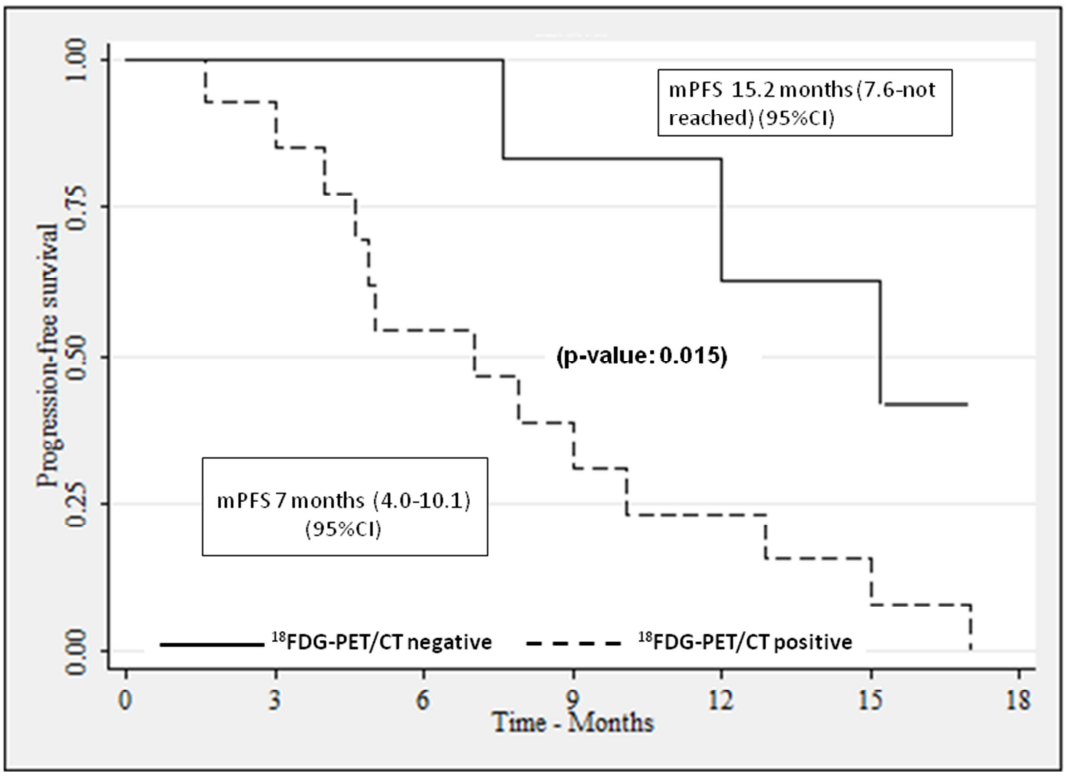


Fig. 5