





Outcomes of patients with metastatic neuroendocrine lung neoplasms: typical versus atypical carcinoids

Resultados de pacientes com neoplasias neuroendócrinas pulmonares metastáticas: carcinoides típicos versus atípicos

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ABSTRACT

Introduction: Well-differentiated neuroendocrine pulmonary tumours (NETp) are morphologically classified as typical carcinoid (TC) and atypical carcinoid (AC). There are limited data on systemic treatment for metastatic disease. **Objective:** Our study evaluated the median progression-free survival of patients with metastatic tumours, comparing TC and AC status for different treatments. **Methods:** Retrospective series of patients with metastatic NETp treated from 2002 to 2019 in a large cancer centre were analysed. Our primary endpoint was progression-free survival according to morphological classification (TC vs. AC). All patients received at least one treatment modality (e.g., somatostatin analogue [SSA], chemotherapy [ChP], and everolimus [Eve]). Variables were analysed using the chi-square test, median progression-free survival (mPFS) rates (months), with comparisons evaluated by the log-rank test. **Results:** Twenty-seven patients were included: 44% with TC and 56% with AC. TC patients were on average 58-years-old, 83.3% were female, and 33.3% received more than one treatment. AC patients were on average 61-years-old, 66.7% were female, and 20% received more than one treatment. All patients were treated more frequently with SSA (TC: 75% vs. AC: 80%, $p=0.756$). Cisplatin and etoposide were the most frequent ChP regimen (TC: 75% vs. AC: 30%, $p=0.248$). Patients with TC and AC treated with SSA had higher mPFS in months (TC mPFS SSA: 14.5, Eve: 2.50, ChP: 4.0, SSA + Eve: 4.50; AC mPFS SSA: 7.50, Eve: 4.50, ChP: 7.50, SSA + Eve: 7.00). **Conclusion:** Although the statistical analyses did not show a significant difference between treatment, numerically, more patients with TC or AC experienced tumor control with SSAs, where the mPFS pairs showed a possible tendency to differentiate themselves from the other regimes (Eve and ChP).

Keywords: Carcinoid tumor; Typical carcinoid; Atypical carcinoid; Everolimus; Somatostatin analogue; Chemotherapy, Adjuvant/ Neuroendocrine tumor.

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RESUMO

Introdução: Os tumores neuroendócrinos pulmonares bem diferenciados (TNPs) são morfológicamente classificados como carcinóide típico (CT) e carcinóide atípico (CA). Os dados são limitados sobre o tratamento sistêmico para a doença metastática. **Objetivo:** Nosso estudo avaliou a sobrevida livre de progressão mediana de pacientes com tumores metastáticos, comparando o TC e o status de AC para diferentes tratamentos.

Métodos: Foram analisadas séries retrospectivas de pacientes com TNPs metastático tratados, de 2002 a 2019, em um grande centro de câncer. Nosso endpoint primário foi a sobrevida livre de progressão de acordo com a classificação morfológica (CT vs. CA). Todos os pacientes receberam pelo menos uma modalidade de tratamento (por exemplo, análogo de somatostatina [SSA], quimioterapia [QT] e everolimus [Eve]). As variáveis foram analisadas pelo teste do qui-quadrado, taxas da mediana da sobrevida livre de progressão (SLPm) (meses), com comparações avaliadas pelo teste de log-rank.

Resultados: Vinte e sete pacientes foram incluídos: 44% com CT e 56% com CA. Os pacientes com CT tinham em média 58 anos, 83,3% eram mulheres e 33,3% receberam mais de um tratamento. Os pacientes com CA tinham em média 61 anos, 66,7% eram mulheres e 20% receberam mais de um tratamento. Todos os pacientes foram tratados com maior frequência com SSA (CT: 75% vs. CA: 80%, $p=0,756$). A cisplatina e o etoposídeo foram os regimes de QT mais frequentes (CT: 75% vs. CA: 30%, $p=0,248$). Pacientes com CT e CA tratados com SSA tiveram maior mPFS em meses (TC SLPm SSA: 14,5, Eve: 2,50, QT: 4,0, SSA + Eve: 4,50; CA SLPm SSA: 7,50, Eve: 4,50, QT: 7,50, SSA + Eve: 7,00). **Conclusão:** Embora as análises estatísticas não tenham mostrado uma diferença significativa entre os tratamentos, numericamente, mais pacientes com CT ou CA tiveram controle do tumor com SSAs, onde os pares de mPFS mostraram uma possível tendência de se diferenciar dos outros regimes (Eve e QT).

Descritores: Carcinoma espinocelular de cabeça e pescoço; Sobrevivência; Polimorfismo Genético; DNA; Gene.

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a group of neoplasms derived from the endocrine system.⁽¹⁾ Within the NEN group, pulmonary neuroendocrine tumours (NETp) constitute approximately 20% of all primary lung tumours. They are divided into four categories: typical carcinoids (TC), atypical carcinoids (AC), small cell lung carcinomas (SCLC), and large cell neuroendocrine carcinomas (LCNEC).^(2,3) These tumours have certain morphologic, ultrastructural, immunohistochemical, and molecular characteristics in common but there are important differences in incidence and survival, and clinical, epidemiologic, histological, and molecular features.^(2,4)

NETp diagnosis can be challenging, given the morphological similarities with other tumours.⁽³⁾ There are limited data on outcomes of systemic treatment for NETp of different cell morphology.⁽³⁾ For example, mitotic rates distinguish TC from AC, and the 2018 World Health Organization (WHO) criteria defined TC as lacking necrosis, 0 to 1 mitosis per 2mm², while AC demonstrates necrosis and/or 2 to 10 mitosis per 2mm².^(1,5)

Among the NETp categories, patients with metastatic TC generally have favourable prognosis.⁽⁶⁻⁸⁾

Treatment options for unresectable/metastatic TC include somatostatin analogue and everolimus, while to date, there is no consensus on the use of chemotherapy for TC patients.^(3,9) In contrast, AC appears to be more frequent, with a higher rate of distant and nodal metastases, and inferior five-year survival rate,⁽¹⁰⁻¹²⁾ even when metastatic disease is present.⁽¹³⁾

Data on real world patients with metastatic NETp are limited. Therefore, given the dearth of information on outcomes of systemic treatment in NETp, our study evaluated the median progression-free survival (mPFS) of metastatic patients, comparing TC and AC subtypes and different therapies.

METHODS

This study was a retrospective analysis that included consecutive patients diagnosed with metastatic lung neuroendocrine tumors, from June 1995 to October 2017, who were treated and followed up at A.C. Camargo Cancer Center, São Paulo, Brazil, from March 2002 to November 2019. The selected patients had a confirmed diagnosis of metastatic typical or atypical carcinoid. They underwent metastasis resection from December 2004 to August 2018. All patients received at least one treatment modality for a progressive disease (somatostatin analogue [SSA],

chemotherapy [ChP], everolimus [Eve]). Only three of the patients assessed received lutecio, which was not considered in this study

The absolute frequency of each variable was calculated. Quantitative variables were assessed for normality using histograms and the Shapiro-Wilk test. The chi-square test was used to compare qualitative variables between patients with TC or AC.

To evaluate the median progression-free survival (mPFS), the time each patient needed for treatment, as well as the cause for disrupting treatment (death, reaction to treatment, or disease progression), were considered. The medical records were accessed to define the morphologic response (RECIST 1.1 guidelines) as criteria for disease progression. We considered each treatment line individually, even if the patient had undergone more than one treatment. The period in which the patients received both SSA and Eve was calculated separately to see if they had a different response from that treatment period alone. The mPFS (calculated in months) was analysed using the Kaplan-Meier method. Statistical tests were considered significant if the two-tailed *p*-value was

<0.05. All analyses were case-complete, with denominators reported for each comparison.

This research, like all studies carried out by A.C. Camargo, was committed to ethics and strict compliance with internal policies and the law.

RESULTS

Twenty-seven patients were included: 12 (44%) with TC and 15 (56%) with AC. TC patients were on average 58 years, 10 (83.3%) were female, and 4 (33.3%) received more than one treatment. AC patients were on average 61 years, 10 (66.7%) were female and 3 (20%) received more than one treatment.

AC patients were numerically more commonly treated with SSA (TC: 75% vs. AC: 80%, *p*=0.75), ChP (TC: 33.3% vs. AC: 66.7%, *p*=0.08) and Eve (TC: 41.7% vs. AC: 80%, *p*=0.04). The cisplatin and etoposide were the most frequent ChP regimen (TC: 75% vs. AC: 30%, *p*=0.248) (see more details in Table 1).

There were no significant differences (*p*<0.05) between regimens, but we observed that, numerically, patients had disease stabilization with SSA as well as with a combination of SSA-Eve (Table 2). PFS times according to treatments are depicted in Figures 1 and 2. When all metastatic NETP patients (TC + AC) were evaluated, we observed that most experienced disease stabilization with SSA (Table 2).

AC: Atypical Carcinoids; ChP: Chemotherapy; Eve: Everolimus; SSA: Somatostatin analogue; TC: Typical carcinoids.

Among TC patients, treatments with SSA offered a longer mPFS (mPFS SSA: 14.50 months, Eve: 2.50 months, ChP: 4.0 months, SSA + Eve: 4.50 months) when compared to other regimens (see Figure 1).

The PFS for AC patients indicated similar mPFS for somatostatin analogues, chemotherapy and somatostatin analogues combined with everolimus (mPFS SSA: 7.50 months, Eve: 4.50 months, ChP: 7.50 months, SSA + Eve: 7.00 months), being inferior mPFS just for everolimus use (see Figure 2).

The progression-free survival curve for 27 patients indicated higher mPFS for SSA when compared to the other regimens (mPFS SSA: 10.50 months, Eve: 3.00 months, ChP: 6.00 months, SSA + Eve: 6.00 months) and inferior mPFS for everolimus use (see Figure 3).

DISCUSSION

Our results indicate that SSA therapy offers tumor control for patients with metastatic NETP. When the groups of AC and TC were assessed separately, disease stabilisation with SSA was observed for both. SSAs that are often recommended for patients with advanced neuroendocrine tumours since they exhibit a high affinity for at least two of the five types of somatostatin receptors.^(14,15) SSAs also exert their inhibitory actions against hormone secretion and cell proliferation,⁽¹⁶⁾ promoting stabilisation in 30-70% of patients with well-differentiated NENs of different origins and prolonged mPFS, although, without proven survival gain.^(14,15,17,20,21) We demonstrated that these results were observed in our patients with NETP, independent of the carcinoid subtype (typical or atypical).

The effectiveness of SSAs combined with Eve have also been described in different types of functioning NENs,^(22,23) including non-functioning NETP, TC, and AC.^(9,17,24-26) However, patients with metastatic NETP, either TC or AC, were under-represented in these clinical trials. This highlights the importance of generating real-world data of treatment outcomes for NETP patients.

In our study, ChP was used more frequently for AC patients, likely reflecting their worse prognosis, which tends to influence treatment decisions towards more aggressive therapies. The efficacy of ChP is limited for advanced NETP, with data coming mainly from small retrospective studies with cisplatin and etoposide.⁽¹⁷⁾ This combination was found to be appropriate for NETP; although, temozolomide-based regimens have also been investigated in small case series, with heterogeneous results.⁽²⁷⁻²⁹⁾

The limitations of our study should be highlighted. There is inherent selection bias because of the nature of the study, which was retrospective and unicentre. Also, given the long-time span covered here, we could not have detailed the information from the medical charts pertaining to treatment-related adverse events or proper evaluation of radiological responses. These factors may have interfered in the selection of patients as well as in the calculation of the survival time that was free of disease progression. Nevertheless, this study is relevant for providing oncological clinical results from real-world patients with NETP treated in Brazil, and is

Table 1. TC and AC patient information with respective treatments.

Variables		TC (N=12)	AC (N=15)	p-valor
Average (mean)		58.3 ± 19.7	61.3 ± 13.5	0.743
Gender	Female (n=20)	83.3% (n=10)	66.7% (n=10)	0.326
	Male (n=7)	16.7% (n=2)	33.3% (n=5)	
Functioning tumor	Yes (n=8)	33.3% (n=4)	26.7% (n=4)	0.962
	No (n=19)	66.7% (n=8)	73.3% (n=11)	
More than one treatment	Yes (n=7)	33.3% (n=4)	20% (n=3)	0.495
	No (n=20)	66.7% (n=8)	80% (n=12)	
Somatostatin analogs	Yes (n=21)	75% (n=9)	80% (n=12)	0.756
	No (n=6)	25% (n=3)	20% (n=3)	
Chemotherapy	Yes (n=14)	33.3% (n=4)	66.7% (n=10)	0.085
	No (n=13)	66.7% (n=8)	33.3% (n=5)	
Everolimus	Yes (n=17)	41.7% (n=5)	80% (n=12)	0.040*
	No (n=10)	58.3% (n=7)	20% (n=3)	
Chemotherapy drug				0.248
Carboplatin and etoposide				
(n=1)		0	10% (n=1)	
Carboplatin and paclitaxel				
(n=1)			0	10% (n=1)
Cisplatin and etoposide (n=6)		75% (n=3)	30% (n=3)	
Darcabazine (n=1)		25% (n=1)	0	
Vinblastine and cisplatin (n=1)		0	10% (n=1)	

Table 2. Median progression-free time, in months [first quartile; third quartile].

Treatment	Diagnosis		
	TC	AC	Total
Eve	2.50 [2.25; 2.75]	4.50 [2.75; 11.00]	3.00 [2.25; 5.25]
ChP	4.00 [2.50; 13.00]	7.50 [5.00; 11.00]	6.00 [3.00; 13.00]
SSA	14.50 [6.00; 23.00]	7.50 [4.25; 10.20]	10.50 [4.25; 15.80]
SSA + Eve	4.50 [3.25; 22.20]	7.00 [3.00; 10.50]	6.00 [3.00; 13.00]

the first Brazilian experiment reporting the outcomes of cancer treatment in metastatic disease.

In conclusion, although the statistical analyses did not show a significant difference between progression-free survival ($p < 0.05$), numerically, more patients with TC or AC experienced tumor control with SSAs,

where the mPFS pairs showed a possible tendency to differentiate themselves from the other regimes (Eve and ChP). Satisfactory results were also achieved in the Eve/SSA combination, with better numbers than the other isolated treatments, which may indicate possible inhibitory effects against cell proliferation

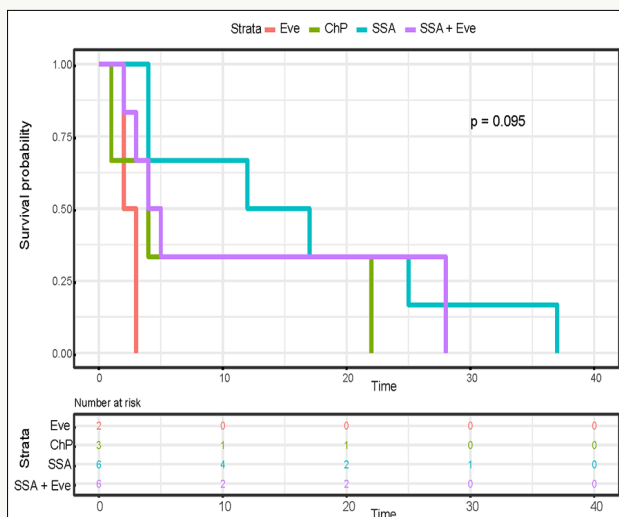


Figure 1. Survival curves for TC patients (n=12), time in month; ChP: Chemotherapy; Eve: Everolimus; SSA: Somatostatin analogue.

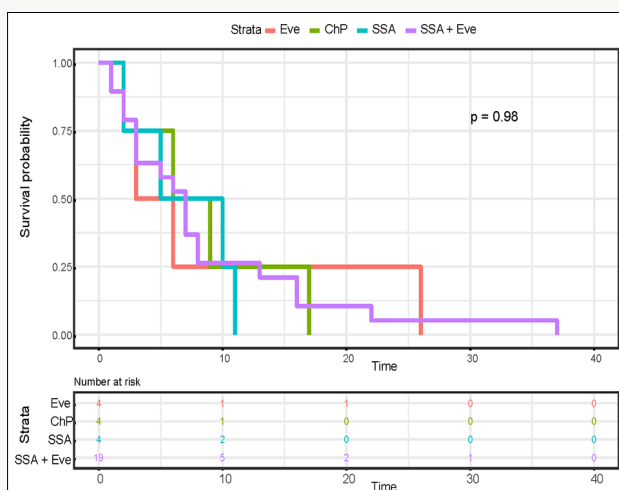


Figure 2. Survival curve for AC patients (n=15), time in month; ChP: Chemotherapy; Eve: Everolimus; SSA: Somatostatin analogue.

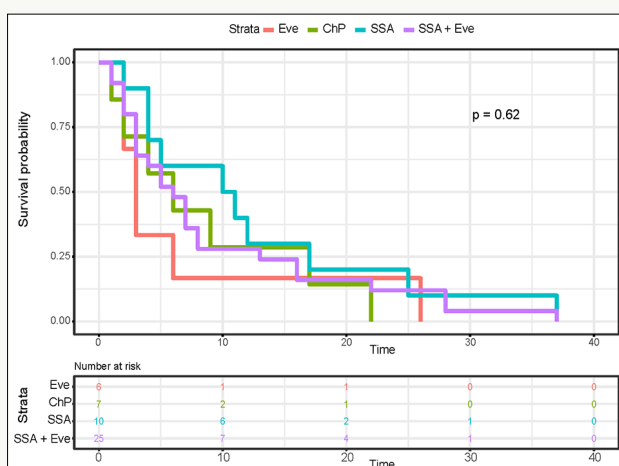


Figure 3. Survival curve for all patients (n=27); time in month; ChP: Chemotherapy; Eve: Everolimus; SSA: Somatostatin analogue.

and comparatively fewer side effects. Despite the limitations of our study and the low number of patients in the sample, our study may be the basis for future prospective studies.

REFERENCES

- Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol.* 2018 Aug;31:1770-86. DOI: <https://doi.org/10.1038/s41379-018-0110-y>
- Travis WD. The concept of pulmonary neuroendocrine tumours. In: Travis WD, Brambilla E, Burke A, Muller-Hermelink HK, Harris CC, eds. *Pathology and genetics of tumors of the lung, pleura, thymus, and heart.* Lyon (France): IARC Press; 2004.
- Hung YP. Neuroendocrine tumors of the lung: updates and diagnostic pitfalls. *Surg Pathol Clin.* 2019 Dec;12(1):1055-71.
- Travis WD. Lung tumours with neuroendocrine differentiation. *Eur J Cancer.* 2009;45(Suppl 1):251-66.
- Travis WD, Gal AA, Colby TV, Klimstra DS, Falk R, Koss MN. Reproducibility of neuroendocrine lung tumor classification. *Hum Pathol.* 1998 Mar;29(3):272-9.
- Ferolla P, Daddi N, Urbani M, Semeraro A, Ribacchi R, Giovenali P, et al. Tumorlets, multicentric carcinoids, lymph-nodal metastases, and long-term behavior in bronchial carcinoids. *J Thorac Oncol* 2009 Mar;4(3):383-7.
- Chong CR, Wirth LJ, Nishino M, Chen AB, Sholl LM, Kulke MH, et al. Chemotherapy for locally advanced and metastatic pulmonary carcinoid tumors. *Lung Cancer.* 2014 Nov;86(2):241-6.
- Quinn AM, Chaturvedi A, Nonaka D. High-grade neuroendocrine carcinoma of the lung with carcinoid morphology: a study of 12 cases. *Am J Surg Pathol.* 2017 Feb;41(2):263-70.
- Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, 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 Mar;387(10022):968-77.
- Beasley MB, Thunnissen FB, Brambilla E, Hasleton P, Steele R, Hammar SP, et al. Pulmonary atypical carcinoid: predictors of survival in 106 cases. *Hum Pathol.* 2000 Oct;31(10):1255-65.
- Fink G, Krelbaum T, Yellin A, Bendayan D, Saute M, Glazer M, et al. Pulmonary carcinoid: presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. *Chest.* 2001 Jun;119(6):1647-51.
- Scott WJ. Surgical treatment of other bronchial tumors. *Chest Surg Clin N Am.* 2003 Feb;13(1):111-28.
- Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer.* 2003 Feb;97(4):934-59.

14. Stueven AK, Kayser A, Wetz C, Amthauer H, Wree A, Tacke F, et al. Somatostatin analogues in the treatment of neuroendocrine tumors: past, present and future. *Int J Mol Sci.* 2019 Jun;20(12):3049.
15. Rai U, Thrimawithana TR, Valery C, Young SA. Therapeutic uses of somatostatin and its analogues: current view and potential applications. *Pharmaco Therapeut.* 2015 Aug;152:98-110.
16. Tsoukalas N, Baxevasanos P, Aravantinou-Fatorou E, Tolia M, Galanopoulos M, Tsapakidis K, et al. Advances on systemic treatment for lung neuroendocrine neoplasms. *Ann Transl Med.* 2018 Apr;6(8):146. DOI: <https://doi.org/10.21037/atm.2018.04.03>
17. Gosain R, Mukherjee S, Yendamuri S, Iyer R. Management of typical and atypical pulmonary carcinoids based on different established guidelines. *Cancers.* 2018 Dec;10(12):510.
18. Aparicio T, Ducreux M, Baudin E, Sabourin JC, Baere T, Mitry E, et al. Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. *Eur J Cancer.* 2001 May;37(8):1014-19.
19. Sullivan I, Le Teuff G, Guigay J, Caramella C, Berdelou A, Leboulleux S, et al. Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids. *Eur J Cancer.* 2017 Apr;75:259-67.
20. Grozinsky-Glasberg S, Shimon I, Korbonits M, Grossman AB. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. *Endocr Relat Cancer.* 2008 Sep;15(3):701-20.
21. Yau H, Kinaan M, Quinn SL, Moraitis AG. Octreotide long-acting repeatable in the treatment of neuroendocrine tumors: patient selection and perspectives. *Biol Targets Ther.* 2017 Dec;11:115-22.
22. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet.* 2011 Dec;378(9808):2005-12.
23. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine tumors of the lung: current challenges and advances in the diagnosis and management of well-differentiated. *J Thorac Oncol.* 2017 Mar;12(3):425-36.
24. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, 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 Jun;26(18):3063-72.
25. Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruzsniwski P, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol.* 2010 Jan;28(1):69-76.
26. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011 Feb;364(6):514-23.
27. Fjällskog ML, Granberg DP, Welin SL, Eriksson C, Oberg KE, Janson ET, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. *Cancer.* 2001 Sep;92(5):1101-7.
28. Ekeblad S, Sundin A, Janson ET, Welin S, Granberg D, Kindmark H, et al. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. *Clin Cancer Res.* 2007 May;13(10):2986-91.
29. Crona J, Fanola I, Lindholm DP, Antonodimitrakis P, Öberg K, Eriksson B, et al. Effect of temozolomide in patients with metastatic bronchial carcinoids. *Neuroendocrinology.* 2013;98(2):151-5.
30. Ito M, Niho S, Nihei K, Yoh K, Ohmatsu H, Ohe Y. Risk factors associated with fatal pulmonary hemorrhage in locally advanced non-small cell lung cancer treated with chemoradiotherapy. *BMC Cancer.* 2012 Jan;12:27. DOI: <https://doi.org/10.1186/1471-2407-12-27>
31. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014 Jul;371(3):224-33.