# Are the $^{18}$F-FDG positron emission tomography/computed tomography findings in bronchopulmonary carcinoid tumors different than expected?

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## Abstract

Bronchopulmonary carcinoid tumors (BPCT) are known as low malignity tumors. Different surgical methods are therapeutically used, ranging from simple excision of the mass to large regional resections. Also, the role of positron emission tomography in the diagnosis and staging of BPCT is controversial as false negative results has been reported in literature. *Our aim* was to study the diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) and the therapeutic effect of specific surgical treatment on BPCT. *We studied* retrospectively from 2005 to 2011 75 cases of BPCT. Preoperative investigations included computerized tomography (CT), bronchoscopy and $^{18}$F-FDG PET. Statistical comparisons were performed based on tumor type, extent of the resection and the standardized uptake value (SUV). Fifty six cases were typical, 15 atypical and 4 oncocytic (a subtype of typical carcinoid). *Of these patients*, 27 (17 with typical, 8 with atypical and 2 with oncocytic carcinoid) had undergone a $^{18}$F-FDG PET scan. Operatory mortality was 0%, while the 7 years survival rate amounted to 97.5%. No recurrences were seen. Mean SUV was 5.28 for typical and 5.08 for atypical BPCT. The oncocytic type exhibited a particularly high SUV. *In conclusion*, our study, contrary to the findings of others, showed that the $^{18}$F-FDG uptake of BPCT was similar to that of malignant diseases. Aggressive surgical treatment resulted in a very good prognosis for these carcinoid tumors.

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## Introduction

Bronchopulmonary carcinoid tumors (BPCT) are rare neuroendocrine tumors with low-grade malignancy originating in the neurosecretory cells of the bronchial mucosa and were first described in 1944 by Engelberth and Holm [1]. These tumors amount 1%-2% of all lung tumors and 21%-25% of all BPCT [2]. Of all histological pathology specimens only 0.6 of 100,000 are evaluated as being carcinoid tumors. They are histologically classified as typical or atypical. Typical carcinoids exhibit rare mitoses and non-specific necrotic areas; their 5 years survival is 87%-100% [3, 4]. Atypical BPCT show evidence of high mitotic activity (2-10 mitoses per high-power field), and focal and diffuse necrotic areas; they are clinically more aggressive and their 5 years survival is 40%-59% [3, 4]. Oncocytic BPCT are a subtype of typical carcinoid tumors.

Carcinoid BPT can be central or peripheral. Neuroendocrine tumors of the lung have been classified in 2004 by the World Health Organization (WHO) as: low-grade, typical; intermediate-grade, atypical; high-grade large-cell carcinomas and small-cell carcinomas. Carcinoid BPT are seen at practically any age and in equal proportions for either sex. About one third of cases are asymptomatic. The most frequent symptoms are hemoptysis, dyspnea, cough and obstructive pneumonia. Preoperative diagnosis is made by means of biopsy assisted by X-rays or bronchoscopy. The recommended treatment for typical BPCT is limited surgical resection and the excision of involved lymph nodes, while for atypical BPCT the suggested procedure includes a wider resection and lymph node dissection [5]. The outcome of radiotherapy, chemotherapy or treatment by the somatostatin analog octreotide is still uncertain. The aim of this report was to share our clinic's experience in diagnosing BPCT by fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) scintigraphy.

## Subjects and methods

A total of 75 patients who had undergone surgery for BPCT in the years 2005-2011 at the Thoracic Surgery Clinic of the Sureyyapasa Teaching and Research Hospital

**Table 1.** *Demographic, clinical, pathological and surgical characteristics (n:75)*

| Characteristics | Number of patients | |
|---|---|---|
| *Age, mean, years* | 47.1 | (18-76 years) |
| *Sex* | | |
| Male | 38 | (50.6%) |
| Female | 37 | (49.3%) |
| *Smoking history* | 35 | (46.6%) |
| *Presenting symptoms* | 53 | (70.6%) |
| Cough | 23 | |
| Dyspnea | 16 | |
| Hemoptysis | 14 | |
| Chest pain | 9 | |
| Fatigue | 7 | |
| Weight loss | 5 | |
| Carcinoid syndrom | 1 | |
| *Asymptomatic patients* | 22 | (29.3%) |
| *Histology* | | |
| Typical | 60 | (80%) |
| Atypical | 15 | (20%) |
| *Location* | | |
| Right | 46 | (61%) |
| Left | 24 | (32%) |
| Trachea | 2 | (2.6%) |
| Mediastinum | 3 | (4%) |
| *Imaging* | | |
| CT scan only | 75 | |
| CT scan plus PET | 27 | |
| *Type of surgery* | | |
| Lobectomy or bilobectomy | 51 | (68%) |
| Pneumonectomy | 4 | (5.3%) |
| Sleeve pneumonectomy | 1 | (1.3%) |
| Sleeve lobectomy | 6 | (8%) |
| Sleeve isolated left main bronchus | 1 | (1.3%) |
| Bronchoplasty isolated | 2 | (2.6%) |
| Wedge resection | 4 | (5.3%) |
| Mediastinal mass excision | 3 | (4%) |
| Endobronchial excision | | |
| With electrosurgery | 3 | (4%) |
| *Complications* | | |
| Prolonged air leakage | 4 | |
| Broncho-pleural fistula | 1 | |
| Wound infection | 2 | |

for Diseases and Surgery of the Chest were evaluated retrospectively. Their average age was 47.1 years (range: 18-76 years). There were 38 (50.6%) men and 37 (49.3%) women. Preoperative evaluation of the patients included their past and present medical history, physical examination, hematology and blood chemistry, chest X-rays, computerized tomography (CT), bronchoscopy and $^{18}$F-FDG PET/CT. Patients with metastases as identified by PET/CT, those considered inoperable and those who had been recommended for adjuvant treatment were not included in our study.

The generally preferred surgical interventions were: lobectomy, pneumonectomy, sleeve resection or combinations of the preceding, wedge resection, mediastinal mass resection, endobronchial excision by bronchoscopic electrosurgery and sleeve bronchoplasty. All patients underwent sampling of hilar and mediastinal lymph nodes. Patients with only radiologically or clinically suspected diagnosis were subjected to mediastinoscopy.

An intraoperative frozen section biopsy was performed in every case. Histological evaluation followed the WHO classification [6].

Standardized uptake value (SUV) was estimated by the PET scan. Due to the extremely high uptake of $^{18}$F-FDG in the oncocytic type of BPCT the SUV of the tumors were divided into three groups and evaluated as typical, atypical and oncocytic. The SUV expected for carcinoid tumors were compared to those measured in our patients and a chi-squared ($\chi^2$) test applied. Postoperative follow-up included physical examination and chest X-rays at 1, 3 and 6 months and yearly thereafter, and a yearly chest CT. Median follow-up duration was 47 months (range, 12-85). The 7 years survival was 97.5% (73/75 patients). Two patients deceased, one with a typical and another with an oncocytic BPCT, at 55 and 59 months of follow-up, respectively. Their cause of death was unrelated to either surgery or the tumor. One of the patients deceased due to myocardial infarction and the other one due to trauma.

## Results

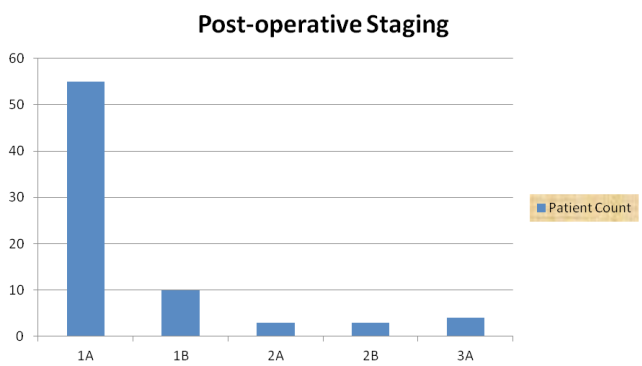
Seventy-five patients who had undergone surgery in our clinic with a diagnosis of BPCT were included in the present study. Of these, 20 patients (29.3%) were asymptomatic, their carcinoid tumor being a chance finding, while 53 (70.6%) had one

or more signs or symptoms. The most frequent symptom was cough (n=23), followed by dyspnea (n=16). Demographic, clinical pathology and surgical characteristics of our patients are found in Table 1.

As for histological type, 56 (74%) cases (28 women and 28 men, average age 54.75 years) had a typical carcinoid and 15 (20%; 6 women and 9 men with average age 45.73 years) an atypical carcinoid, while 4 other patients (3 women and one man, average age 62.75 years) had an oncocytic carcinoid (Table 1). Surgical treatment was used for these tumors in order to entirely resect a single tumor without leaving any residual tumor tissue, no matter the specific method used. Hilar (N1) and mediastinal (N2) lymph node sampling were also performed for the same reason at the time of thoracotomy.

In one of our patients was given neoadjuvant treatment. The kind of surgery of the 75 patients is mentioned in Table 1. The most frequent complication was prolonged air leak in 4 (5.3%) patients; there was a bronchopleural fistula in 1 case and a surgical wound infection in another 2. There was no surgery-related mortality. The duration of postoperative hospitalization was 2-40 days, with an average of 9.98 days. All patients had undergone lymph node sampling; 73 (97.3%) were negative for tumor involvement (N0) and 2 were positive (N2; both in atypical carcinoid tumors). The latter 2 N2 patients with atypical carcinoid received adjuvant chemotherapy. None of the patients had a recurrence during follow-up. Tumor size ranged from 1.1cm to 7.5cm (mean 2.7cm; SD±1.3). At the postoperative staging, 55 patients were considered staged as IA, 10 IB, 3 IIA, 3 IIB and 4 patients stage IIIA (Table 2). This staging followed TNM, 7th edition by the American Joint Committee on Cancer (AJCC).

**Table 2.** *The patient count of the operated patients with carcinoid tumors based on post-operative staging*




Twenty-seven of the 75 patients had undergone $^{18}$F-FDG PET/CT. Of these, 17 had typical and 8 atypical carcinoid tumor, while 2 others were diagnosed with oncocytic type carcinoid (Fig. 1). Average SUV was 5.28 (0-16.2) in the typical carcinoids and 5.08 (1.5-10) in the atypical ones, with no statistically significant difference between them. The SUV value in the 2 oncocytic carcinoma cases was 37.9 and 43.4 (Table 3). Fifteen of the SUV measurements were between 2.5 and 5. The chi-squared test was statistically significant between 2.5-5 SUV group and the other groups in Table 3 (P<0.001). We note that the oncocytic tumors exhibited very high SUV. A SUV higher than 20 was considered as significantly increased (P<0.001).

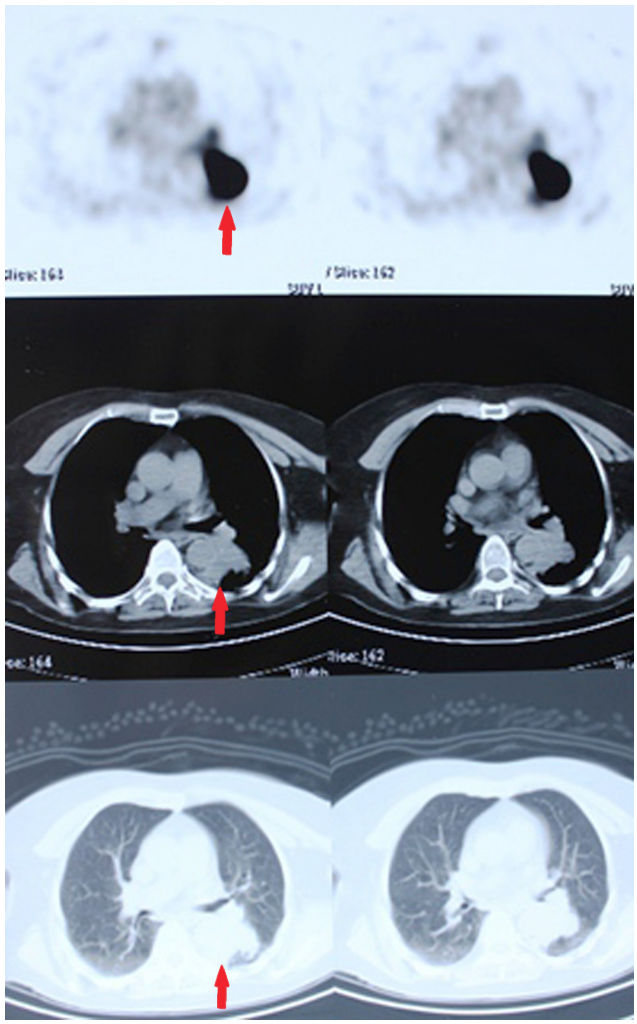


**Figure 1**. The PET/CT of an atypical BPCT in the left lung.

**Table 3.** *The standardized uptake values of carcinoid tumors based on histopathology*

| | | SUV | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | [0.0-2.499] | [2.500-4.999] | [5.000-9.999] | [10.000-19.999] | [20.000 +] | |
| Type | Typical | 1 | 11 | 2 | 3 | 0 | 17 |
| | Atypical | 1 | 4 | 1 | 2 | 0 | 8 |
| | Oncocytic | 0 | 0 | 0 | 0 | 2 | 2 |
| Total | | 2 | 15 | 3 | 5 | 2 | 27 |

SUV: Standardized uptake value.

## Discussion

Recent publications show a rather favorable long-term prognosis for BPCT patients following surgical resection. The prognosis of advanced or metastatic atypical carcinoids is, however, significantly worse, with a 5 years survival rate ranging from 56% to 77% [7].

No correlation between carcinoid tumors and family history, smoking or asbestos exposure has been established [8]. These tumors are more frequently seen in the fourth decade of life [9, 10]. Average age at diagnosis of our patients was 47.1 (range, 18-76) and 35 patients (46.6%) had smoking history.

While BPCT can manifest themselves by various signs and symptoms, 1/3 of the patients may remain asymptomatic [4]. In our study, 22 patients (29.3%) were asymptomatic and diagnosed by chance by the PET/CT scan. The most frequent symptom is irritative cough [11] as in our study. Carcinoid syndrome may be observed infrequently (1%-2%) with large and metastatic bronchial carcinoids [12, 13]. We diagnosed one carcinoid syndrome in a patient with an endobronchial carcinoid with no metastases.

It has been reported that more atypical than typical carcinoids may be found later in life. In contrast to these reports, we diagnosed more typical than atypical carcinoids in advanced age. Oncocytic type carcinoids are seen later in life than either typical or atypical ones [12, 14].

The most frequent location of BPCT is main left bronchus [11] or according to others, the main right bronchus, as in our study (46/24 cases) [12]. In the 46 patients with right-bronchus-sided carcinoid was localized in the upper lobe in 12, in the middle lobe in 19 and in the lower lobe in 15 patients. Carcinoids in the left lung were in the upper lobe in 10 cases and in the lower lobe in 14 on a total of 24. Same as our study, right sided BPCT appear to be more frequent than left sided ones in literature [15].

The size and stage of the tumor is important for the determination of the appropriate surgical approach in carcinoid tumors. According to the literature, most of our patients were staged as IA and IB (65 patients, 86%) and the mean tumor size for all patients was 2.7cm [16]. Four patients were staged as IIIA (two of them for N2 lymph node metastasis, two of them for trachea invasion).

The preoperative diagnostic workup of carcinoid tumors includes, chest CT, bronchoscopy, fine needle biopsy and $^{18}$F-FDG-PET/CT. Pulmonary carcinoids, especially typical carcinoids, show a lower uptake value in the $^{18}$F-FDG scan than lung carcinomas [17].

On CT, typical carcinoid tumors usually appear as spherical or ovoid masses that narrow, deform or obstruct airways. They are located more close to the central bronchi while atypical carcinoid tumors are generally located peripherally in the lung. Calcification occurs in 30% of the tumors and lymph node involvement may also be present [18]. Although CT findings of carcinoid tumors are well defined, histopathological diagnosis is necessary.

The uptake values of $^{18}$F-FDG in lung tumors are proportional to their proliferation rate, as the increase in glucose metabolism causes $^{18}$F-FDG to accumulate in tumor tissue. Considering this, low $^{18}$F-FDG uptake values on the PET/CT scan may suggest that the lung lesion is of low malignancy, and the opposite [19]. Thus, a SUV<2.5 is generally considered as pointing to a benign lesion [20, 21]. $^{18}$F-FDG PET/CT is a valuable imaging tool for early detection of primary tumors, staging, metastases identification and diagnosis of recurrences [22, 23]. A recent study suggested that a SUV of 6 or higher has a predictive value of more than 95% for indicating malignant histology [24].

Typical BPCT are slow-growing tumors and their $^{18}$F-FDG SUV values are low (1.6-2.4) as intermediate between those of benign and malignant tumors [12, 25]. In 15/27 of our patients who had SUV values between 2.5-5, a chi-squared test was positive to differentiate them from the remaining 12 patients (P<0.001). We notice that in our study the average SUV values of typical and atypical carcinoids were higher than those reported in the published literature [17, 25, 26]. Also, contrary to the literature, the average SUV values of typical carcinoids were found higher than atypical carcinoid tumors [15]. However, there was no statistically significant difference between them.

The $^{18}$F-FDG PET/CT is more successful than plain CT in indicating lymph node involvement [27]. In our study two patients had lymph node metastases (N2; both in atypical carcinoid tumors). The issue of indicating lymph node involvement with $^{18}$F-FDG PET/CT could not be analysed in our study as these two patients were scanned with CT only and were not included in the $^{18}$F-FDG PET/CT group. Still, due to the unlikely potential of distant metastases in carcinoid tumors, the use of PET/CT in preoperative staging is controversial.

Carcinoids of the oncocytic type are rather rare [28]. Published reports are usually case presentations. Even though oncocytic carcinoids are a subgroup of typical carcinoids, they are generally more centrally located [29]. Four of our patients had an oncocytic carcinoid with high SUV above 20 (P<0.001). The high $^{18}$F-FDG uptake in this type has been related to its high glucose transmembrane protein (Glut-1) content [29].

Aggressive surgical treatment is the treatment of choice of BPCT. In atypical carcinoid tumors that have lymph node involvement and in inoperable cases, surgical adjuvant treatment is also needed [30, 31]. Our 2 cases with lymph node involvement were also treated with surgery and adjuvant treatment.

Broncho PCT are refractory to radiation treatment (RT) but RT could be suggested for patients with lymph node metastases who are unoperable [12].

The reported 5 years survival for bronchial carcinoid tumors after complete resection is 95% for typical and 60% for the atypical tumors [7]. The most important unfavorable prognostic factors are: age over 60, atypical histology, mediastinal node involvement and early diagnosis of distant metastases. Sex, tumor localization or diameter and the choice of surgical treatment do not affect prognosis [11]. The 5 years and 10 years survival rates for typical and atypical carcinoids have been reported, respectively, as 89% and 72%, while in our study the 7 years survival rate was 97.5% [12]. During our 7 years follow-up 2 patients died, on 4-5 years one with a typical carcinoid and another with an oncocytic carcinoid tumor, at 55 and 59 months, respectively. Their cause of death was unrelated to either surgery or the tumor. One of the patients deceased due to myocardial infarction and the other one due to trauma.

*In conclusion*, our study, in contrast with the findings of others, shows that the $^{18}$F-FDG uptake of BPCT is similar to the $^{18}$F-FGD uptake of malignant tumors, as estimated by increased SUV values >5.08. The $^{18}$F-FDG uptake is very high in the oncocytic type of BPCT.

*The authors declare that they have no conflicts of interest.*

## Bibliography


1. Engelbreth-Holm, J. Benign bronchial adenomas. *Acta Chirurg Scandin* 1944; 90: 383.
2. Soga J, Yakuwa Y. Bronchopulmonary carcinoids: an analysis of 1,875 reported cases with special reference to a comparison between typical carcinoids and atypical varieties. *Ann Thorac Cardiovasc Surg* 1999; 5: 211-9.
3. Oberg K, Hellman P, Kwekkeboom D, Jelic S. ESMO Guidelines Working Group. Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21(Suppl 5): v220–2.
4. Bertino EM, Confer PD, Colonna JE et al. Pulmonary neuroendocrine/carcinoid tumors: a review article. *Cancer* 2009; 115: 4434-41.
5. Gustafsson BI, Kidd M, Chan A et al. Bronchopulmonary neuroendocrine tumors. *Cancer* 2008; 113: 5-21.
6. Gibbs AR, Thunnissen FB. Histological typing of lung and pleural tumours, third edition. *J Clin Pathol* 2001; 54(7): 498-9.
7. Rea F, Rizzardi G, Zuin A et al. Outcome and surgical strategy in bronchial carcinoid tumors: single institution experience with 252 patients. *Eur J Cardiothorac Surg* 2007; 31: 186-91.
8. Kurul Ï.C. Topcu S, Tastepe Ï et al. Surgery in bronchial carcinoids: experience with 83 patients. *Eur J Cardiothorac Surg* 2002; 21: 883-7.
9. Ducrocq X, Thomas P, Massard G et al. Operative risk and prognostic factors of typical bronchial carcinoid tumours. *Ann Thorac Surg* 1998; 65: 1410-4.
10. Porpodis K, Karanikas M, Zarogoulidis P et al. A case of typical pulmonary carcinoid tumor treated with bronchoscopic theraphy followed by lobectomy. *J Multidiscip Helathc* 2012; 5: 47-51.
11. Bagheri R, Mashhadi MTR, Haghi SZ et al. Tracheobronchopulmonary carcinoid tumors: analysis of 40 patients. *Ann Thorac Cardiovasc Surg* 2011; 17: 7-12.
12. Aydín E, Yazící U, Gulgösteren M et al. Long-term outcomes and prognostic factors of patients with surgically treated pulmonary carcinoid: our institutional experience with 104 patients. *Eur J Cardiothorac Surg* 2011; 39: 549-54.
13. Schrevens L, Vansteenkiste J, Deneffe G et al. Clinical-radiological presentation and outcome of surgically treated pulmonary carcinoid tumours: a long-term single institution experience. *Lung Cancer* 2004; 43: 39-45.
14. El Jamal M, Nicholson AG, Goldstraw P. The feasibility of conservative resection for carcinoid tumours: Is pneumonectomy ever necessary for uncomplicated cases? *Eur J Cardiothorac Surg* 2000; 18: 301-6.
15. Escalon J, Detterbeck F. Carcinoid Tumors. In: Shields T, LoCicero JI, Reed C, Feins R Eds. *General Thoracic Surgery.* 7th edn. Philadelphia: Lippincott Williams &Wilkins; 2009; p: 1539-54.
16. Rugge M, Fassan M, Clemente R et al. Bronchopulmonary carcinoid: phenotype and long-term outcome in a single-institution series of Italian patients. *Clin Cancer Res* 2008; 14(1): 149-54.
17. Chong S, Lee KS, Kim B-T et al. Integrated PET/CT of pulmonary neuroendocrine tumors: diagnostic and prognostic implications. *Am J Roentgenol* 2007; 188: 1223-31.
18. Gustafsson BI, Kidd M, Chan A et al. Bronchopulmonary neuroendocrine tumors. *Cancer* 2008; 113(1): 5-21.
19. Demirci I, Herold S, Kopp A et al. Overdiagnosis of a typical carcinoid tumor as an adenocarcinoma of the lung: a case report and review of the literature. *World J Surg Oncol* 2012; 10: 19.
20. Harada S, Sato S, Suzuki E. The usefulness of pre-radiofrequency ablation SUV(max) in $^{18}$F-FDG PET/CT to predict the risk of a local recurrence of malignant lung tumors after lung radiofrequency ablation. *Acta Med Okayama* 2011; 65(6): 395-402.
21. Lowe VJ, Fletcher JW, Gobar L et al. Prospective investigation of positron emission tomography in lung nodules. *J Clin Oncol* 1998; 16: 1075-84.
22. Scott WJ, Gobar LS, Terry JD et al. Mediastinal lymph node staging of non-small-cell lung cancer: a prospective comparison of computed tomography and positronemission tomography. *J Thorac Cardiovasc Surg* 1996; 111: 642-8.
23. Weder W, Schmid RA, Bruchhaus H et al. Detection of extrathoracic metastases by positron emission tomography in lung cancer. *Ann Thorac Surg* 1998; 66: 886-93.
24. Moore W, Freiberg E, Bishawi M et al. FDG-PET Imaging in Patients With Pulmonary Carcinoid Tumor. *Clin Nucl Med* 2013; 38(7): 501-5.
25. Króger S, Buck AK, Blumstein NM et al. Use of integrated FDG PET/CT imaging in pulmonary carcinoid tumours. *J Inter Med* 2006; 260: 545-50.
26. Erasmus JJ, McAdams HP, Patz EF Jr et al. Evaluation of primary pulmonary carcinoid tumors using FDG PET. *Am J Roentgenol* 1998; 170: 1369-73.
27. Tinteren H, Hoekstra OS, Smit EF et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002; 359: 1388-92.
28. Turan O, Ozdogan O, Gurel D et al. Growth of a solitary pulmonary nodule after 6 years diagnosed as oncocytic carcinoid tumor with a high 18-fluorodeoxyglucose ($^{18}$F-FDG) uptake in positron emission tomography computed tomography (PET/CT). *Clin Respir J*2013; 7(1): e1-15.
29. Kadowaki T, Yano S, Araki K et al. A case of pulmonary typical carcinoid with an extensive oncocytic component showing intense uptake of FDG. *Thorax* 2011; 66: 361-2.
30. Thomas CF Jr, Tazelaar HD, Jett JR. Typical and atypical pulmonary carcinoids outcome in patients presenting with regional lymph node involvement. *Chest* 2001; 119: 1143-50.
31. Mackley HB, Videtic GM. Primary carcinoid tumors of the lung: a role for radiotherapy. *Oncology* 2006; 20: 1537-43.