Bronchial carcinoids with oncocytic features and expressing GLUT1 receptor: does the intense ^{18}F-FDG uptake correlate with long-term survival?

To the Editor: Lung neuroendocrine tumors (LNETs) have been traditionally described as tumors with low grade of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) uptake, most likely because of their metabolism and slow growth. In literature, several authors evaluated the role of ^{18}F-FDG. Positron Emission Tomography (PET) scan in bronchial carcinoids (BCs) reporting conflicting results on detection rate (range 14%-90%) [1]. In this setting, the ^{18}F-FDG-avidity seems to be overall higher in atypical carcinoids compared to typical carcinoids (TCs) due to the more aggressive behavior and high proliferation rate of atypical ones [1].

In this setting, we wish to discuss on the recent article by Alpay L. and coll., published in HJNM 2013; 16(3): 213-7 [2] describing a different pattern of ^{18}F-FDG uptake in TCs with oncocytic features when compared with the "non-oncocytic" TCs. The Authors reported a very intensive uptake (SUVmax 37.9 and 43.4, respectively) in 2 out of 4 oncocytic carcinoids: in particular, if compared to uptake of other BCs, a SUV cutoff (higher than 20) was statistically associated (P<0.001) to oncocytic ones.

Despite rarely reported in literature, oncocytic features are most likely associated to such cases of lung cancers with high ^{18}F-FDG-avidity [3]. On the other hand, as reported by Kaira K. et al (2014) [4], the amount of ^{18}F-FDG accumulation in lung cancer cells is associated with molecules relevant to glucose metabolism, such as glucose transporter 1 (GLUT1). As suggested by ourselves [3], the GLUT1 overexpression could be suggestive of large amount of mitochondria in oncocytic cells, this explaining the high uptake (SUV>20) reported in some cases of BCs [2]. As well, Ozbudak IH and coll. (2009) [5] analyzed the distribution of GLUT1 expression in a cohort of 178 LNET patients and documented the GLUT-1 expression in 7% (3/46) of TCs and 21% (6/29) of atypical carcinoids. At statistical analysis, they found that GLUT-1 expression was significantly associated with poorer long-term survival in overall sample (P<0.001) and BCs group (P=0.01). Furthermore, survival curves showed a statistically significant separation of GLUT-1-positive vs GLUT-1-negative cases for all neuroendocrine carcinomas and BCs but not for high-grade LNETs.

Considering the potential more aggressive biological behavior of this subset of patients and waiting for more evidences in this challenging issue, we suggest a certain degree of caution in the post-operative surveillance (that we recommend to be as accurate and long as possible) of patients affected by BCs with high SUV and GLUT1 overexpression, even after radical resection. Obviously, further investigations on larger clinical series (despite hard to collect considering the rarity of this subset of BCs) are required to better define the prognostic role of ^{18}F-FDG-avidity and GLUT1 in LNETs.

According to the data reported and at the light of their experience on 75 BCs, we would really appreciate the Authors' reflections and reaction on the need of accurate evaluation of GLUT1 overexpression in surgical specimen (in order to obtain a further potential prognostic stratification in LNETs) and on the outcome in the subset of patients with oncocytic features.

The authors report that they have no conflicts of interest.

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Giovanni Leuzzi[1] MD, Francesco Facciolo[1] PhD, Giorgio Treglia[2] MD, Filippo Lococo[3] MD

1. Department of Surgical Oncology, Thoracic Surgery Unit, Regina Elena National Cancer Institute - IFO, Rome, Italy.
2. Department of Nuclear Medicine, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland.
3. Unit of Thoracic Surgery, IRCCS-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy

Giovanni Leuzzi MD
Department of Surgical Oncology, Thoracic Surgery Unit, Regina Elena National Cancer Institute - IFO, Rome, Italy,
Tel: +39-3488893788, gio.leuzzi@yahoo.it

Authors' reply:

Bronchopulmonary carcinoid tumors (BPCT) are described in

literature as rare neuroendocrine tumors with low grade malignancy. The role of positron emission tomography (PET) in the diagnosis and staging of these tumors is controversial [1].

In our study we aimed 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 in these tumors [2].

In the letter of Leuzzi et al, it was asked if the intense ^{18}F-FDG uptake correlates with long-term survival. Also, do we need to show glucose transporter 1 (GLUT1) overexpression in surgical specimen for accurate evaluation of the tumor or in other words is GLUT1 overexpression in surgical specimen a prognostic indicator for BPCT?

There are limited papers in literature on this subject. It is known that GLUT1 mediates the transport of glucose across the cellular membrane. Its elevated levels and/or activation have been shown to be associated with malignancy [3]. GLUT1 molecules are overexpressed in oncocytic cells and the ^{18}F-FDG uptake is high as a result.

In the study of Ozbudak et al it was reported that the GLUT-1 expression was positive in 7% (3/46) of typical and 21% (6/29) of atypical carcinoids. Also, GLUT-1 expression was associated with an increased risk of death for neuroendocrine carcinomas as a group ($P<0.001$) and for carcinoids [3].

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. Pulmonary carcinoids, especially typical carcinoids, show a lower uptake value in the ^{18}F-FDG scan than lung carcinomas [4]. However, our study showed that the ^{18}F-FDG uptake of BPCT was similar to that of malignant diseases. Even though oncocytic carcinoids are a subgroup of typical carcinoids, a very intensive ^{18}F-FDG uptake can be observed in these tumors. The high uptake, in this type has been related to its high GLUT1 content [5].

With aggressive surgical and adjuvant oncological treatment in cases with lymph node involvement, the survival rate of these patients is high. Five years survival for bronchial carcinoid tumors after complete resection is 95% for typical and 60% for the atypical tumors [6].

Post operative follow-up is extremely important especially in R1 cases and in cases with lymph node involvement. We thank that the authors of the Letter to the Editor for highlighting the importance of this issue that BPCT can behave as biologically aggressive tumors.

It has been shown that GLUT1 can be used for determining the prognosis in pancreatic neoplasia and malignant peritoneal mesothelioma [7, 8]. Although we did not look for GLUT1 molecules in our study, we think that GLUT1 may be used in bronchopulmonary carcinoid tumors as well. However, there is a challenging issue. Different than other GLUT1 studies (pancreatic neoplasia and mesothelioma survival time is shorter) carcinoid tumors have good survival and follow-up period for a study like this should be for about 20 years. Follow-up for atypical carcinoid tumors can be a better idea as they have worse survival and more GLUT1 expression.

The prognostic value of PET/CT and GLUT1 expression seems similar. We believe there is need for more studies comparing the prognostic values of PET/CT and GLUT1 expression in this challenging group of patients, to find out if examining the surgical †specimen for GLUT1 overexpression is needed.

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Levent Alpay MD, Tunc Lacin MD, Serda Kanbur MD, Hakan Kiral MD, Elcin Ersoz MD, Serkan Bayram MD, Talha Dogruyol MD, Volkan Baysungur MD, Irfan Yalcinkaya MD

Sureyyapasa Training and Research Hospital, Department of Thoracic Surgery

Levent Alpay, MD, Thoracic Surgeon
Sureyyapasa Training and Research Hospital, Department of Thoracic Surgery, BasibuyukMah, Maltepe, 34844, Istanbul, Turkey. Tel: +90 532 3310478, Fax: +90 216 4214110, Email: leventalpay@yahoo.com

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