Which is the best strategy for diagnosing bronchial carcinoid tumours? The role of dual tracer PET/CT scan

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Abstract

Bronchial carcinoids (BC) are rare well-differentiated neuroendocrine tumours (NET) sub-classified into typical (TC) and atypical carcinoids (AC). A correct pathological identification in the pre-operative setting is a key element for planning the best strategy of care, considering the different biological behavior of TC and AC. Controversial results have been reported on the diagnostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in BC. On the other hand, there is increasing evidence supporting the use of PET with somatostatin analogues (dotanoc, dotatoc or dotatate) labeled with gallium-68 (^{68}Ga) in pulmonary NET. Based on information obtained by using different radiopharmaceuticals and different ^{68}Ga labeled somatostatin analogues in PET and PET/CT studies, we are able to diagnose BC. *In conclusion*, by using somatostatin receptor imaging and 18F-FDG PET/CT scan, we can differentiate BC from benign pulmonary lesions and TC from AC by specific diagnostic patterns. Clinical trials on larger groups of patient would allow for a better and "tailored" therapeutic strategy in NET patients using dual-tracer PET/CT to identify BC and distinguish between TC and AC.

Introduction

Bronchial carcinoids (BC) are rare malignant neoplasms, accounting for 2%-5% of all lung tumors, with an approximate annual incidence of 2.3-2.8 cases per million of the population [1]. They are well-differentiated neuroendocrine tumours (NET) arising from Kulcitsky's cells, a specialized network of neuroendocrine cells which synthesize bioactive amines, such as serotonin, and peptide hormones. Bronchial carcinoids may be sub-classified into typical (TC) and atypical carcinoids (AC), the former, in contrast with the latter, has a good to very good prognosis [2]. For the purposes of clinical decision making, the pre-operative staging for these tumours is crucial. While in BC, surgical resection is the gold-standard of treatment, the extension of local resection and especially the extension of systematic lymph nodes resection are determined by cyto/histology characteristics diagnosing TC or AC [3, 4]. It has been reported that: a) the non-anatomic resection is suggested only for peripheral TC and not for AC and b) extended mediastinal dissection should be limited to cases with central TC or AC [5]. Nevertheless, especially for small peripheral BC, the overall pathology differentiation between TC and AC appears not to be accurate. Furthermore, TC and AC share certain radiological characteristics, thus implying that a radiological differentiation between these two entities is also not reliable [5].

Several functional imaging methods have been applied to evaluate BC [6, 7]. The diagnostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been reported to be non-optimal for assessing BC [8], due to the usually low growth of these tumours in particular if compared to more aggressive pulmonary NET such as large-cell and small-cell carcinomas [9]. A recent retrospective study reported that AC usually show a higher ^{18}F-FDG uptake compared to TC due to the more aggressive behavior of AC. This study showed that a size of ≥3.5cm and maximal standardized uptake value (SUVmax) of ≥6 had a predictive value of >95% for malignant histology [10]. Furthermore, ^{18}F-FDG PET/CT may provide useful prognostic information in patients with lung NET, because high SUVmax values are related with poor prognosis and short survival [9].

Due to the high expression of somatostatin receptors on the cell surface of BC, somatostatin receptor imaging has been widely used in the diagnosis, staging and restaging of these tumours [11-15]. Indium-111-pentetreotide (^{111}In-P) is the radiolabelled somatostatin analogue most widely used for assessing NET [11]. Scintigraphy by hybrid single photon emission tomography (SPET)/CT using this radiopharmaceutical in patients with BC showed a diagnostic accuracy of >90% [11-13].

To date, there is increasing evidence supporting the use of PET with somatostatin analogues (dotanoc, dotatoc or dotatate) labeled with ^{68}Ga in BC [14, 15]. A recent meta-analysis demonstrated that PET using ^{68}Ga labeled somatostatin analogues is quite accurate in evaluating thoracic NET, including 83 BC cases. With this technique the administered dose=2-2.5MBq/kg; and the uptake time:60±10min after

tracer injection, has been demonstrated to be superior compared to ^{111}In-P, due to the superior spatial resolution of PET compared to SPET [15]. Nevertheless, there are about 5%-10% false negative results at somatostatin receptor imaging, which may be due to BC with low (up to absent) expression of somatostatin receptors. Inflammatory lesions may also cause false positive results due to the high expression of somatostatin receptors on the cell surfaces of the inflammatory cells [15].

By using different ^{68}Ga somatostatin analogues and ^{18}F-FDG, PET preliminary results showed the usefulness of dual-tracer PET/CT in diagnosing BC [16-18].

In their retrospective study Kayani et al. (2009) compared ^{68}Ga-dotatate and ^{18}F-FDG PET/CT in 11 TC and 2 AC patients with pulmonary NET, scanning them for staging or restaging. The TC patients showed higher and more selective uptake of ^{68}Ga-dotatate than of ^{18}F-FDG. On the other hand, AC showed less ^{68}Ga-dotatate but good ^{18}F-FDG-avidity. No false-positive uptake of Ga-dotatate was reported in this study, but there were 3 sites of false-positive uptake of ^{18}F-FDG due to inflammation [16].

Other researchers evaluated retrospectively 13 TC and 7 AC patients by ^{18}F-FDG PET/CT and 68Ga-dotatoc. Six cases of TC failed to reveal a significant ^{18}F-FDG uptake. The other 7 TC had low SUVmax (2.6-3.2). Thus, the overall detection rate of ^{18}F-FDG PET/CT for TC was only 54%. All AC cases revealed significant uptake on ^{18}F-FDG PET/CT (detection rate: 100%). The SUVmax ranged from 2.9 to 8.4 (median SUVmax: 5.9). On the other hand, all TC cases revealed significant uptake on ^{68}Ga-dotatoc PET/CT (detection rate, 100%) with SUVmax from 8.80 to 66 (median SUVmax: 33). As for the AC cases, one AC did not reveal any significant uptake on ^{68}Ga-dotatoc PET/CT thus the detection rate of ^{68}Ga-dotatoc PET/CT for AC was 86% and the SUVmax ranged from 1.1 to 18.5 (median SUVmax: 10.3) [17].

By using somatostatin receptor imaging and ^{18}F-FDG PET/CT, BC are usually reliably differentiated from benign pulmonary lesions, except in the rare case of BC with simultaneous low or absent somatostatin receptor expression and low glucose metabolism. Furthermore, specific dual tracer PET patterns appear to be useful in differentiating TC from AC. Based on data from medical literature, the most frequent pattern for TC at dual tracer PET/CT imaging is increased uptake of radiolabeled somatostatin analogues and low or absent uptake of ^{18}F-FDG (Fig. 1). Conversely, AC usually present increased ^{18}F-FDG uptake with low or, less frequently, moderate uptake of radiolabeled somatostatin analogues (Fig. 2) [16-19].

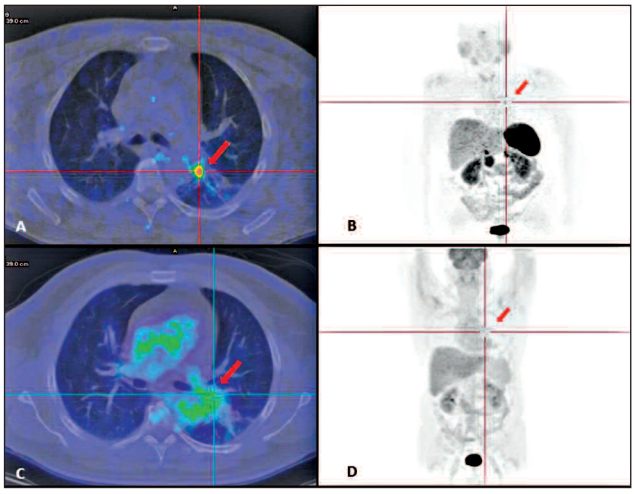

Figure 1. Metabolic pattern for TC, in CT (A and C) and in PET scans (B and D). Increased uptake of radiolabeled somatostatin analogues (A-B) and low or absent uptake of ^{18}F-FDG (C-D). (Images from IRCCS, Arcispedale, Santa Maria, Nuova, Regio, Emilia, Italy)

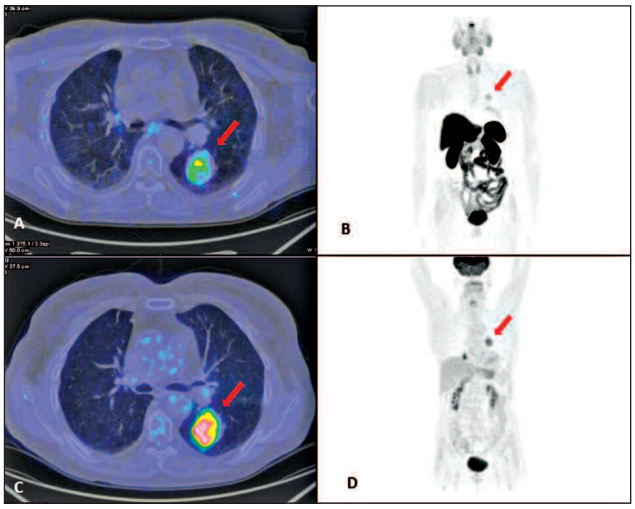

Figure 2. Radiometabolic pattern for AC. Increased uptake (A and B) and moderate or low uptake of radiolabeled somatostatin analogues (C and D) as studied by CT on the left and by ^{18}F-FDG PET on the right side. (Images from IRCCS, Arcispedale, Santa Maria, Nuova,Regio, Emilia, Italy)

If the ability of dual-tracer PET/CT in distinguishing between TC and AC will be finally confirmed, it could allow for a better and "tailored" therapeutic strategy in these patients. In this setting, we are planning in the future a multicentric retrospective study analysis.

It should be noted that other PET tracers beyond ^{18}F-FDG and ^{68}Ga somatostatin analogues can be used in the assessment of BC, like carbon-11-hydroxytryptophan (^{11}C-HTP) and fluorine-18-dihydroxyphenylalanine (^{18}F-DOPA). Reports about the use of these tracers in BC are few [20-22]. Some recent PET studies also refer to the functional characteristics of BC tumours [23-25] and also of gastrointestinal paraganglioma and of medullary thyroid carcinoma.

In conclusion, the use of ^{18}F-FDG and labeled somatostatin analogues in the same patient may provide additional information in assessing BC. However, this strategy is expensive and more work needs to be done before its introduction into clinical practice.

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The authors declare that they have no conflicts of interest.

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