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# 1. Title page

**Title (80 characters)**:

68Gallium DOTANOC-PET imaging in Lung Carcinoids: impact on patients’ management

**Short Title (46 characters incl. spaces)**:

68Ga-DOTANOC PET in Lung Carcinoids

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# 2. Abstract

**Background**

68Gallium DOTA-PET imaging is preferable to standard somatostatin receptor scintigraphy where available; however, its role in the management of Lung Carcinoid tumours (LC) remains unclear.

**Methods**

All consecutive patients with histologically-confirmed LC from two ENETS Centres of Excellence were identified retrospectively. The primary objective was to assess the impact of 68Ga-DOTANOC-PET on clinical management in patients with LC.

**Results**

Of 166 patients screened, 46 were eligible: 52% female, median age 57 years (range 21-86); type of LC: DIPNECH (4%), typical (44%), atypical (35%), not reported (17%); stage: localised (63%), locally advanced (13%) and metastatic (17%) (7% unknown). A total of 47 68Ga-DOTANOCs were performed with the following rationale: LC diagnosis confirmation (4; 9%), primary tumour identification (2; 4%), post-surgical assessment (19; 40%), staging (patients with known LC present at time of 68Ga-DOTANOC) (19; 40%) and consideration of Peptide Receptor Radionuclide Therapy (PRRT) (3; 7%). Twenty-seven (57%) scans showed evidence of non-physiological uptake: median SUVmax 7.2 (range 1.42-53). 68Ga-DOTANOC provided additional information in 37% (95%CI 22-51) of patients and impacted on management in 26% (95%-CI 12-41); 9 patients (21%) were identified to have occult sites of metastases. Out of the 19 patients with post-surgical 68Ga-DOTANOC, 3 (16%) were identified to have distant metastases. There were no differences in the rate of practice changing 68Ga-DOTANOC results by type of LC (p-value 0.5).

**Conclusions**

Our results support the role of 68Ga-DOTANOC for optimizing the management of patients with LC, including post-surgical re-staging due to potential for identifying occult metastases.

# 3. Text

## Introduction

Lung neuroendocrine malignancies include a spectrum of neoplasia which share neuroendocrine features [1]. Lung neuroendocrine tumours (NETs) are classified according to their pathological characteristics (**Table 1**) [2]. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is considered a pre-invasive lesion with a potential toward the development of lung NETs [3, 4]. Lung carcinoids (LC) are rare tumours [5], however incidence is increasing due to improvement in diagnostic techniques [6]. They account for approximately 2% of all lung malignancies and around 20-30% of all NETs. They characteristically have an indolent clinical behaviour with longer survival intervals compared to poorly differentiated lung neuroendocrine malignancies [7]. LCare divided into typical or atypical carcinoid tumours according to pathological characteristics, such as amount of mitosis and necrosis (**Table 1**). In contrast to the well-differentiated NETs arising from the gastrointestinal tract where the Ki-67 index is one of the parameters used in their grading classification [8, 9], the role of Ki-67 index immunohistochemistry has not been validated as yet in lung NETs [10, 11].

There are differences in survival between patients with typical and atypical LC, however clinical management does not vary significantly [12, 13]. For localised stages, surgery is the treatment of choice, performed with curative intent; there is no approved adjuvant treatment and patients are allocated into a surveillance-only pathway; the only exception to this statement may be patients with atypical LC with positive lymph nodes in whom adjuvant therapy could be considered on a patient by patient basis [12]. Locally advanced inoperable or metastatic tumours are treated with palliative approaches based on somatostatin analogues (SSAs) [14], temozolomide-based chemotherapy combination [12]) and Peptide Receptor Radionuclide Therapy (PRRT) [15-18]. Other treatment options such as targeted therapies (everolimus) have shown positive results and may become available in the near future [19].

In addition to the pathological diagnosis and biochemical tumour markers which include chromogranin and 5- Hydroxy Indol Acetic Acid (5-HIAA) (of interest in patients with carcinoid syndrome, which accounts for around 2-5% of the LC), diagnosis, staging and assessment of response to treatment is based on radiologic findings using computerised tomography (CT) scans and magnetic resonance imaging (MRI) scans [12]. Nuclear medicine imaging, such as somatostatin receptor scintigraphy, has been employed for staging of LC and patient selection for specific treatments such as PRRT. Development of new nuclear medicine imaging techniques, including Positron Emission Tomography (PET) combined with CT has improved diagnosis, staging and treatment of patients diagnosed with LC [20, 21]. 18-Fluoro-deoxyglucose (18FDG), was one of the first tracers developed in oncology. Its role in lung neuroendocrine malignancies is considered more relevant in poorly-differentiated lung NETs compared to the LC [22-25].

Approximately 80% of LC express somatostatin receptors by immunohistochemistry. Based on this, 68-Gallium(68Ga)-radiolabeled PET (68Ga-DOTA-PET) tracers for functional NET imaging have emerged as potentially useful tools. These include [68Ga-DOTA0-Tyr3]octreotate (68Ga-DOTATATE), [68Ga-DOTA0-Tyr3]octreotide (68Ga-DOTATOC, 68Ga-EDOTREOTIDE) and [68Ga-DOTA0-1NaI3]octreotide (68Ga-DOTANOC) [26, 27]. 68Ga-DOTA imaging, has shown superiority to somatostatin receptor scintigraphy (such as Octreoscan), iodine-131-meta-iodobenzylguanidine (MIBG) scintigraphy and MRI [28]. In addition, 68Ga-DOTA-PET has shown superiority to 18FDG-PET imaging in well differentiated NETs [29]. All 68Ga-DOTA-PET tracers can bind subtypes 2 of somatostatin receptors, while only 68Ga-DOTANOC presents a good affinity for subtypes 2,3 and 5. However, a class effect is emerging with all of them providing similar diagnostic accuracy [30]. It is unclear whether any of these tracers are superior to others for LC, since such patients have been underrepresented in previously published large series on patients with NETs exploring 68Ga-DOTA-PET imaging (accounting for 10-12% of the patients reported [29, 31]) due to their low incidence [20]. Previously published series which focused exclusively / mainly on patients diagnosed with LC were small [20, 27], the largest including only 26 patients [32]. As per European Neuroendocrine Tumour Society (ENETS) [12], North American Neuroendocrine Tumor Society (NANETS) [33] and National Comprehensive Cancer Network (NCCN) [34] guidelines, the use of 68Ga-DOTA-PET scans is preferable to standard somatostatin receptor scintigraphy whenever available, having a potential role for selection of patients for treatment with PRRT, identification of primary tumour and pre-surgical staging. Unfortunately, none of these guidelines specify indications for performing such imaging to LC patients [12, 13] which remains an additional challenge for daily practice, since the real impact on clinical management has not been specifically investigated in this patient population [31]. Therefore, the role of these new imaging techniques in patients with LC remains unclear. This study aims to assess the impact on clinical management of performing 68Ga-DOTANOC PET in patients with lung carcinoids.

## Materials and methods

Patients were retrospectively identified from local electronic case-note records at two ENETS Centre of Excellence in the United Kingdom. All consecutive patients who underwent a 68Ga-DOTANOC PET imaging scan between December 2013 and April 2016 were screened for eligibility. Patients diagnosed with LC were eligible: typical LC, atypical LC and DIPNECH were included. Other inclusion criteria included biopsy/cytology confirmation of LC. Patients with high grade malignancies, non-lung primary and those whose malignancy was not confirmed pathologically at time of inclusion in the study were considered ineligible. This study was approved in each institution by the corresponding local audit department.

Clinical data were retrospectively collected by clinicians with an expertise in the field of LC; these data included demographic details, together with information of stage (localised, locally advanced or metastatic; according to American Joint Committee on Cancer (AJCC) 7th Edition [35]), treatment and survival. Whenever feasible, samples were reviewed by experienced pathologist: type of LC, Ki-67 index (%) and mitotic account (x10 high-power fields (HPF)) were collected. The mitotic rate was assessed over 10 consecutive HPF in the mitotically most active area (“hottest spot”) of each sample at a magnification of x400 using a Nikon Eclipse microscope with a x40 objective and a x10 ocular lens )equivalent to 2mm2 field area). In addition, all 68Ga-DOTANOC PET images were reviewed by nuclear medicine consultants with an expertise in NETs. At the time of 68Ga-DOTANOC data interpretation, the radiologist had access to both medical information and other imaging techniques such as MR or CT scan whenever these had been performed in the past. Collected radiological data included standardised uptake value (SUV) information such as maximum SUV (SUVmax). Specific information regarding primary tumour, liver, lung, bone and lymph node metastases was collected, including size of largest lesion and tracer uptake by site. In addition, all 68Ga-DOTANOC PET scans were classified as “uptake” or “no-uptake” according to whether there was or not a pathological tracer uptake, respectively. Finally, the impact of 68Ga-DOTANOC PET on patients’ management and its addition of new information (i.e. identification of occult metastases) was assessed by clinicians, with joint input from radiologists whenever necessary.

The primary objective of this study was to assess the role of 68Ga-DOTANOC PET in patients with lung neuroendocrine tumours; the primary end-point was the rate at which the 68Ga-DOTANOC results were changing practice or adding additional information. Secondary objectives included an analysis of the role of 68Ga-DOTANOC results in different patient subgroups (i.e. resected/advanced; typical/atypical), correlation between Ki-67 index and SUVmax and the impact of size of metastatic deposits upon 68Ga-DOTANOC results. Impact of 68Ga-DOTANOC results (binary outcome (uptake/no uptake) and SUVmax) on patients’ prognosis (overall survival (OS)), relapse-free survival (RFS) and progression-free survival (PFS) was also analysed.

Statistical analysis

Statistical T-test and Chi-Squared test and Pearson-correlation test were applied as appropriate. Receiver operating characteristic (ROC) curves were built for identification of the AUC (area under the curve) and the most informative cut-off (as per higher sensitivity and higher specificity) of the size of the metastatic lesions for predicting a non-physiological tracer uptake in the 68Ga-DOTANOC PET. Logistic regression was used for identification of factors predictive of a change in patients’ management.

Relapse free-survival was measured for patients who underwent curative resection and was defined as the time between date of surgery and date of tumour relapse. For patients who received any kind of palliative treatment, PFS was defined as the time from starting first-line treatment for advanced LC to the time of progression (radiological or clinical) or the date of death or last follow-up without progression (if patient alive). OS was calculated for all patients as the time from diagnosis to the date of death or last follow-up without death. Median RFS, PFS and OS were estimated by the Kaplan-Meier method. The log-rank test and univariate/multivariable Cox regression models were used for survival analysis. Those variables which showed statistically significant p-value in the univariate analysis (defined as p-value <0.05) were included in multivariable analysis. Two-sided significance test with a p-value of <0.05 was considered significant. Stata version 12.0 software was employed for the statistical analysis.

## Results

A total of 166 patients were screened and reviewed for eligibility: 46 patients were eligible for inclusion into the study (**Figure 1; Supplementary Material A**), who accounted for a total of 47 68Ga-DOTANOC PET scans (one patient was scanned twice).

Baseline characteristics

Baseline characteristics for the 46 eligible patients are summarised in **Table 2**. Subtype of lung carcinoid was as follows: 44% typical carcinoid, 35% atypical carcinoid, 4% DIPNECH and 17% not specified (however subtype was not specified, tumours were confirmed to be LC). All patients diagnosed with DIPNECH were based on pathological findings only and were asymptomatic (not meeting criteria for DIPNECH syndrome). Mean Ki-67 index was higher in atypical LC (7.2% (95% CI 5.1-9.3) compared to typical LC (2.3% (95% CI 0.8-3.9)); p-value <0.001. Similar findings were shown with the mitotic count: atypical LC (4.6 per 10 HPF (95% CI 1.8-7.7) compared to typical LC (0.4 per 10 HPF (95% CI 0.1-0.7)); p-value 0.002.

Most patients were diagnosed at localised stages (63%). Median time of follow-up for this study was 11.3 months (range 3.2-266.1). Treatment characteristics are specified in **Table 3**; for one of the patients, information about treatment was not available. The majority of patients were treated with curative resection (59%); achieving a median RFS was 44.9 months (95% CI 11.9-59.1). Only 39% received any form of palliative treatment during the follow-up period, such as somatostatin analogues (67%) or chemotherapy (23%); median PFS to first-line palliative treatment was 17.9 months (95% CI 3.02-not reached). Median overall survival was not reached (**Table 2**).

68Ga-DOTANOC PET imaging

A total of 47 68Ga-DOTANOC imaging scans were performed. In total, 27 scans (57%) showed pathological uptake, while 20 (43%) were classified as “no-uptake” (no uptake or physiological uptake only identified). Out of the 28 patients who had primary or metastatic LC *in situ* at the time of 68Ga-DOTANOC-PET, 24 showed pathological uptake (sensitivity of 86%). Median SUVmax was 7.2 (95% CI 6.1-19.9). There was neither significant correlation between Ki-67 index index and SUVmax (16 observations; Spearman rho=0.004; p-value 0.9) nor differences in SUVmax between typical and atypical LC (mean SUVmax 9.7 (95% CI 1.3-18.1) vs 23.6 (95% CI 11.1-36.1), respectively; p-value 0.07).

The maximum size and tracer uptake of primary tumour and metastatic sites are summarised in **Table 4 (Supplementary Material B)**. Overall, the biggest lesions were identified within the liver (median of 7 cm), however all tumour sites explored showed a high rate of tracer uptake (between 80-100%): 68Ga-DOTANOC showed high sensitivity regardless of the organ been explored. Regarding the most suitable size cut-off of the largest metastatic lesion per cancer site for predicting tracer uptake in 68Ga-DOTANOC imaging, ROC curves identified 1.4 cm and 2 cm as the most informative cut-offs for primary lung tumour and lung metastases, respectively (**Table 4; Supplementary Material B**).

Rationale for performing 68Ga-DOTANOC imaging

Regarding the rationale behind performing the 68Ga-DOTANOC imaging, most scans were performed as a post-surgical assessment of patients assumed to be cancer-free (post-surgical re-staging) (40%) or for completing staging of patients with localised/advanced lung carcinoid tumours (**Table 5)**. Other reasons included confirmation of diagnosis of NET (9%), consideration of treatment with PRRT (7%) and identification of primary tumour site (4%). Rate of positivity in the 68Ga-DOTANOC PET changed according to rationale behind performing such imaging (Chi square p-value < 0.001). As expected, the lowest uptake rate (16%) was shown in the post-surgical re-staging group, followed by patients in whom 68Ga-DOTANOC was performed in order to confirm NET diagnosis (75%).

Impact of Ga-DOTANOC results on patients’ management

A total of 17 (37%) 68Ga-DOTANOC-PET imaging scans added additional information to the previous imaging techniques (including CT and MR imaging), and 10 (26%) impacted patients’ management. As detailed in **Table 5**, lower rate of additional information and change in patients’ management was shown in the post-surgical re-staging group (21% and 12%, respectively), followed by patients in whom 68Ga-DOTANOC-PET was performed as staging (42% and 29%, respectively). The rationale behind the PET imaging did not have a statistically significant impact on whether the 68Ga-DOTANOC added any extra information or not (Chi square p-value 0.065).

Type of additional information provided by the 68Ga-DOTANOC scan was analysed further. Out of the 47 scans performed, 9 (21%) identified new sites of disease, three of which were performed in patients who were expected to be “cancer free” after curative resection (**Figure 2**). These accounted for 16% (3 out of 19) scans performed in this population; none of these patients were early stage (pT1aN0 completely resected (R0)) typical LC or DIPNECH. In addition, one scan changed options of treatment, identifying a patient suitable for PRRT. See **Table 5** for full information.

Subtype of LC did not change the rate of the 68Ga-DOTANOC-PET scan impacting patients’ management: DIPNECH (0%), typical LC (16%) and atypical LC (29%) (Chi square p-value 0.541); however our data showed a trend for more significant benefit in patients diagnosed with typical or atypical LC compared to DIPNECH.

Factors predictive of change in patients’ management and Survival analyses

Our data were unable to specify which population of patients may benefit more from performing a 68Ga-DOTANOC-PET scan (**Supplementary Material C**). Baseline factors and 68Ga-DOTANOC results (such as SUVmax) were explored as potential prognostic factors impacting OS, RFS or PFS. No prognostic factors were identified (all p-values >0.05; full data not shown) (**Supplementary Material C**).

## Discussion

Previously published series which focused exclusively / mainly on patients diagnosed with LC were small [20, 27], the largest including only 26 patients [32] (**Table 6**). To our knowledge, our series is one of the largest series exploring “real” role of 68Ga-DOTANOC PET exclusively in patients diagnosed with LC. Our results showed that 68Ga-DOTANOC PET often changes management in patients with LC tumours and should, therefore, be part of the baseline staging imaging (for both metastatic and post-resected patients) regardless of site of metastases and grade (**Table 7**).

Our results confirmed similar sensitivity to that previously reported with 68Ga-DOTATATE [40, 41] and was agreement with previous literature regarding none of the patients diagnosed with DIPNECH showed any uptake [36]. Based on this, we would question whether performing such imaging in patients with DIPNECH is of any value? 68Ga-DOTANOC PET could be beneficial to exclude presence of small foci of typical LC in patients with DIPNECH, but its role is, otherwise, limited. On the other hand, we did not identify any differences in 68Ga-DOTANOC uptake (in terms of SUVmax) between typical and atypical LC; however this has been previously suggested by other researchers [36]. Finally, all organs explored (lung, liver bone and lymph node) showed a good sensitivity and therefore capacity of 68Ga-DOTANOC for identification of LC primary or metastases seems independent of the organ being investigated. We would therefore suggest that 68Ga-DOTA-PET imaging is performed regardless of type of LC (with the exception of DIPNECH) and site (organ) and size of metastases.

The proportion of 68Ga-DOTANOC PET scans providing the clinician with additional information was clinically relevant (37%), which translated into an impact on management in 26% of patients. These results are in agreement with previous experience [39]. Interestingly, this benefit was not limited to a specific sub-population, since no factors predictive of impact in patients’ management were identified in our series: all patients seemed to benefit from performing the 68Ga-DOTA-PET, regardless of the rationale behind such investigation or other baseline characteristics (including type of LC).

The predominant ways in which the 68Ga-DOTANOC PET scan impacted management were by the identification of occult sites of metastases, assessment of disease distribution and tumour burden and selection of patients suitable for PRRT.

Identification of new metastatic sites was retrospectively evaluated by Ambrosini *et al*. who assessed the capacity of 68Ga-DOTANOC PET to identify occult bone metastases in 223 patients diagnosed with NET (any site): 68Ga-DOTANOC PET was more accurate than CT for the identification of bone lesions and led to a change in clinical management in nine patients who had a previous negative CT scan [42]. Our results concur with these findings by identifying new occult bone and lung metastases in patients who had the PET performed for accurate staging of metastatic disease (20%) and also in patients in whom the PET scan was performed as a post-surgical re-staging test and who were thought to be tumour-free (16%). This is therefore a novel indication for 68Ga-DOTANOC PET imaging in LC; based on our results we would suggest incorporating a baseline 68Ga-DOTA-PET scan in all patients following curative resection of LC due to the risk of identification of occult metastases as has been previously suggested by other colleagues [38]. The potential role of 68Ga-DOTA-PET as a pre-surgical staging evaluation could not be addressed by this study, since none of the patients had this imaging performed pre-operatively. This aspect should be explored in further studies; in the mean-time, pre-surgical 68Ga-DOTA-PET would be worth considering due to the same rationale for recommending performing post-surgical re-staging.

Regarding the assessment of disease distribution and tumour burden in patients with LC, it is worth highlighting that 68Ga-DOTANOC PET impacted on clinical management in 29% of patients with known metastatic disease. This is comparable to rates previously described by other colleagues in smaller series (33%) [39]. In fact, an accurate staging for assessment of tumour burden may be useful for selection of treatment approaches, such as 1) assessment of liver remnant for patients due to have liver embolisation; 2) assessment of extrahepatic disease in order to select patients for liver directed therapies, such as liver embolisation, debulking surgery, liver radioembolisation; 3) selection of systemic approaches such as SSA or chemotherapy based on tumour burden (SSA for patients with low tumour burden; chemotherapy in scenarios with high tumour burden when rapid tumour volume reduction is desirable) [13]. In summary, assessment of tumour distribution and tumour burden may be helpful for the decision making process in the context of multidisciplinary case discussion, when planning the treatment pathway for patients with advanced disease; 68Ga-DOTA-PET should be part of the baseline assessment of patients with advanced LC and part of the multidisciplinary discussion.

Finally, the role of 68Ga-DOTA-PET as a selection tool for patients with PRRT is widely accepted by the NET community [12]; our results support such a use, since findings will help with the selection of patients likely to respond to treatment and also to assess tumour burden and predict toxicity [13, 43-45].

Limitations of all retrospective studies apply, such as reporting bias, since clinical data available was restricted to previously collected information. Although all consecutive patients were included in order to reduce to a minimum patient selection bias, it is impossible to completely avoid such a problem. Patients who were referred for 68Ga-DOTANOC PET in the first instance could be somewhat selected due to the clinical picture. Finally, the sample size was small, which is not surprising taking into account the extremely selected patient population that this study was targeting. The limited sample size, reduced the power of our study which should be considered a “proof of concept” study and which conclusions should be confirmed in a larger cohort. In order to attenuate the above mention limitations, it is worth highlighting the following. First, our population was as homogeneous as possible, by exclusion of patients without pathological confirmation of LC and with high-grade lung NETs. Second, all 68Ga-DOTA-PET reported in this study employed the same tracer (68Ga-DOTANOC) providing consistency. Third, both centres involved in the study are recognised as high volume and high expertise centres, not only in NETs, but also in nuclear medicine. Finally, all patients had a pathology review by pathologist with an expertise in NETs; reflection of this is the fact that the mitotic count was significantly higher in atypical LC compared to typical and that such differences were significant, as expected according to international classifications of LC.

In summary (See **Table 7**), 68Ga-DOTANOC PET often changes management in patients with LC tumours and should, therefore, be part of the baseline staging imaging (for both metastatic and post-resected patients) regardless of site of metastases and grade. Results should be discussed in a multidisciplinary meeting for planning patients’ management according to disease distribution and tumour burden, including consideration of suitability for PRRT.

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This study did not receive any external funding.

# 5. Author contributions

* Formulating the research question: AL, GP, WM
* Designing the study: AL, GP, WM
* Data collection: AL, MP, SV, PM
* Analysing the data: AL
* Result interpretation: All authors
* Manuscript writing: All authors

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# 7. Compliance with Ethical Standards

Compliance with Ethical Standards: All authors declares that there is no conflict of interest.

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# 9. Figures and tables

### Table 1

**Table 1**: Classification of lung neuroendocrine tumours (adapted from features [1, 2, 4]).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Premalignant | Lung carcinoids | | Lung NECs | |
|  | **DIPNECH** | **Typical LC** | **Atypical LC** | **Large-cell NEC** | **Small-cell NEC** |
| Grade | Low | Low | Intermediate | High | High |
| Mitotic rate (x10 HPF) |  | <2 | 2-10 | >10 | >10 |
| Necrosis |  | None | Often (focal) | Often (diffuse) | Often (diffuse) |
| Morphology | Well-differentiated | Well-differentiated | Well-differentiated | Poorly-differentiated | Poorly-differentiated |
| Pathological characteristics | Characterised by widespread neuroendocrine cell hyperplasia and tumourlets | Cells are bland, polygonal in shape with round nuclei and finely dispersed chromatin. Cells are arranged in distinct organoid, trabecular, or insular growth patterns with a delicate vascular stroma.  Immunohistochemical staining for neuropeptides (i.e. CD56 chromogranin, synaptophysin) is usually present. | | Cells are arranged in organoid, trabecular, or palisading patterns.  Cells are large and present abundant eosinophilic cytoplasm. Nuclear chromatin tends to be granular. Cells present immunoreactivity for chromogranin and synaptophysin. | Round, oval and angulated cells, small amounts of cytoplasm, nuclei with dispersed "salt and pepper" chromatin  Tumour cells are usually positive for one or more of chromogranin or synaptophysin, although around 10 percent may be unreactive for neuroendocrine markers. |

LC: lung carcinoid; HPF: high-power fields: HPF; NEC: neuroendocrine carcinoma. DIPNECH: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. The mitotic rate was assessed over 10 consecutive high-power fields (HPF) in the mitotically most active area (“hottest spot”) of each sample at a magnification of x400 using a Nikon Eclipse microscope with a x40 objective and a x10 ocular lens (equivalent to 2mm2 field area).

### Supplementary material A (Fig 1)

**Figure 1 (supplementary material)**: Patients’ flow.

Out of the 166 patients screened, 46 were eligible. All patients included had pathological diagnosis of lung carcinoid and had a gallium DOTANOC-PET scan performed. LC: lung carcinoid.

Table 2

**Table 2**: Summary of patients’ characteristics (46 patients).

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **N** | **%** |
| **Gender** | Female | 24 | 52 |
| Male | 22 | 48 |
| **Age at diagnosis (years)** | Median (95% CI) | 57.9 (53.1-64.3); range 21.3-86.1 | |
| **NET familial syndrome** | Yes | 1 | 2 |
| **Hormone secretion related symptoms** | No | 46 | 100 |
| **Pathological subtype** | DIPNECH | 2 | 4 |
| Typical LC | 20 | 44 |
| Atypical LC | 16 | 35 |
| LC (typical/atypical not specified) | 8 | 17 |
| **Diagnosis performed based on** | Biopsy simple | 18 | 39 |
| Resection specimen | 27 | 59 |
| Not specified | 1 | 2 |
| **Ki-67 index** | Median (95% CI) | 3 (1.5-6.2) | |
| Not specified | 17 | 37 |
| **Mitotic count** | Median (95% CI) | 1 (0-2.5) | |
| Not specified | 20 | 43 |
| **Stage at initial diagnosis** | Localised | 29 | 63 |
| Locally advanced | 6 | 13 |
| Metastatic | 8 | 17 |
| Number of metastatic sites median (range) | 2 (1-5) | |
| Not specified | 3 | 7 |
| **Overall survival (months)** | Median (95% CI) | Nr (60.1-Nr) | |
| Events  (deaths) | 4 | 9% |

Nr: not reached; LC: lung carcinoid; NET: neuroendocrine tumour; N: number; % percentage; 95CI: 95% confidence interval; DIPNECH: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; Nr: not reached.

### Table 3

**Table 3**: Summary of patients’ treatment; information was not available for one of the patients (information for 45 patients is provided).

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **N** | **%** |
| **Curative resection** | Yes | 27 | 59 |
| **T Pathological Stage (based on resection specimen)** | T1 | 11 | 41 |
| T2 | 16 | 59 |
| **N Pathological Stage (based on resection specimen)** | N0 | 17 | 63 |
| N1 | 6 | 22 |
| Not specified | 4 | 15 |
| **Resection Margins** | R0 | 21 | 78 |
| R1 | 1 | 4 |
| Not specified | 5 | 18 |
| **RFS (months)** | Median (95% CI) | 44.9 (11.9-59.1) | |
| Events  (tumour relapse) | 11 | 41 |
| **Palliative treatment** | Yes | 18 | 39 |
| **Type of treatment** | SSA | 12 | 67 |
| Chemotherapy | 4 | 23 |
| PRRT | 1 | 5 |
| Palliative surgery | 1 | 5 |
| **PFS (months)** | Median (95% CI) | 17.9 (3.02-Nr) | |
| Events  (progression) | 5 | 28 |

T: tumour size; N: lymph node; R0: complete resection; R1: microscopic involvement of resection margin; N: number of patients; % percentage; 95CI: 95% confidence interval; RFS: relapse-free survival; PFS: progression-free survival; SSA: somatostatine analogue; PRRT: Peptide Receptor Radionuclide Therapy; Nr: not reached.

### Supplementary material B (Table 4)

**Table 4 (Supplementary material)**: Size of largest metastatic deposit and tracer uptake by metastatic site: primary lung tumour, liver, lung, bone and lymph node metastases.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Primary tumour in situ | Liver metastases | Lung metastases | Bone metastases | Lymph node metastases |
| **Patients with these lesions present at the time of performing 68Ga-DOTANOC scan (N (%))** | 16 (24%) | 10 (21%) | 10 (21%) | 13 (28%) | 12 (26%) |
| **If yes, maximum size of metastatic deposit within this site (cm; median (95% CI))** | 4.3 (1.9-21.1) | 7.5 (1.8-7.8) | 2.7 (1.2-13) | 2.15 (1.5-2.5) | 2.6 (1.9-3.6) |
| **If present, did this tumour site show tracer uptake in the** **68Ga-DOTANOC? (Sensitivity) (N (%; 95% CI))** | 13/16 (81%; 95% CI 67.2-100) | 8/10 (80%; 95% CI 49.8-100) | 8/10 (80%; 95% CI 49.8-100) | 13/13 (100%; 95% CI 100-100) | 11/12 (91.7%; 95% CI 73.3-100) |
| **ROC curve (AUC), prediction of tracer uptake according to size of metastases** | 0.9231 | Cannot calculate\* | 1 | Cannot calculate\* | Cannot calculate\* |
| **Most informative size cut-off to predict tracer uptake (cm) (Se/Sp)** | 1.4  (Se 92% / Sp 100%) | Cannot calculate\* | 2  (Se 100% / Sp 100%) | Cannot calculate\* | Cannot calculate\* |

N: number of patients; % percentage; 95% CI: 95% confidence interval; cm: centimeter; ROC: receiver operating characteristic; AUC: area under the curve; Se: sensitivity; Sp: specificity. \*ROC curve cannot be drawn due to not having enough information for the analysis (i.e. all lesions with maximum size available showed tracer uptake).

### Table 5

**Table 5**: Rationale and outcome (total of 47 scans) and clinical impact (information available for 42 scans) of 68Ga-DOTANOC PET imaging.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | **Outcome of the 68Ga-DOTANOC** | | | **Impact of the 68Ga-DOTANOC on patients’ management** | |
| How many showed uptake? (N=47) | How many added extra information? (N=46) | How many changed management? (N=38) | Identified new sites of disease (N=42) | Changed options of treatment (in terms of PRRT) (N=42) |
|  | TOTAL | 27/47 (57%) | 17/46 (37%) | 10/38 (26%) | 9/42 (21%) | 1/42 (2%) |
| **Rationale for performing 68Ga-DOTANOC** | **Confirmation of NET (N=4)** | 3/4 (75%) | 2/4 (50%) | 1/3 (33%) | 1/4 (25%) | 0/4 (0%) |
| **Identification of primary tumour (N=2)** | 2/2 (100%) | 0/1 (0%) | 0/1 (0%) | 0/2 (0%) | 0/2 (0%) |
| **Post-surgical re-staging (N=19)** | 3/19 (16%) | 4\*/19 (21%) | 2&/17 (12%) | 3/19 (16%) | 0/19 (0%) |
| **Staging (patients with cancer) (N=19)** | 16/19 (84%) | 8/19 (42%) | 4/14 (29%) | 3/15 (20%) | 0/15 (0%) |
| **Consideration of PRRT (N=3)** | 3/3 (100%) | 3/3 (100%) | 3$/3 (100%) | 2/3 (67%) | 1/3 (33%) |

Four reasons for performing 68Ga-DOTANOC imaging were evaluated: confirmation of diagnosis of NET (4 scans; 9%), identification of primary tumour in patients originally diagnosed with unknown primary malignancy (2 scans; 4%), post-surgical re-staging in patients who were thought to be “cancer free” after curative resection (19 scans; 40%), completion of staging (for patients known to have localised, locally advanced or metastatic cancer *in situ*) (19 scans; 40%) and pre-PRRT assessment (3 scans; 7%). Outcome was measured as per the rate of pathological tracer uptake, whether the imaging added or not additional information and whether that additional information impacted patients’ management or not. Data information regarding the additional information provided by the 68Ga-DOTANOC PET scan (if any) was collected whenever available. **\***3 pts were identified to have metastatic disease; 1 patient showed suspicious uptake within lungs which did not change the management (patient continued follow-up); **&**for one of the patients in whom metastatic disease was identified, information regarding impact on management was not available; $two patients were found to have too much tumour burden for PRRT. NET: neuroendocrine tumour, PRRT: Peptide Receptor Radionuclide Therapy; N: number of scans; %: percentage.

### Figure 2

**Figure 2**: Bone metastasis identified in patient who underwent a post-surgical re-staging 68Ga-DOTANOC PET imaging.

### Supplementary material C

**Factors predictive of change in patients’ management**

Our data were unable to specify which population of patients may benefit more from performing a 68Ga-DOTANOC-PET scan. Logistic regression was performed to explore selected baseline characteristics which may be able to identify patient subgroups with more benefit from performing 68Ga-DOTANOC PET in terms of impact on patients’ management. Univariate analysis did not identify any significant factors: type of LC (OR (odds ratio) 2.3 (95% CI 0.5-11.6); p-value 0.308), stage (OR 1.4 (95% CI 0.5-3.7); p-value 0.474), previous curative resection (OR 1.3 (95% CI 0.3-6.2); p-value 0.744), aim of the 68Ga-DOTANOC (all p-values > 0.05). Other factors such as Ki-67 index, mitotic count and sites of metastases were also not significant (all p-values > 0.05; full data not shown).

**Survival analyses**

Baseline factors and 68Ga-DOTANOC results (such as SUVmax) were explored as potential prognostic factors impacting OS, RFS or PFS. Tracer uptake and SUVmax did not show impact on OS (Hazard Ratio (HR) 0.2 (95% CI 0.01-3.3; p-value 0.233) and HR 0.8 (95% CI 0.6-1.2; p-value 0.385), respectively), RFS (HR 2.5 (95% CI 0.2-27.6; p-value 0.457) and HR 1.01 (95% CI 0.9-1.05; p-value 0.840), respectively) or PFS (HR 1.8 (95% CI 0-not estimated; p-value 1) and HR 1.04 (95% CI 0.9-1.1; p-value 0.249), respectively). No prognostic factors were identified (all p-values >0.05; full data not shown).

### Table 6

**Table 6**: Summary of the largest LC series exploring the role of 68Ga-DOTA-PET imaging.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author, reference | Number of LC patients | Total number of patients | Tracer | Findings |
| Kayani *et al*. [36] | 18 | 18 | 68Ga-DOTATATE | Typical and atypical LC showed higher and lower uptake of 68Ga-DOTATATE, respectively. DIPNECH showed no uptake. |
| Jindal *et al*. [37] | 20 | 20 | 68Ga-DOTATOC | Typical and atypical LC showed higher and lower uptake of 68Ga-DOTATOC, respectively.  Ratios of SUVmax on 68Ga-DOTATOC to that 18F-FDG were significantly higher in typical LC compared with atypical LC. |
| Jindal *et al*. [38] | 19 | 19 | 68Ga-DOTATOC | Tumour detection rate of 95%. SUVmax ranged from 1.1 to 66, with a median value of 21.6. In one patient (out of 20), 68Ga-DOTATOC PET revealed additional lesions: recommended to be included in the diagnostic work-up of these patients. |
| Ambrosini *et al*. [39] | 11 | 11 | 68Ga-DOTANOC | 68Ga-DOTANOC was useful in LC patients because it led to a better evaluation of the extent of the disease, detecting higher number of lesions in 5 patients (out of 11) and providing additional information in nine of 11 patients leading to the changes in the clinical management of three of nine patients (33%). |
| Venkitaraman *et al*. [32] | 26 | 32 | 68Ga-DOTATOC | The sensitivity, specificity and accuracy of 68Ga-DOTATOC in the diagnosis of LC were 96%, 100% and 97%, respectively; whereas those of 18F-FDG were 78%, 11% and 59%, respectively. Authors concluded that 68Ga-DOTATOC was useful for the evaluation of LC, while 18F-FDG PET suffered from low sensitivity and specificity. |
| Lamarca *et al*. (This series) | 46 | 46 | 68Ga-DOTANOC | 68Ga-DOTANOC PET often changes management in patients with LC tumours (26%) and should, therefore, be part of the staging imaging (for both metastatic and resected patients) regardless of site of metastases and grade. |

68Ga-DOTA-PET: 68-Gallium-radiolabeled positron emission tomography; LC: lung carcinoid.

### Table 7

**Table 7**: Summary of recommendations (applicable whenever 68Ga-DOTA-PET is available).

|  |  |
| --- | --- |
| Recommendations (applicable whenever 68Ga-DOTA-PET is available) | |
| #1 | 68Ga-DOTA-PET imaging should be performed regardless of type of LC (typical/atypical), with the exception of DIPNECH. 68Ga-DOTA-PET could be beneficial to exclude presence of small foci of typical LC in patients with DIPNECH, but its role in DIPNECH seems, otherwise, limited. |
| #2 | 68Ga-DOTA-PET imaging should be performed regardless of site (organ) and size of metastases. |
| #3 | 68Ga-DOTA-PET should be considered and incorporate to the baseline imaging to be performed to all patients following curative resection of LC due to the potential for identification of occult metastases; exceptions may include pT1aN0R0 typical LC and DIPNECH. Its role pre-surgery could not be explored in the current study but would be worth considering due to the same rational. |
| #4 | 68Ga-DOTA-PET should be part of the baseline assessment of patients with advanced LC and part of the multidisciplinary discussion, in order to provide information regarding tumour distribution and tumour burden. |
| #5 | All patients to be considered for PRRT should require previous assessment with 68Ga-DOTA-PET whenever available. |

68Ga-DOTA-PET: 68-Gallium-radiolabeled positron emission tomography; DIPNECH: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; LC: lung carcinoid; PRRT: peptide receptor radionuclide therapy; R0: complete resection.