Bronchial NET: A Multimodality Imaging Review

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Learning objectives

- An introduction to bronchial neuroendocrine tumours (NET).
- Multi-modality cased based discussion of imaging appearances of bronchial NET and associated extra pulmonary metastases.
- The role of nuclear medicine (NM) in the therapy and treatment of bronchial NET.
Background

An Introduction to Bronchial NET

Bronchial NET’s arise from neuroendocrine differentiation of kulchitzky cells that are normally present in the bronchial mucosa.

This review does not discuss poorly differentiated bronchial NETs namely small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC).

Bronchial NET account for **25% of all neuroendocrine tumours** and 1-2% of all pulmonary neoplasms.

These can be divided into two broad categories

- **Typical carcinoid** (80-90%)
- **Atypical carcinoid** (10-20%)

Classification is made on histological findings (e.g. mitotic count, presence or absence of necrosis)

Clinical presentation:

- Haemoptysis
- Cough
- Recurrent pulmonary infections
- Wheezing
- Carcinoid syndrome (rare)
- Cushing’s syndrome (rare)

Imaging features of Bronchial NET

Majority of tumours arise **centrally** and involve the main lobar or segmental airways (60-70%).
The mean age of presentation is **46 years** and is lower than the mean age for presentation of primary lung cancer.

Typical carcinoids are predominantly centrally located and present with symptoms of **airway obstruction** (cough, wheeze, haemoptysis). They present earlier than atypical carcinoid tumours.

1. Carcinoid tumours can be centrally or peripherally located
   - Chest radiographs may show a well defined hilar or a **peri-hilar mass** (non specific)(**Fig. 1**)

2. There may also be associated distal parenchymal disease such as **atelectasis or consolidation**. (**Fig. 2&3**)

3. Distal parenchymal disease may manifest as mucus plugging, where this is a **'gloved finger' pattern** when multiple contiguous bronchi are dilated. (**Fig. 4**)

4. On CT, bronchial neuroendocrine tumours appear as an ovoid or spherical mass/nodule with a well defined and slightly **lobulated border**.

The They are typically located close to central bronchi or distal to segmental bronchi (peripheral carcinoids)(**Fig 5**).

5. Bronchial NET can present as a nodule located entirely within the lumen of a segment of bronchus (**Fig 6**).

6. **Eccentric calcification** is common, especially in central carcinoids, with foci of calcification or even ossification seen at histologic analysis in up to 30% of cases (**Fig 7**).

7. Carcinoids are characteristically highly vascular. On CT, a carcinoid in a peri-hilar location with marked, homogeneous contrast enhancement may mimic a pulmonary varix or pulmonary artery aneurysm.

However, not all carcinoids enhance, and enhancement alone can neither confirm or refute a diagnosis of bronchial carcinoid (**Fig.8**)

8. Although MRI has limited value in the diagnosis of bronchial NET, Bronchial carcinoids have high signal intensity on T2- weighted and short-inversion-time inversion recovery MR.
MR Imaging may be helpful in distinguishing small carcinoids from the adjacent normal vascular structures (Fig 9).

Use of MR imaging should also be considered when an ACTH-producing carcinoid is suspected but is not found at CT.

**The use of NM in imaging Bronchial NET:**

- Some carcinoid tumors express somatostatin receptors, which allow imaging with radio-labelled somatostatin analogues.
- PET/CT with $^{68}$Ga labelled somatoatatin analogues (eg $^{68}$Ga-DOTA Octreotate) is more sensitive than SPECT/CT with $^{111}$In Octreotide (better spatial resolution and higher receptor affinity).
- Somatostatin receptor imaging is helpful in staging, detecting occult tumors (particularly those with para-neoplastic symptoms), and may be helpful in treatment planning.
- Tracer uptake with $^{18}$fluorine fluorodeoxyglucose (FDG) is usually lower in TC than AC (the latter having a higher proliferation index). Many carcinoid tumors do not exhibit increased FDG uptake (Fig 9).

**Imaging features in extrapulmonary metastases of Bronchial NET**

- Both typical and atypical carcinoids may be associated with hilar or mediastinal lymphadenopathy due to reactive hyperplasia from recurrent pneumonia or to lymph node metastasis. **Lymph node metastases** occur more frequently with atypical carcinoids. (Fig.10)
- Lymph node involvement may be the first sign of recurrence.
- In addition to lymph node metastases, bronchial carcinoids tend to metastasise to liver, lung and bone (Fig 11).
- Bone metastases are frequently sclerotic and may have the appearance of multiple small punctate sclerotic deposits
- Neuroendocrine hepatic metastases may be difficult to identify on CT as they may be iso-intense to the liver on portal venous phase (PVP) imaging.
- A combination of pre-contrast, hepatic arterial-dominant phase (HAP) and PVP imaging will improve the sensitivity of detection, as in some cases a lesion may only be seen on one of the three phases (Fig 12).
• Evidence points to the HAP being particularly helpful in the detection of liver metastases.

• Bronchial NET metastases can commonly manifest outside the liver, lungs (Fig 13) and bones (for example the soft tissues) and it is important to look thoroughly for such metastases due to their hypervascular nature (Fig 14&15).
Fig. 1: Chest radiograph showing a large right hilar mass (bronchial NET)

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Fig. 2: CT chest demonstrating a subcarinal mass which occludes the bronchus intermedius and the right lower lobe bronchus with consequent right lower lobe collapse

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**Fig. 3:** CT chest demonstrating a subcarinal mass which occludes the bronchus intermedius and the right lower lobe bronchus with consequent right lower lobe collapse

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Fig. 4: Single slice axial CT demonstrating a 13-mm-diameter nodule (arrow) in the superior segmental bronchus of the right lower lobe with distal mucus plugging (arrowheads)

**Fig. 5:** Axial CT slice showing large lobulated well defined right hilar mass

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**Fig. 6:** Axial and coronal CT images of an endobronchial mass within the left lobe segmental bronchus.

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**Fig. 7:** Left: Axial CT scans showing a mass with eccentric calcification Right: Nodular calcification and calcification of the adjacent right pleura (arrows)

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Fig. 8: Axial contrast-enhanced CT scan (mediastinal windowing), the nodule (arrow) demonstrates marked contrast enhancement and mimics a vascular structure

**Fig. 9:** Above: Typical carcinoid in a 56-year-old man. Coronal reformatted image shows a 41-mm-diameter, moderately enhancing, homogeneous mass (arrow) in the right lower lobe. Below: On a PET image, the mass demonstrates low grade FDG uptake (arrow)

Fig. 10: Above: T1-weighted MR image shows a well-circumscribed hyperintense nodule in the middle lobe. Below: On a short-inversion-time inversion recovery MR image, the nodule demonstrates high signal intensity

**Fig. 11:** Axial PET/CT showing Increased uptake in the left hilar area of soft tissue thickening compared to the previous scan is suspicious for nodal recurrence of the neuroendocrine tumour.

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**Fig. 12:** Ga-68 and FDG PET scans showing avid bone metastasis with both tracers, but mediastinal disease only demonstrating significant uptake on the Ga-68 in a patient with bronchial NET.

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**Fig. 13:** Left: CT shows this segment 3 low attenuation lesion has increased in size from 9mm to 20mm compared to previous imaging. The density is higher than a simple liver cyst and therefore is likely to represent a metastasis. Right: CT shows multiple low attenuation lesions within both lobes of the liver, in keeping with metastases.

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**Fig. 14:** Axial CT (lung windows) shows multiple pulmonary metastases, the largest one measuring 12mm as first radiological evidence of recurrence following surgical resection of a right upper lobe bronchial NET tumor

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**Fig. 15:** CT shows within the posterior subcutaneous tissues of the thorax, there is a new 16mm soft tissue nodule, which appears slightly hypervascular.

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Fig. 16: A further deposit is seen superficially in the left lateral chest wall, which has increased in size measuring 10mm and also appears hypervascular in keeping with metastases.

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Findings and procedure details

Treatment options in Bronchial NET

- Surgery (curative or debulking)
- Somatostatin analogues (SSAs)
- Locoregional therapies e.g. radiofrequency ablation or chemoembolisation
- Systemic chemotherapy
- Targeted therapy e.g. Everolimus (rapamycin inhibitor) now licenced by FDA for use in progressive unresectable disease following Radiant-4 study
- Peptide Receptor Radionuclide therapy (PRRT) eg $^{177}$Lu DOTA-Octreotate

Nuclear medicine radiopharmaceuticals labelled with B emitters can be used in the treatment of bronchial NET through peptide radionuclide therapy (PRRT).

Many NETs express an overabundance of somatostatin receptors. Physiologically, the hormone somatostatin binds to somatostatin receptors (SSR). This interaction is exploited in PRRT.

Somatostatin analogues such as Octreotide and Octreotate are synthetic versions of somatostatin that will bind to SSRs (Fig 16&17).

Peptide radionuclide therapy (PRRT)

- Synthetic somatostatin peptides such as octreotate are conjugated with a $\beta$ particle emitting radionuclide to form a radiopharmaceutical with the aim of delivering a high dose of radiation to the NET.
- $^{177}$Lutetium ($^{177}$Lu) and $^{90}$Yttrium ($^{90}$Y) are the most commonly used radionuclides.
- Patients typically undergo 3-4 therapy treatments at 2-3 month intervals.
- PRRT is an option for therapy in patients who:
  - Have advanced and/or progressive NETs
  - Are not surgical candidates
  - Have symptoms that do not respond to other medical therapies
• The main goals of PRRT are to provide symptom relief, to stop or slow tumour progression and to improve overall survival.

**PRRT in bronchial NET therapy**

**Benefits:**

Targeted therapy: limits radiation to healthy tissue as highly selective to NET cells.

Effective in controlling symptoms in patients with advanced or progressive disease.

Slows progression of disease.

Well tolerated

**Limitations:**

Not curative

Initial side effects: nausea (25%) and vomiting (10%) primarily during amino acid infusion (given for renal protection).

Delayed side-effects: bone marrow toxicity (grade 3 or 4, up to 9%), renal impairment (<1%). More likely if heavily pre-treated.
Fig. 17: Prior to therapy: CT imaging demonstrating a large well-defined mediastinal mass occupying the anterior left hemithorax. It contains multiple enhancing foci with central low density necrotic foci. There is deviation of the trachea and oesophagus to the right.

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Fig. 18: Post Therapy Imaging: 177Lu DOTA-Octreotide. Uptake seen within the mediastinal mass. 177Lu decays predominantly by # particle emissions. There are some gamma photon emissions which allow post therapy imaging using SPECT/CT. Uptake seen within the mediastinal mass

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Conclusion

1. Neuroendocrine tumours of the lung present in a **younger** patient cohort than other lung cancers and are more often **endobronchial** in location.

2. Typical imaging features include a **lobulated peri-hilar mass** with **calcification**, **distal parenchymal disease** and **enhancing nodules**. Metastatic spread is classically to the lymph nodes as well as the lungs, bone and liver.

3. Somatostatin receptor imaging useful in staging and if positive may allow additional treatment options in the form of **PRRT**, providing symptom relief, to stop or slow tumour progression and improve overall survival.
References


