# Case report: Positron emission tomography fails to detect pulmonary adenocarcinoma recurrence after radiofrequency ablation

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ABSTRACT

We describe the case of late recurrence of a focus of invasive mucinous adenocarcinoma (formerly mucinous bronchioloalveolar carcinoma) following radiofrequency ablation, despite a negative positron emission tomography/computed tomography scan at 13 months following the ablation. A computed tomography scan performed at 24 months demonstrated unequivocal recurrence of the lesion. Combined positron emission tomography/computed tomography has been described as an adequate modality for the follow-up of thermally ablated pulmonary lesions. However, its utility in the follow-up of well-differentiated pulmonary adenocarcinoma may be limited. Lesion activity may be underestimated by an inherently low metabolic activity. Small lesions may also be susceptible to partial volume effect. Long-term imaging follow-up of well-differentiated pulmonary adenocarcinoma beyond two years after thermal ablation is prudent to avoid missing late recurrence.





## CASE REPORT

### CASE REPORT

In September 2008, a 50-year-old woman was referred to our department for computed tomography (CT) guided radiofrequency ablation (RFA) of a left upper lobe focus of invasive mucinous adenocarcinoma. The patient had been receiving treatment for multifocal pulmonary adenocarcinoma for 6 years prior to referral; this included right upper lobectomy in 2002, left lower lobectomy in 2004, and radiation therapy for recurrence of the right sided lesion in 2007. The present lesion of interest was located inferiorly in the left upper lobe, and measured 15.9 mm in longest axial diameter (Figure 1). Apart from changes consistent with the patient's previous treatments, the CT was otherwise unremarkable. Positron emission tomography (PET) was not performed as part of workup of this new lesion, due to the patient's extensive history of multifocal disease.

The patient elected to undergo thermal ablation of the lesion, rather than surgery, due to concerns of surgical morbidity related to previous surgical and radiotherapeutical procedures. Under sterile conditions and CT guidance, a 15cm (2cm active tip) Cooltip Radiofrequency Ablation Device (Covidien, Boulder, Colorado, USA) was initially inserted eccentrically through the lesion, which was in proximity to larger pulmonary vessels (Figure 2). Three overlapping ablations were performed, totalling 25 minutes ablation time. The intra-procedural alveolar haemorrhage remained clinically silent.

Follow-up CT scans of the chest was performed at 3 months (Figure 3) and 6 months (Figure 4) following the ablation, demonstrating initial cavitation and subsequent progressive resolution of the ablated left upper lobe lesion, with residual scar formation. No other suspicious lesions were identified on these scans. 18F-fludeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was not utilised in ablation follow-up, as it was not part of the protocol within our institution.

A follow-up CT scan of the chest was again performed at 12 months following the ablation; the ablated lesion did not

demonstrate any CT evidence of recurrence (Figure 5). However, on this scan a new right-sided retrocardiac intrapulmonary paramediastinal lesion was identified, located posterior to the right atrium at the level of T8, measuring 25.8 x 20.8 x 12.6 mm (Figure 6). As part of tumor staging, an FDG-PET/CT scan was performed, at 13 months post ablation of the left-sided lesion. Negligible FDG uptake was registered at the previous left upper lobe ablation site; this was considered benign (Figure 7). The new right-sided lung lesion demonstrated minor FDG-uptake (Figure 8). There was no other evidence of local or distant metastatic disease.

The patient received radiotherapy for the new right-sided lung tumor, with subsequent follow-up CT scans performed at 6-monthly intervals. One such monitoring CT scan, performed 24 months following initial referral, demonstrated unequivocal recurrence of the previously ablated left-sided lesion, measuring 19.9 x 17.4 x 14.9 mm (Figure 9).

## DISCUSSION

### *Etiology and Demographics*

Bronchioloalveolar carcinoma (BAC) represents a spectrum of disease ranging from noninvasive, to multifocal advanced disease [1]. The disease encompassed by the term BAC includes several subgroups of differing clinical and histopathological significance [1]. In response to this, a 2011 study sponsored by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS), published a new classification of adenocarcinoma of the lung [2]. Within this classification, the entity previously known as bronchioloalveolar carcinoma (BAC) has been divided into five distinct entities [2]: 1) adenocarcinoma in situ (AIS); 2) minimally invasive adenocarcinoma (MIA); 3) lepidic predominant adenocarcinoma, nonmucinous; 4) acinar, papillary, micropapillary or solid predominant adenocarcinoma, plus a lepidic component; 5) invasive mucinous adenocarcinoma. The committee has acknowledged that this new terminology will be a major adjustment for radiologists; thus, it has been suggested that the disease spectrum be referred to as "formerly BAC" [1].

Formerly BAC demonstrate lepidic and/or aerogenous growth on histology [3]. The disease constitutes between 2 to 5% of all primary lung cancers [3]. Most epidemiological studies support a higher prevalence in women than in men [4-6]. Onset is typically at a younger age than other types of non-small-cell lung carcinoma (NSCLC) [7].

Several studies have suggested that the proportion of non-smoking patients with formerly BAC is higher than in other types of lung carcinoma [6-8]. Patients with nonmucinous formerly BAC are more likely to be nonsmokers [9]. Other proposed risk factors for formerly BAC include viral infection and pulmonary scarring [7].

### *Clinical and Imaging Findings*

The most common finding of formerly BAC on plain radiograph is a solitary peripheral nodule or mass of solid consistency [6]. 30% of all BAC are multifocal [6].

Early focal formerly BAC may have three appearances on CT: 1) pure ground glass opacification (GGO), appearing as hazy increase in attenuation without obscuration of bronchovascular markings; 2) solid, with complete obscuration of bronchovascular markings; 3) mixed, with both of the above components [10]. Features of serial CT examination that may be suggestive of malignancy include increased size of GGO, evolution of a solid region in an area of GGO, or increased size of the solid component in a mixed lesion [10]. Advanced disease may be unifocal or multifocal, with pseudocavitations and air-bronchograms [10]. The CT angiogram sign may be present in contrast-enhanced CT, where enhancing vessels have higher attenuation than the surrounding mucinous lesion [10].

FDG-PET may provide an advantage over CT in the investigation of malignant pulmonary disease through its ability to demonstrate the metabolic activity of tissues. However, there may be a high false-negative rate in the detection of BAC with FDG-PET, due to the slow proliferation and well-differentiated nature of the disease [7, 11]. A recent small series of seven patients with BAC found negative FDG-PET scans in four (57%) of the patients [11]. It has been suggested that positive scans are more likely to occur in patients with multifocal BAC [10]. The literature relating to ablation therapy of bronchioloalveolar carcinoma is in its early stages, and as such, there is no consensus relating to pre-ablation FDG-PET/CT.

### *Treatment and prognosis*

The gold standard management for solitary BAC is surgical excision [3, 7]. Thermal ablation therapies, including microwave and radiofrequency ablation, have become increasingly utilised in those patients who are ineligible for resection.

Ablation therapies aim to destroy the target malignant cells whilst minimising damage to surrounding normal parenchyma [12]. Since histopathological assessment of ablated tumour margins is not possible, close follow-up of patients undergoing lung tumour ablation is essential. However, there is no consensus in the literature regarding the appropriate modality, frequency or length of follow-up.

The prognosis of formerly BAC is considered better than that of other types of NSCLC, with micropapillary subtype having the worst prognosis; however, estimates are varied [3]. Prior to the new classification, formerly BAC was estimated to have overall survival rates of 72.5% at one year, and 41% at five years, with a mortality rate of 80% [3].

Our case describes the recurrence of a focus of formerly BAC following CT-guided radiofrequency ablation (RFA), despite a negative FDG-PET/CT scan at 13 months post ablation. The use of CT in the follow-up of pulmonary malignancies following ablative therapies is limited by the

difficulty in distinguishing treatment-related change from tumor recurrence/incomplete ablation [13]. Combined FDG-PET/CT has been recommended by a small number of authors for follow-up of ablated lung tumours [13, 14]. As previously described, FDG-PET of formerly BAC is fraught by a high rate of false-negatives [7, 11]. Well-differentiated pulmonary adenocarcinomas in particular exhibit mild degrees of atypia, desmoplasia and mitosis on histologic examination, which may lead to lower peak standardised uptake values (SUVs) when compared to other types of lung tumors [15]. In the short-term following lesion ablation, this problem is compounded, as inflammation and tissue regeneration can result in increased tracer uptake at the ablated site [16]. Most authors recommend that FDG-PET not be performed until at least 3 months post-ablation, to reduce the risk of false-positive results [13, 14].

The standardised uptake value (SUV) on PET scans has been used to evaluate local tumour progression following ablation of pulmonary tumours. In 2003, Herrera et al described a modification of the Response Evaluation Criteria in Solid Tumours (RECIST) to assess treatment response following lung tumour ablation, with one of their criteria for complete response being an SUV of <2.5 on FDG-PET [17]. However, SUV may not be the most reliable predictor of ablation therapy success. Not only is there a risk of false-negatives in the identification of formerly BAC, SUV may be unreliable in small lung lesions, as partial volume effects may lead to an underestimation of glucose uptake [15].

***Differential Diagnosis***

Differential diagnoses for formerly BAC include: pulmonary metastases, pneumonia, pulmonary hamartoma and granuloma [18-20]. These lesions may be difficult to differentiate on plain chest radiography. CT provides more detailed information to distinguish between potential diagnoses. As described, the CT appearance of BAC may appear as a poorly defined hazy area of increased attenuation, with or without a solid component and areas of pseudocavitation [10]. Pulmonary metastases are typically enhancing nodules of varied margins, with associated lymphadenopathy [18]. Pulmonary pneumonia is often associated with atelectasis [19]. A pulmonary hamartoma is often more sharply marginated, with areas of calcification and fat [18, 20]. Similarly, a granuloma may have associated areas of calcification, with associated hilar lymph node calcification [18, 20].

***Conclusion***

The literature to date has failed to address the issue of false-negatives in follow-up FDG-PET/CT scans after pulmonary thermal lesion ablation. To our knowledge, ours is the first described case of a false-negative FDG-PET/CT scan beyond one year following ablation. Ablation therapy of pulmonary malignancies remains an emerging field. It is clear that further research is needed into the ideal modality, and length of follow-up of thermally ablated pulmonary lesions.

## TEACHING POINT

The utility of FDG-PET/CT scans for well-differentiated pulmonary adenocarcinoma may be limited by the lesions' low metabolic activity, and the susceptibility of small lesions to partial volume effect. Long-term imaging follow-up beyond two years after thermal ablation is considered prudent to avoid missing late local recurrence and allows for potential re-treatment.

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FIGURES

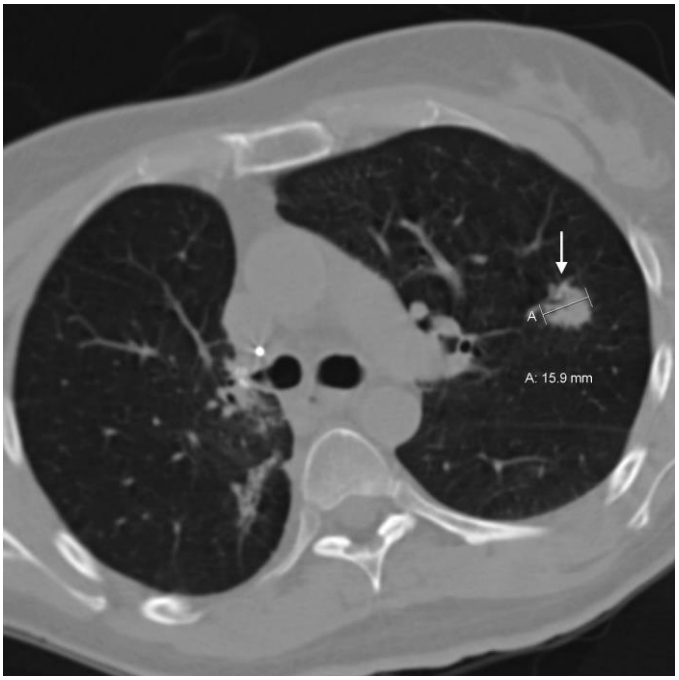



**Figure 1:** 50-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, presents for radiofrequency ablation of a new left upper lobe lung lesion. FINDINGS: Left upper lobe lung lesion, longest axial diameter 15.9 mm, with features consistent with pulmonary adenocarcinoma. TECHNIQUE: Non-contrast-enhanced CT scan of the chest. (Siemens Somatom Volume Zoom CT Scanner. Protocol: 56 mAs, 140 kVp, 3.0 mm slice thickness, no intravenous contrast)

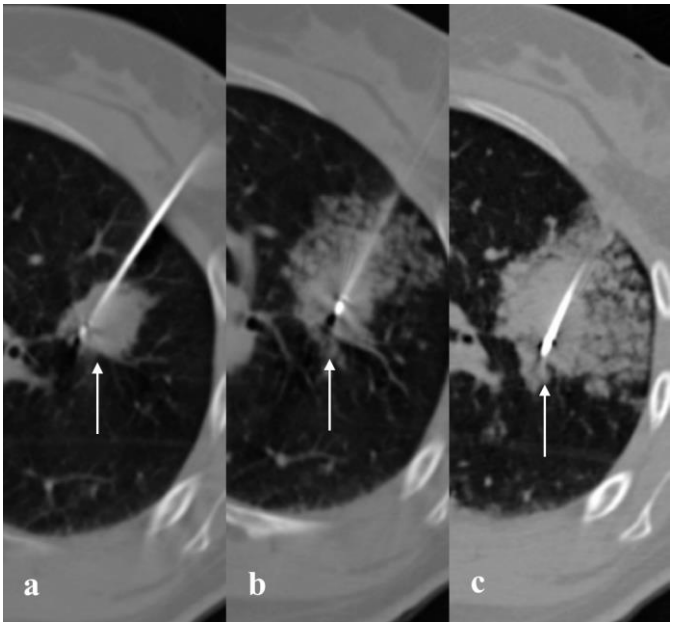



**Figure 2:** 50-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, presents for radiofrequency ablation of a new left upper lobe lung lesion. FINDINGS: a) Radiofrequency probe located medially within the lesion; b) radiofrequency probe located centrally within the

lesion; c) radiofrequency probe located laterally within the lesion. Progressive increase in parenchymal haemorrhage observed across the image series, as indicated by arrow tips. TECHNIQUE: Non-contrast-enhanced CT scan of the chest. (Cooltip Radiofrequency Ablation Device, Covidien, Boulder, Colorado, USA; Siemens Somatom Volume Zoom CT Scanner, Protocol: 56 mAs, 140 kVp, 3.0 mm slice thickness, no intravenous contrast)

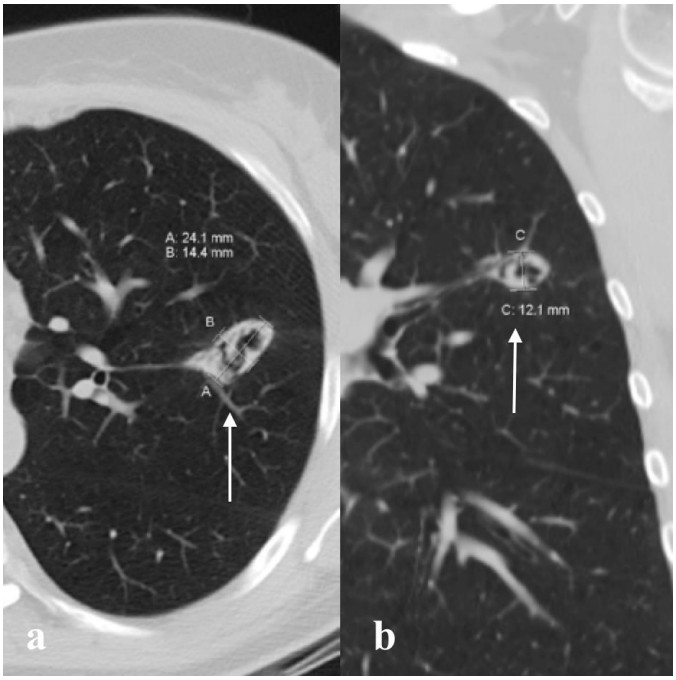



**Figure 3:** 50-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, presents for follow-up scan 3 months following radiofrequency ablation of a left upper lobe lesion. FINDINGS: a) Axial view, and; c) coronal view of the chest, lung windows, demonstrate partial resolution and central cavitation of the ablated left upper lobe lesion. TECHNIQUE: Non-contrast-enhanced CT scan of the chest. (Siemens Definition CT Scanner; Protocol: 56 mAs, 140 kVp, 3.0 mm slice thickness, no intravenous contrast)

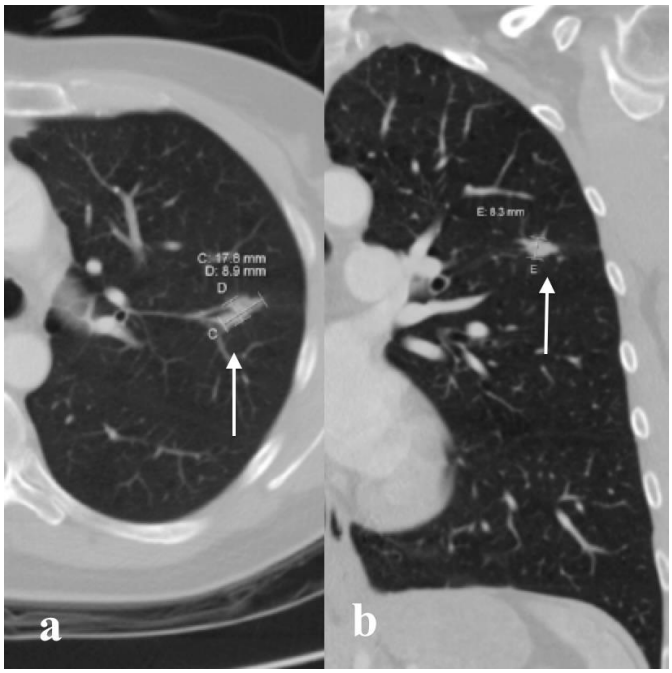



**Figure 4:** 50-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, presents for follow-up scan 6 months following radiofrequency ablation of a left upper lobe lesion. FINDINGS: a) Axial view, and; c) coronal view of the chest, lung window, demonstrate further tissue shrinkage at the site of the previously ablated tumour, with no evidence of local tumour progression. Scarred remnant measures 17.8 x 8.9 x 8.3 mm. TECHNIQUE: Contrast-enhanced CT scan of the chest. (Phillips Brilliance 64 Slice CT Scanner; Protocol: 105 mAs, 120 kVp, 3.0 mm slice thickness; Images obtained 30 seconds following intravenous injection of 75 ml Iopromide 300)

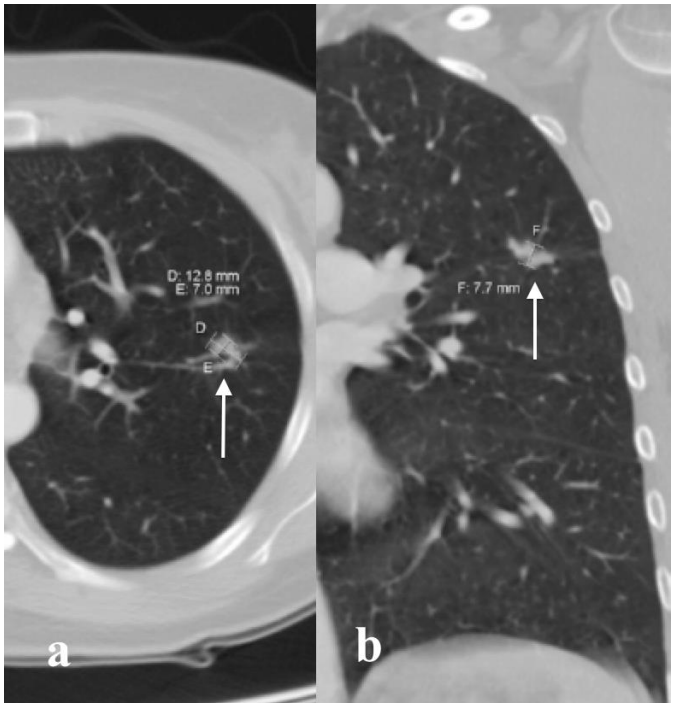



**Figure 5 (right):** 51-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, presents for follow-up scan 12 months following radiofrequency ablation of a left upper lobe lesion. FINDINGS: a) Axial view, and; c) coronal view of the chest, demonstrate further cavitation of the ablated left upper lobe lesion, which now measures 12.8 x 7.7 x 7.0 mm. TECHNIQUE: Contrast-enhanced CT scan of the chest. (Phillips Brilliance 64 Slice CT Scanner; Protocol: 126 mAs, 120 kVp, 3.0 mm slice thickness; Images obtained 30 seconds following intravenous injection of 75 ml Iopromide 300)

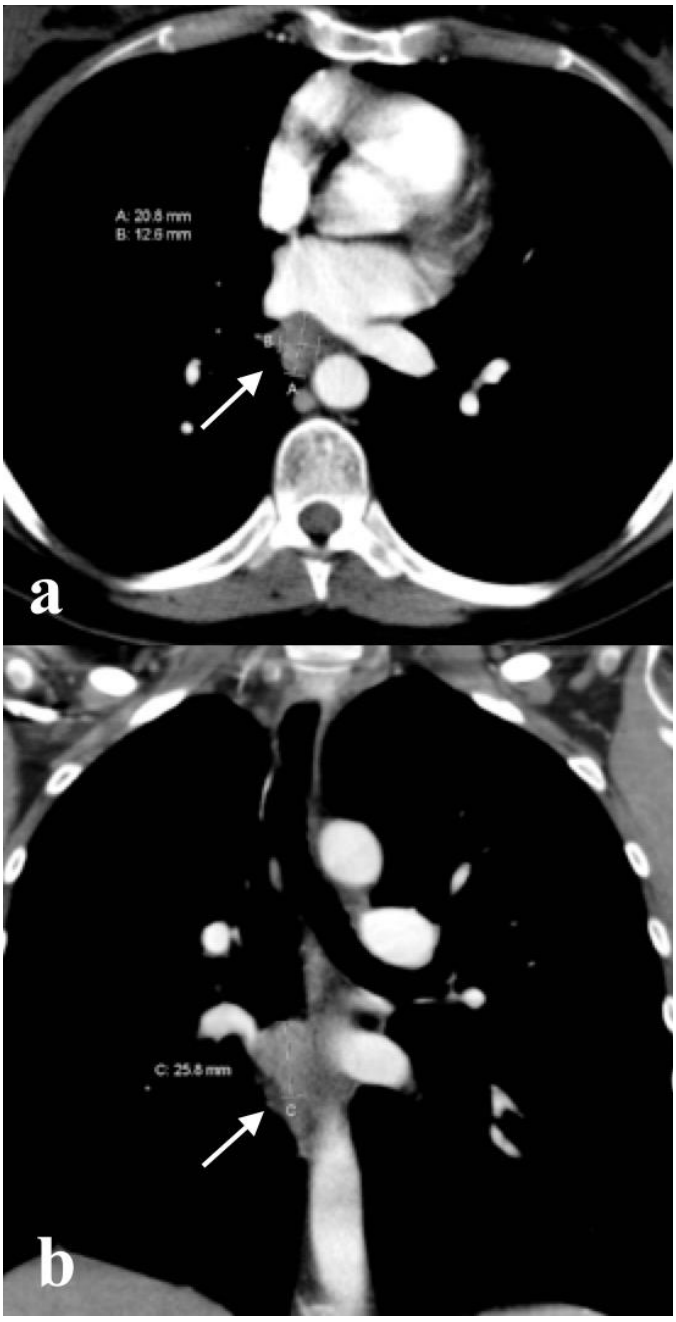
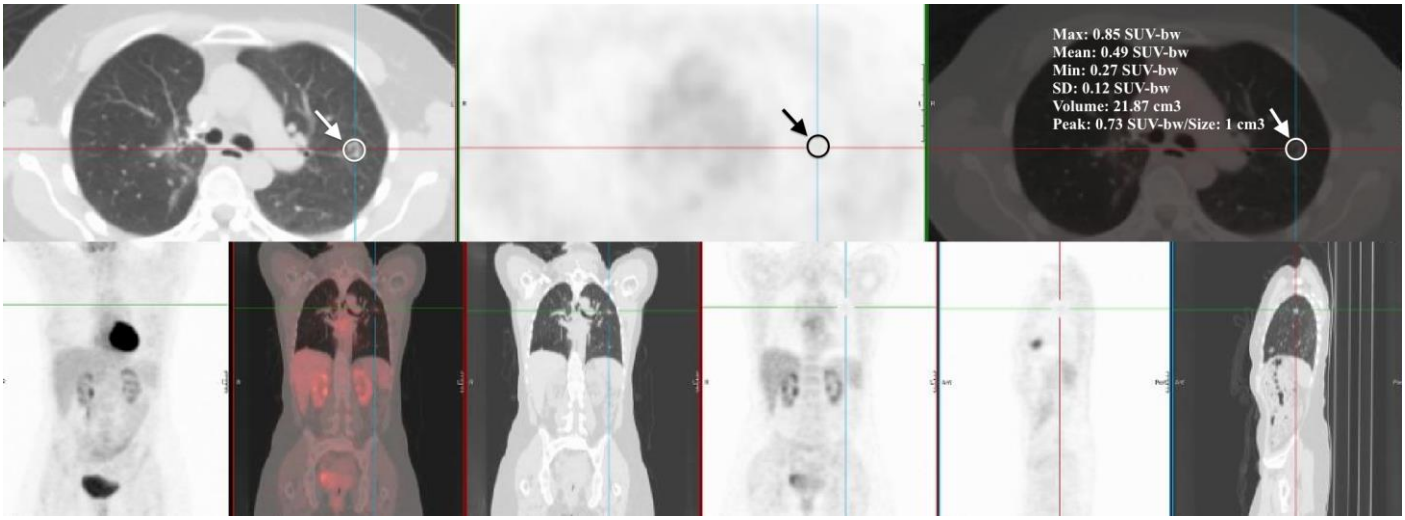



**Figure 6 (left):** 51-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, presents for further imaging following the identification of a new right-sided lesion, 12 months following radiofrequency ablation of a left upper lobe lesion. FINDINGS: a) Axial view, and; b) coronal view of the chest, demonstrate a new right sided retrocardiac intrapulmonary paramediastinal lesion, located posterior to the right atrium at the level of T8, measuring 25.8 x 20.8 x 12.6 mm.
TECHNIQUE: Contrast-enhanced CT scan of the chest. (Phillips Brilliance 64 Slice CT Scanner; Protocol: 104 mAs, 120 kVp, 5.0 mm slice thickness; Images obtained 30 seconds following intravenous injection of 75 ml Iopromide 300)

**Figure 7 (bottom):** 51-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, staging PET/CT scan for a newly diagnosed right sided lesion; 13 months post radiofrequency ablation of a left upper lobe lung cancer. There is negligible uptake at the left upper lobe lesion. Phillips Gemini GXL 16 PET/CT Scanner; Protocol: Images acquired 60 minutes after injection of 292 MBq of F-18 flurodeoxyglucose (FDG) with subsequent low-dose CT during tidal respiration for attenuation correction and lesion localisation, 56 mAs, 140 kVp, 5.0 mm slice thickness.



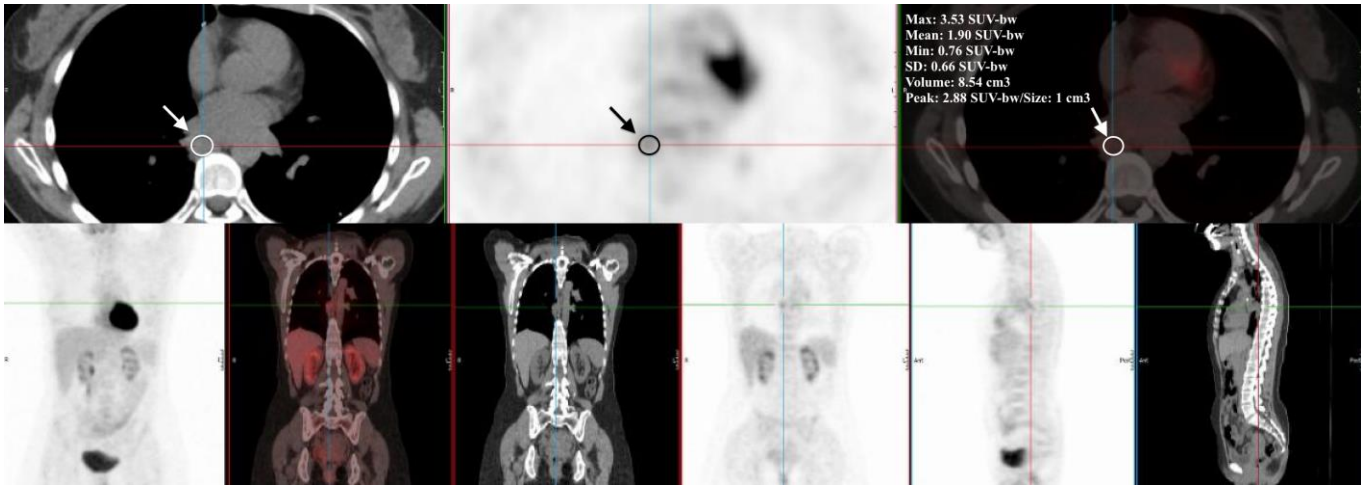



**Figure 8:** 51-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, staging PET/CT scan for a newly diagnosed right sided lesion; 13 months post radiofrequency ablation of a left upper lobe lung cancer. This PET/CT scan demonstrates minor FDG uptake at the right-sided lesion. Phillips Gemini GXL 16 PET/CT Scanner; Protocol: Images acquired 60 minutes after injection of 292 MBq of F-18 flurodeoxyglucose (FDG) with subsequent low-dose CT during tidal respiration for attenuation correction and lesion localisation, 56 mAs, 140 kVp, 5.0 mm slice thickness.





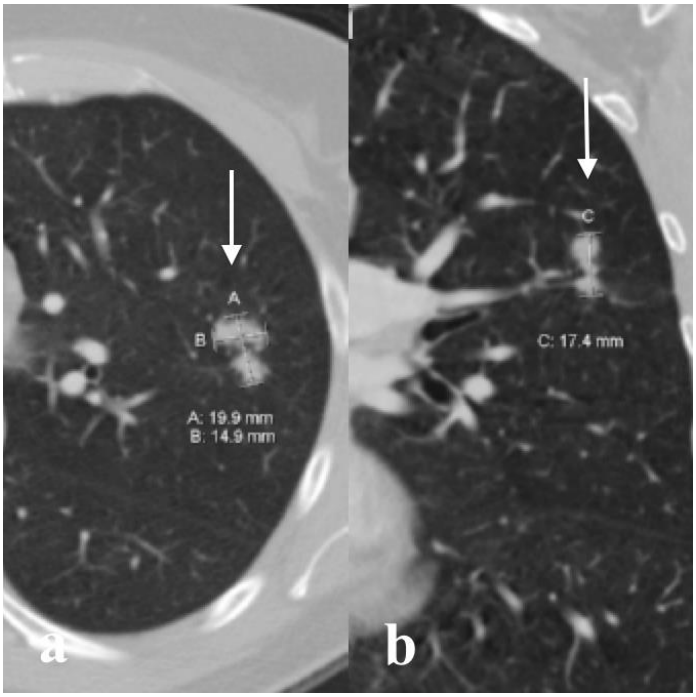



**Figure 9 (left):** 52-year-old female with past multifocal well-differentiated pulmonary adenocarcinoma, presents for a routine monitoring CT, 24 months after initial radiofrequency ablation. FINDINGS: a) Axial view, b) coronal view, and c) sagittal view of local recurrence of the left upper lobe lung focus of pulmonary adenocarcinoma, measuring 19.9 x 14.9 x17.4 mm (12 months before measuring 12.8 x 7.7 x 7.0 mm). TECHNIQUE: Contrast-enhanced CT scan of the chest. (Phillips Brilliance 64 Slice CT Scanner; Protocol: 150 mAs, 120 kVp, 3.0 mm slice thickness; Images obtained 35 seconds following intravenous injection of 75 ml Iopromide 300)

| | |
|---|---|
| **Etiology** | • Develop from terminal bronchiolar and acinar epithelia |
| **Incidence** | • Exact incidence uncertain<br>• Constitutes between 2 to 5% of all primary lung cancer |
| **Gender ratio** | • Studies have suggested both males and females represent a greater proportion |
| **Age predilection** | • Younger than other types of non-small-cell lung carcinoma |
| **Risk factors** | • Smoking<br>• Other proposed risk factors: viral infection, pulmonary fibrosis |
| **Treatment** | • Surgical excision<br>• Adjuvant chemotherapy<br>• Radiation therapy<br>• Thermal ablation therapy |
| **Prognosis** | • Better than other types of non-small cell lung cancer<br>• Overall survival of 72.5% at one year, 41% at five years<br>• Mortality rate of 80%<br>• Mucopapillary subtype has the worst prognosis |
| **Findings on imaging** | • Lesions may be unifocal or multifocal<br><br>***X-ray:***<br>• Characteristically a solitary, solid peripheral nodule<br>• May resemble pneumonia<br>• Focal consolidation<br><br>***CT:***<br>• Ground glass opacification<br>• Solid, with complete obscuration of bronchovascular markings<br>• Mixed<br><br>***PET:***<br>• Focal area of increased uptake |
| **Findings on histology** | ***Histological features of BAC:***<br>• Well-differentiated cytology<br>• Origin distal to recognizable bronchi<br>• Tendency to lymphatic and aerogenous spread, resulting in multicentric development of lesions<br>• Lepidic growth pattern with preservation of underlying lung architecture<br>• Mucinous and nonmucinous<br><br>***IASLC/ATS/ERS classification:***<br>• Adenocarcinoma in situ (AIS): small (≤3 cm), localized adenocarcinoma with a noninvasive lepidic growth pattern; mucinous and nonmucinous variants<br>• Minimally invasive adenocarcinoma (MIA): solitary, small (≤3 cm) adenocarcinoma with predominantly lepidic growth pattern, with ≤5 mm invasion in greatest dimension; cannot invade lymphatics, blood vessels or pleura; must not contain necrosis; mucinous and nonmucinous variants<br>• Lepidic predominant adenocarcinoma: solitary nonmucinous adenocarcinoma >3 cm in greatest diameter<br>• Adenocarcinoma: predominantly invasive adenocarcinoma; some nonmucinous lepidic growth<br>• Invasive mucinous adenocarcinoma: mucinous adenocarcinoma >3 cm in largest diameter; presumed invasive |

**Table 1:** Summary table of pulmonary adenocarcinoma (formerly bronchioloalveolar carcinoma)

| Differential | X-ray | Contrast-enhanced CT |
|---|---|---|
| **Bronchioloalveolar carcinoma (BAC)** | Peripheral nodule of increased density, characteristically peripheral and solitary [6] | Poorly marginated nodule, characterized by focal areas of low attenuation (pseudocavitation) [18]; vessels may appear prominent (CT angiogram sign) [19] |
| **Pulmonary metastases** | Focal or diffuse nodular opacification, not usually associated with calcification [20] | Enhancing nodule with variable margins and location; may demonstrate associated lymphadenopathy [18] |
| **Lymphoma** | Nodule of increased density | Enhancing nodule with characteristic air bronchograms within [18] |
| **Rib fracture/bone island** | Increased density overlying a rib [18] | Intraosseous increased density within rib [18] |
| **Cutaneous nodule** | Well-marginated areas of increased opacity projected over lung fields [18] | Increased density within cutaneous soft tissues [18] |
| **Pneumonia** | Poorly marginated nodule, variable location | Enhancing area of consolidation, often with associated atelectasis; tendency to resolve on serial scans [19] |
| **Pulmonary hamartoma** | Well-marginated nodule, variable location | Sharply marginated, heterogeneous lesion with focal areas of calcification and fat [18, 20] |
| **Granuloma** | Well-marginated nodule, variable location; may be multiple | Soft-tissue density nodule often with calcification; may be associated hilar lymph node calcification [18] |

**Table 2:** Differential diagnosis for pulmonary adenocarcinoma





## ABBREVIATIONS

AIS = Adenocarcinoma in situ
BAC = Bronchioloalveolar carcinoma
CT = Computed tomography
FCG = 18F-fludeoxyglucose
FDG-PET/CT
GGO = Ground glass opacification
IASLC/ATS/ERS = International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society
MIA = Minimally invasive adenocarcinoma
NSCLC = Non-small-cell lung carcinoma
RECIST = Response Evaluation Criteria in Solid Tumours
RFA = Radiofrequency ablation
SUV = Standardised uptake value

## KEYWORDS

Pulmonary adenocarcinoma; Invasive Mucinous Adenocarcinoma; BAC; PET; Radiofrequency ablation; Microwave ablation; Recurrence

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