Nadia Corcione[1], Antonio Ponticiello[2], Severo Campione[3], Alfonso Pecoraro[1], Livio Moccia[1], Giuseppe Failla[1]

✉ nadia.corcione@gmail.com

in https://www.linkedin.com/in/nadia-corcione-401942120

Case report

A case of haemoptysis and bilateral areas of lung consolidation sparing the right lower lobe

A 49-year-old Caucasian male, with a past medical history of essential arterial hypertension treated with β-blockers, presented to our hospital with complaints of exertional dyspnoea and dry cough for 2 months, associated with mild haemoptysis (~20–30 mL) and a sensation of warmth in the thorax starting 1 day before admission. He had no history of smoking or allergy, nor of occupational/ environmental exposures; he also denied trauma or illicit drug and alcohol abuse. His body mass index was 22 kg·m^{-2}. Vital signs were as follows: body temperature 36.5ºC; respiration rate 18 breaths per minute; blood pressure 120/75 mmHg; pulse rate 76 beats per minute, regular. Peripheral oxygen saturation (S_{pO_2}) at rest on room air was 85%. His dyspnoea was grade 3 on the modified Medical Research Council (mMRC) scale. Vesicular murmur was markedly reduced in the right thoracic base in the upright position; palpable lymph nodes were not found. Finger clubbing was absent, and no signs of thrombophlebitis were detected. Routine laboratory analyses of peripheral blood and urine showed no alterations, except mildly elevated lactate dehydrogenase (LDH) (389 UI·L^{-1}), C-reactive protein (CRP) (14 mg·dL^{-1}) and white blood cells count (WBC) (12×10^3 cells·mm^{-3}), with normal differential. D-dimer was <500 ng·mL^{-1}, prothrombin time was 12.1 s and international normalised ratio (INR) was 0.9. Arterial blood gas (ABG) analysis revealed an arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio of 238 on room air, with hyperventilation (arterial carbon dioxide tension 30 mmHg, pH 7.51). Electrocardiogram was normal. Full-body computed tomography (CT) with contrast showed: no pulmonary embolism; no pulmonary vascular abnormalities; large bilateral areas of consolidation and partially confluent macro-nodules, almost completely sparing the right lower lobe (RLL) (figure 1a, b); right lower lobe bronchus (RLLB) lumen occluded by a hypodense mass with calcific nuclei with marked, homogeneous contrast enhancement (figure 1c); enlarged mediastinal lymph nodes located in right upper paratracheal (station 2R), bilateral lower paratracheal (station 4R and 4L), sub-carinal (station 7) and right hilar (station 10R) regions (maximum of 24 mm in the short axis); and RLL bronchiectasis, with no mucoid impaction (figure 1d). No other abnormalities were detected.

Task 1
What is the most likely diagnostic hypothesis?

a) Disseminated tuberculosis
b) Lung cancer
c) Non-infectious granulomatous disease
d) Fungal pneumonia
e) Organising pneumonia (OP)

Go to Answers >>

@ERSpublications
Multiple primary lung cancers (MPLC) are often neglected. Obtaining pre-operative specimens through bronchoscopy could play a role. It is important to distinguish aerogenous metastasis from MPLC in the adenocarcinoma spectrum due to the different prognosis. https://bit.ly/3zbdVrw
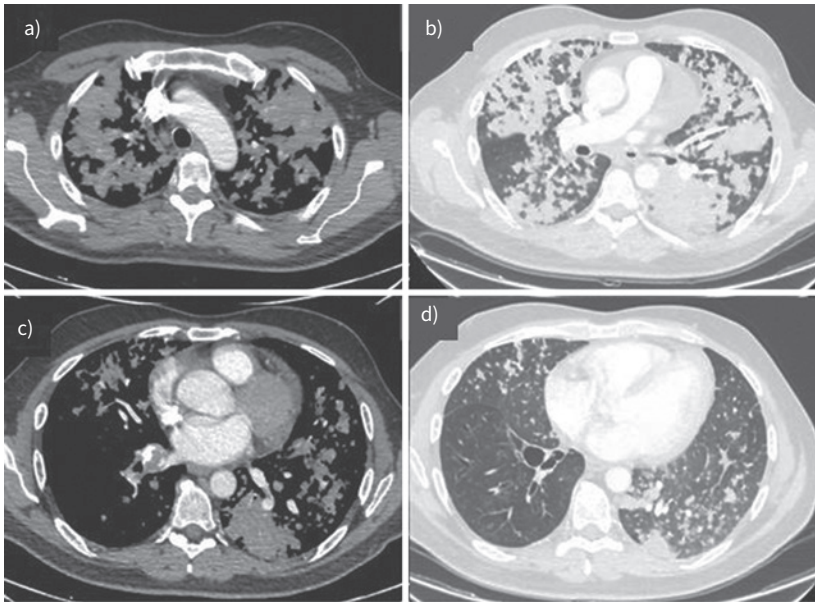
Figure 1 *a) CT thorax axial section showing bilateral consolidation. b) CT thorax lung window showing bilateral, partially confluent macronodules. c) CT thorax axial section showing RLLB occluded by hypodense mass with calcific nuclei. d) CT thorax axial section showing RLL bronchiectasis. The parenchyma of the RLL is relatively spared by consolidation and nodules.*

Task 2

What would be the next step?

a) Flexible bronchoscopy
b) CT-guided fine needle aspiration biopsy (CT-FNAB) of areas of consolidation
c) Surgical biopsy of areas of consolidation

Go to Answers >>

Bronchoscopy revealed a vascularised vegetation with a smooth surface, occluding the RLLB and partially protruding into right main bronchus lumen during expiration (figure 2a and b). Exploration of the RLL beyond the vegetation, with an ultrathin bronchoscope (3.0 mm distal-end outer diameter), showed normal airway patency. Neither active bleeding nor other abnormalities were detected in the remaining tracheo-bronchial tree.
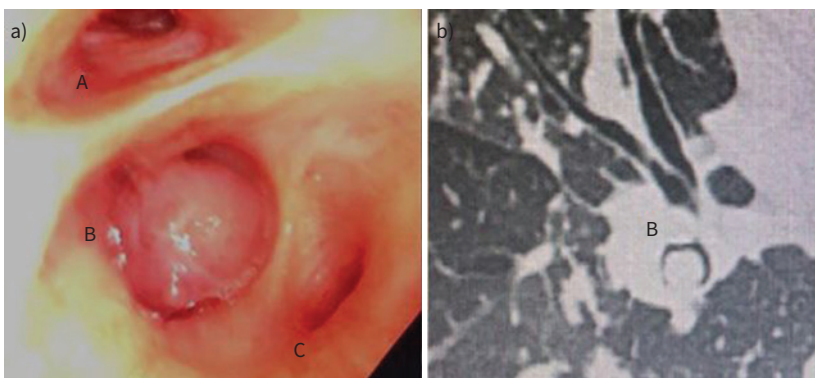

Figure 2 *a) Bronchoscopic view. A: right middle lobe; B: vegetation with smooth surface occluding the RLLB; C: segmental bronchus rB6. b) CT thorax axial section showing the vegetation, detail.*

Task 3

How would you proceed during bronchoscopy?

a) Biopsy of the vegetation occluding the RLLB plus linear EBUS-guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal lymph nodes
b) Radial EBUS-guided transbronchial lung biopsy (rEBUS-TBLB) of areas of consolidation plus linear EBUS-TBNA of mediastinal lymph nodes
c) Resection of vegetation occluding the RLLB plus rEBUS-TBLB of areas of consolidation plus linear EBUS-TBNA of mediastinal lymph nodes
d) Linear EBUS-TBNA of mediastinal lymph nodes plus BAL

Go to Answers >>

Histological examination of the endobronchial vegetation revealed a typical pulmonary carcinoid (figure 5a shows organoid growth pattern; figure 5b shows positive synaptophysin stain), while examination of tissue specimens from the left lower lobe revealed primary lung adenocarcinoma (PLA) (figure 5c shows acinar growth pattern and positive thyroid transcription factor 1 stain; figure 5d shows programmed death-ligand 1 (PD-L1) >1% and <50%). All of the lymph nodes sampled revealed metastatic cells of PLA. Restoring the patency of the RLLB improved the patient's clinical status: S_{pO_2} at rest on room air rose from 85% up to 93% and his dyspnoea scored 1 on the mMRC scale.

Task 4

How should TNM (tumour, node, metastasis) classification be applied to multiple primary lung cancers (MPLC)?

a) A separate TNM category should be provided for each tumour
b) One TNM category should be used in cases of the same histology
c) Maximum T category should be assigned both in synchronous and metachronous MPLC

Go to Answers >>

Then, in this case, the stage of the PLA is IVA (cT4N3M1a). The stage of the typical carcinoid is IB (cT2aN0M0). Molecular analyses of biomarker expression in the PLA tissue showed: anaplastic lymphoma kinase (ALK) rearrangement negative; *ROS-1* rearrangement negative; PD-L1 expression >1% and <50%; epidermal growth factor receptor (EGFR) mutation negative; and *BRAF* mutation negative. First-line treatment with ipilimumab plus nivolumab was started. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and

programmed cell death protein 1 (PD-1) are inhibitory checkpoints commonly expressed by activated T-cells. Immune checkpoint inhibitors (ICIs) enhance anti-tumour T-cells' responses, reducing the acquired immune system tolerance overexpressed by cancer. As reported by various studies, a combination of ICIs targeting PD-1 (including nivolumab) and CTLA-4 (including ipilimumab) seems result in a longer duration of overall survival compared with classic platinum-based chemotherapy in stage IV non-small cell lung cancer [17, 18]. After carcinoid resection with a rigid bronchoscope, right lower lobectomy was not performed, given the improvement of respiratory failure with RLLB recanalisation. 3 months after the diagnosis, the patient died from ischaemic cerebral stroke.

Discussion

MPLC occurs in 0.2–20% of all lung cancers. In 1975, Martini and Melamed [19] proposed an empirical definition of MPLC as tumours physically separated with a different malignant histology. In cases of the same histology, the following circumstances should be satisfied: no metastatic dissemination in mediastinal lymph nodes; no extrapulmonary metastasis; for synchronous MPLC (sMPLC), tumours should be separate with location in a different segment, lobe or lung; and for metachronous MPLC (mMPLC), there should be at least a 2-year disease-free interval between the two cancers [19]. These criteria were updated in 1995 by Antakli et al. [20], introducing the concept that DNA ploidy should be proven in cases with the same histology. In 2013, the American College of Chest Physicians (ACCP) elongated the disease-free interval to 4 years for mMPLC [21]. MPLC are easy to define if they are clearly of different histological types. However, the demonstration that two or more lesions have the same histotype is not sufficient to prove that they are multiple foci of a single tumour, that is clonally related cancers [15]. A detailed assessment of tumour relatedness should be based on genetic characterisation, including detection of specific driver mutations by PCR sequencing techniques, comparative genomic hybridisation and next generation DNA sequencing [22–24]. These techniques are probably the best way to determine if tumours are of a single lineage or not, but the data are still limited and the assessment is complex. In addition, clinical criteria for separate *versus* related pulmonary tumours have been developed [11, 15]: arguments that relatively favour separate tumours are different radiological appearance, different metabolic uptake, different rates of growth and absence of nodal or systemic metastasis. In our case, the features of the mass occluding the RLLB were highly suggestive of a bronchial carcinoid, given the location in the central airways, the presence of
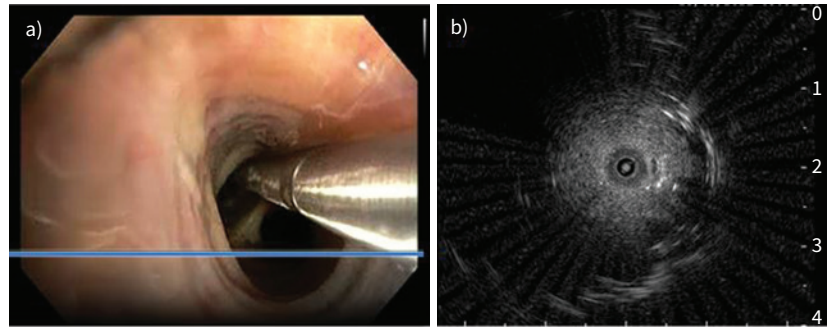
Figure 3 *a) Bronchoscopic view of the radial probe entering segmental bronchus IB6. b) Ultrasonographic view of the lesion in segmental bronchus IB6: lobulated shape, with a distinct but not sharp margin, absence of blood vessels and linear air bronchogram.*

punctate calcification and the endoscopic aspect of a vascularised lesion, approximatively rounded with a smooth surface [9, 25]. This is why we choose to sample not only the mass but also the areas of consolidation, which showed, in contrast, an indistinctive margin, no bronchial obstruction and diffusion throughout the lungs. All these latter characteristics are typical of PLA [26, 27]; however, the coexistence of a pulmonary carcinoid and PLA has rarely been reported [28–31]. It is still unclear whether identification of sMPLC in resected specimens (including a comprehensive histological assessment) can be applied to limited preoperative biopsy samples, but performing multiple biopsies on different lung sites during bronchoscopy could be particularly useful, especially in the presence of different endoscopic characteristics of the lesions. Careful assessment by a multidisciplinary team, including a pulmonologist, pathologist and thoracic radiologist, probably remains the most important factor in the diagnostic workup of MPLC [21].

The aerogenous spread of cancer cells, detaching from the basal membrane, going through the airways and reattaching along alveolar septa away from the primary focus, has been proposed as an underrecognised pathway of metastatic PLA, so-called "aerogenous dissemination" [32]. This
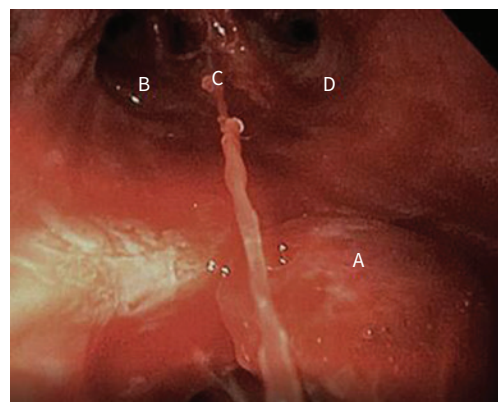
Figure 4 *Bronchoscopic view of the RLLB after removal of the vegetation. A: peduncle of the vegetation emerging from the segmental bronchus rB7; B: segmental bronchus rB9; C: segmental bronchus rB10; D: segmental bronchus rB8.*
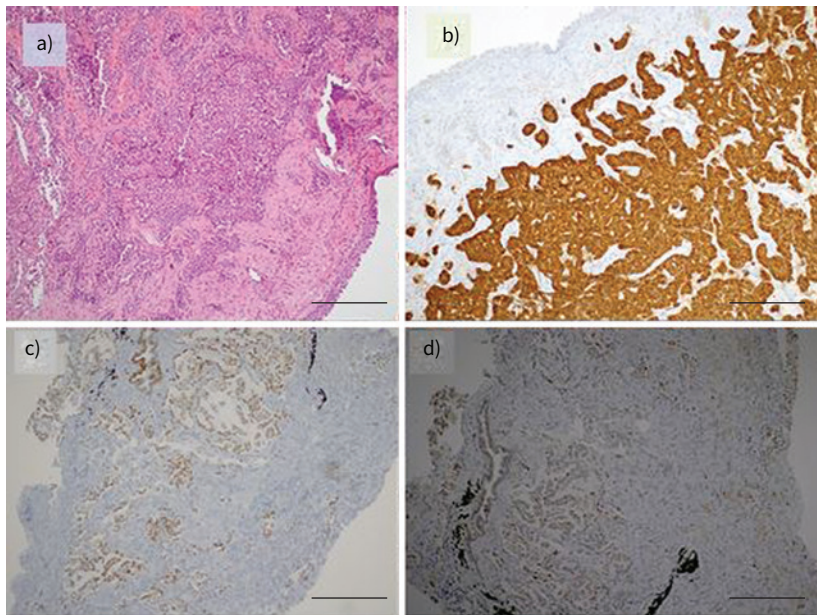
Figure 5 *Typical pulmonary carcinoid: a) organoid growth pattern (scale bar=100 µm), b) cells demonstrating intense synaptophysin immunoreactivity (scale bar=50 µm). Lung adenocarcinoma: c) acinar growth pattern (scale bar=100 µm), d) the percentage of cells showing PD-L1 was >1% and <50% (scale bar=100 µm).*

pattern of invasion is unique to the lung due to the presence of air spaces (a path through which cancer cells can spread) [33]. In 2015, Kadota *et al.* [34] first formally named this phenomenon as spread through air spaces (STAS), that is the presence of tumour cells (micropapillary clusters, solid nests or single cells) going beyond the edge of the main tumour to at least the first alveolar layer in the lung parenchyma. In the same year, the World Health Organization stated that STAS should be listed as an exclusion criterion for the diagnosis of adenocarcinoma *in situ* and minimally invasive adenocarcinoma [35]; however, STAS has been identified not only in PLA, but also in other types of lung cancer, including squamous cell carcinoma [36] and neuroendocrine tumours [37]. The concept of STAS remains a subject of debate [38]. According to some authors, STAS is not a pattern of invasion but just an artefact associated with lung resection and specimen preparation (tumour cells displaced by the knife along the plane of sectioning) [39, 40]. Furthermore, from a biological perspective, the cells can't live on air [41, 42]. However, STAS has been observed without cutting through the main tumour [43], and, with the help of three-dimensional reconstruction, it has been found that detached tumour islands, after migration through air spaces, reattach in close apposition to alveolar vessels, which is a potential mechanism for cell survival [44, 45]. Furthermore, positivity for STAS is an independent prognostic factor for both recurrence-free survival and overall survival in patients with resected pathologic stage I adenocarcinoma [46]. Surgery is the only method for evaluating STAS; however, in our patient, the extension of PLA in the RLL was minimal, suggesting the intriguing concept that the occlusion of the RLLB by the carcinoid has probably prevented STAS of malignant cells.

Conclusion

In the presence of radiological, clinical and endoscopic findings suggestive of MPLC, bronchoscopic examination could play an important role, allowing extensive sampling of different pathological sites. More efforts are needed to differentiate aerogenous metastasis from multiple synchronous lesions in the spectrum of lung adenocarcinoma and to predict STAS preoperatively, based on the imaging features.

Answers

Answer 1
b and e. The imaging features of non-infectious granulomatous disease are rarely specific: predominantly consolidation and macro-nodules in a peribronchovascular distribution, as shown in the CT in question, are often seen in eosinophilic granulomatosis with polyangiitis (EGPA) and granulomatosis with polyangiitis (GPA) [1]. However, EGPA is associated with asthma, peripheral eosinophilia and sinus abnormalities, which do not appear in the clinical history nor in the laboratory findings. GPA manifests with a classic triad of both upper and lower airways symptoms (*i.e.*, sinusitis, haemoptysis) and glomerulonephritis (with haematuria), which was not demonstrated in this case. Disseminated tuberculosis is characterised by diffuse micro-nodules (2–3 mm in diameter) with a predominance in the upper lobes [2]. Both tuberculosis and fungal pneumonia would be expected to be associated with a history of immunosuppression, fever and more pronounced changes in WBC count and CRP. Multilobar and multifocal solid masses and consolidation with air bronchogram on CT are commonly seen in adenocarcinoma of the lung, reflecting a lepidic growth pattern as its predominant component [3–5]. OP could be a plausible alternative to lung cancer: the typical OP syndrome encompasses dyspnoea on exertion, non-productive cough and CT findings of mass-like lesions and acinar pattern of nodules of ~8 mm in diameter [6].

Answer 2

a. Unlike CT- FNAB and surgical biopsy, flexible bronchoscopy allows an extensive diagnostic workup, including cytological and microbiological analysis of bronchoalveolar lavage (BAL), endobronchial-ultrasound (EBUS)-guided biopsy, and direct-vision biopsy.

<< Go to Task 2

Answer 3

c. A multidisciplinary tumour board, including an interventional pulmonologist, pathologist, thoracic radiologist and thoracic surgeon, carefully reviewed the case before bronchoscopy. The radiological features of the mass occluding the RLLB (centrally located, with eccentric foci of calcifications) significantly differed from those of areas of consolidation (extension through the lung parenchyma, bilateral distribution). Slow growing endobronchial lesions can cause focal bronchiectasis with a ball-valve mechanism [7–9]: in this case, RLL bronchiectasis could be the expression of a different growth rate of the endobronchial mass compared to that of the consolidations. These elements suggested the coexistence of two pathologies. Therefore, according to the advice given by the multidisciplinary team, both of the lesions were sampled. Since both endoscopic and CT features of the RLL beyond the obstruction were almost completely normal, we hypothesised that restoring the patency of the RLLB could have a beneficial impact on the ventilation/perfusion ratio. A radial probe was introduced into the apical segment of the left lower lobe (lB6), revealing an area with lobulated shape, a distinct but not sharp margin, the absence of blood vessels and no linear discrete air bronchogram (figure 3a–b); these characteristics are common in malignant lesions [10]. Multiple rEBUS-TBLB were performed at this level. The vegetation was removed with a rigid bronchoscope and laser photoresection (figure 4). Finally, EBUS-TBNA of the 10R, 7, 4R and 4L nodes were made.

<< Go to Task 3

Answer 4

a. The eight edition American Joint Commission on Cancer (AJCC)/Union for International Cancer Control (UICC) stage classification for lung cancer describes four different scenarios in cases of multiple sites of pulmonary involvement [11–16]. 1) MPLC: unrelated primary malignancies with different histotypes or with the same histotype but different morphology by comprehensive histological assessment. In these cases, separate clinical and pathological staging should be provided for each tumour. 2) Lung cancer with separate but related tumour nodules: the location of the nodule(s) determines T3, T4 or M1a assignment. 3) Multiple ground-glass opacities (GGO): T is based on highest T lesion; single N and M for all lesions. 4) Consolidation: single tumour with diffuse pulmonary involvement; single N and M for all lesions.

<< Go to Task 4

Affiliations

Nadia Corcione[1], Antonio Ponticiello[2], Severo Campione[3], Alfonso Pecoraro[1], Livio Moccia[1], Giuseppe Failla[1]

[1]Interventional Pulmonology Unit, Dept of Pulmonology, Oncology and Hematology, Cardarelli Hospital, Naples, Italy. [2]University of Naples Federico II, School of Medicine and Surgery, Naples, Italy. [3]Pathology Unit, Dept of Advanced Technology, Cardarelli Hospital, Naples, Italy.

Conflict of interest

None declared.

References

1. Naeem M, Ballard DH, Jawad H, *et al.* Noninfectious granulomatous diseases of the chest. *Radiographics* 2020; 40: 1003–1019.
2. Franquet T. Imaging of pneumonia: trends and algorithms. *Eur Respir J* 2001; 18: 196–208.
3. Austin JH, Garg K, Aberle D, *et al.* Radiologic implications of the 2011 classification of adenocarcinoma of the lung. *Radiology* 2013; 266: 62–71.
4. Kim SK, Kim TJ, Chung MJ, *et al.* Lung adenocarcinoma: CT features associated with spread through air spaces. *Radiology* 2018; 289: 831–840.
5. Lederlin M, Puderbach M, Muley T, *et al.* Correlation of radio- and histomorphological pattern of pulmonary adenocarcinoma. *Eur Respir J* 2013; 41: 943–951.
6. Oikonomou A, Hansell DM. Organizing pneumonia: the many morphological faces. *Eur Radiol* 2002; 12: 1486–1496.

7. Milliron B, Henry TS, Veeraraghavan S, *et al.* Bronchiectasis: mechanisms and imaging clues of associated common and uncommon diseases. *Radiographics* 2015; 35: 1011–1030.

8. Munakata H, Higashi M, Tamura T, *et al.* Fatal airway obstruction due to a ball-valve clot with identical signs of tension pneumothorax. *Acute Crit Care* 2020; 35: 298–301.

9. Jeung MY, Gasser B, Gangi A, *et al.* Bronchial carcinoid tumors of the thorax: spectrum of radiologic findings. *Radiographics* 2002; 22: 351–365.

10. Zheng X, Wang L, Chen J, *et al.* Diagnostic value of radial endobronchial ultrasonographic features in predominant solid peripheral pulmonary lesions. *J Thorac Dis* 2020; 12: 7656–7665.

11. Brierley J, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 8th Edn. Oxford, John Wiley & Sons, Inc., 2017.

12. Detterbeck FC, Boffa DJ, Kim AW, *et al.* The eighth edition lung cancer stage classification. *Chest* 2017; 151: 193–203.

13. Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 39–51.

14. Detterbeck FC, Nicholson AG, Franklin WA, *et al.* The IASLC lung cancer staging project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol* 2016; 11: 639–650.

15. Detterbeck FC, Franklin WA, Nicholson AG, *et al.* The IASLC lung cancer staging project: background data and proposed criteria to distinguish separate primary lung cancers from metastatic foci in patients with two lung tumors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 651–665.

16. Detterbeck FC, Marom EM, Arenberg DA, *et al.* The IASLC lung cancer staging project: background data and proposals for the application of TNM staging rules to lung cancer presenting as multiple nodules with ground glass or lepidic features or a pneumonic type of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol* 2016; 11: 666–680.

17. Hellmann MD, Paz-Ares L, Bernabe Caro R, *et al.* Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med* 2019; 381: 2020–2031.

18. Rijavec E, Indini A, Ghidini M, *et al.* Nivolumab plus ipilimumab for the first-line treatment of metastatic NSCLC. *Expert Rev Anticancer Ther* 2021; 21: 705–713.

19. Martini N, Melamed MR. Multiple primary lung cancers. *J Thorac Cardiovasc Surg* 1975; 70: 606–612.

20. Antakli T, Schaefer RF, Rutherford JE, *et al.* Second primary lung cancer. *Ann Thorac Surg* 1995; 59: 863–866.

21. Kozower BD, Larner JM, Detterbeck FC, *et al.* Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143: Suppl, e369S–e399S.

22. Chang YL, Wu CT, Lin SC, *et al.* Clonality and prognostic implications of p53 and epidermal growth factor receptor somatic aberrations in multiple primary lung cancers. *Clin Cancer Res* 2007; 13: 52–58.

23. Wang X, Wang M, MacLennan GT, *et al.* Evidence for common clonal origin of multifocal lung cancers. *J Natl Cancer Inst* 2009; 101: 560–570.

24. Girard N, Deshpande C, Azzoli CG, *et al.* Use of epidermal growth factor receptor/Kirsten rat sarcoma 2 viral oncogene homolog mutation testing to define clonal relationships among multiple lung adenocarcinomas: comparison with clinical guidelines. *Chest* 2010; 137: 46–52.

25. Papaporfyriou A, Domayer J, Meilinger M, *et al.* Bronchoscopic diagnosis and treatment of endobronchial carcinoid: case report and review of the literature. *Eur Respir Rev* 2021; 30: 200115.

26. Feng SH, Yang ST. The new 8th TNM staging system of lung cancer and its potential imaging interpretation pitfalls and limitations with CT image demonstrations. *Diagn Interv Radiol* 2019; 25: 270–279.

27. Carter BW, Lichtenberger JP 3rd, Benveniste MK, *et al.* Revisions to the TNM staging of lung cancer: rationale, significance, and clinical application. *Radiographics* 2018; 38: 374–391

28. Saladi L, Maddu SM, Niazi M, *et al.* Adenocarcinoma of lung and bronchial carcinoid presenting as double synchronous primary lung cancer: a case report and review of literature. *World J Oncol* 2018; 9: 110–114.

29. Sen F, Borczuk AC. Combined carcinoid tumor of the lung: a combination of carcinoid and adenocarcinoma. *Lung Cancer* 1998; 21: 53–58.

30. Drpa G, Sreter KB, Manojlovic S, *et al.* Erlotinib for coexisting typical bronchial carcinoid and advanced lung adenocarcinoma: does the epidermal growth factor receptor mutation status matter? *Anticancer Drugs* 2018; 29: 281–285.

31. Kashif M, Ayyadurai P, Thanha L, *et al.* Triple synchronous primary lung cancer: a case report and review of the literature. *J Med Case Rep* 2017; 11: 245.

32. Gaikwad A, Souza CA, Inacio JR, *et al.* Aerogenous metastases: a potential game changer in the diagnosis and management of primary lung adenocarcinoma. *AJR Am J Roentgenol* 2014; 203: W570–W582.

33. Toyokawa G, Yamada Y, Tagawa T, *et al.* Significance of spread through air spaces in resected lung adenocarcinomas with lymph node metastasis. *Clin Lung Cancer* 2018; 19: 395–400.e1.

34. Kadota K, Nitadori JI, Sima CS, *et al.* Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. *J Thorac Oncol* 2015; 10: 806–814.

35. Travis WD, Brambilla E, Nicholson AG, *et al.* The 2015 world health organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 2015; 10: 1243–1260.

36. Lu S, Tan KS, Kadota K, *et al.* Spread through air spaces (STAS) is an independent predictor of recurrence and lung cancer-specific death in squamous cell carcinoma. *J Thorac Oncol* 2017; 12: 223–234.

37. Aly RG, Rekhtman N, Li X, *et al.* Spread through air spaces (STAS) is prognostic in atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma of the lung. *J Thorac Oncol* 2019; 14: 1583–1593.

38. Uruga H, Fujii T, Kishi K. What is spread through air space? *J Thorac Dis* 2017; 9: E943–E944.

39. Thunnissen E, Blaauwgeers HJ, de Cuba EM, *et al. Ex vivo* artifacts and histopathologic pitfalls in the lung. *Arch Pathol Lab Med* 2016; 140: 212–220.

40. Blaauwgeers H, Flieder D, Warth A, *et al.* A prospective study of loose tissue fragments in non-small cell lung cancer resection specimens: an alternative view to ';spread through air spaces'. *Am J Surg Pathol* 2017; 41: 1226–1230.

41. Jia M, Yu S, Gao H, *et al.* Spread through air spaces (STAS) in lung cancer: a multiple-perspective and update review. *Cancer Manag Res* 2020; 12: 2743–2752.

42. Warth A. Spread through air spaces (STAS): a comprehensive update. *Transl Lung Cancer Res* 2017; 6: 501–507.

43. Lu S, Rekhtman N, Eguchi T, *et al.* P3.01-029. Cases demonstrating spread through air spaces (STAS) reflects invasive growth and not an artifact. *J Thorac Oncol* 2017; 12: Suppl., S1137.

44. Onozato ML, Klepeis VE, Yagi Y, *et al.* A role of three-dimensional (3D)-reconstruction in the classification of lung adenocarcinoma. *Anal Cell Pathol (Amst)* 2012; 35: 79–84.

45. Yagi Y, Aly RG, Tabata K, *et al.* Three-dimensional histologic, immunohistochemical, and multiplex immunofluorescence analyses of dynamic vessel co-option of spread through air spaces in lung adenocarcinoma. *J Thorac Oncol* 2020; 15: 589–600.

46. Toyokawa G, Yamada Y, Tagawa T, *et al.* Significance of spread through air spaces in resected pathological stage I lung adenocarcinoma. *Ann Thorac Surg* 2018; 105: 1655–1663.