



Bilateral synchronous multiple lung cancer: an emerging problem

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Aim: Multiple primary lung cancers are becoming increasingly recognised and pose diagnostic and staging uncertainties with challenging management options and prognostication. **Case report:** We describe a case of synchronous multiple primary lung cancer occurring bilaterally, and the steps in reaching the diagnosis, initial surgical management, the intensive follow-up this underwent, and how its subsequent recurrence led to treatment with radiation therapy in light of the patient's declining fitness. **Discussion:** This case highlighted that cytological recurrence could occur prior to radiological recurrence, especially for endobronchial tumors, and intensive follow-up both radiologically and endoscopically with multidisciplinary input is crucial in the management of these challenging cases where evidence-based guidelines are limited.

Plain language summary: This article discusses an unusual presentation of two separate lung cancer occurring in both lungs at the same time, how it was treated in the first instance, and the difficulties encountered by the clinical team during the post-treatment monitoring period. After initial treatment with surgery, the patient underwent a period of monitoring through CT scans and camera tests into the lungs to visually assess the treated areas, with managed to detect that the cancer came back at an early stage. With further surgery not being a viable option, radiation therapy was used instead to manage this recurrence. This report demonstrates the importance of close monitoring of these types of lung cancers following treatment with a multidisciplinary approach given their unusual nature and lack of available evidence to guide treatment, in order to achieve a successful outcome for the patient.

Tweetable abstract: MPLCs are becoming increasingly recognised and pose diagnostic and management uncertainties. Intensive follow-up both radiologically and endoscopically following initial management is crucial in these challenging cases where evidence-based guidelines are limited.

First draft submitted: 12 August 2023; Accepted for publication: 7 November 2023; Published online: 19 December 2023

Keywords: bronchoscopy • lung cancer • MPLC • multiple lung cancers • radiotherapy • thoracic oncology

Background

Multiple primary lung cancers (MPLCs) are an increasingly common diagnosis which pose challenging diagnostic and therapeutic issues [1]. Patients with primary lung cancer can develop a secondary tumor at the same time as the first (synchronous) or later in life after their initial cancer has been treated (metachronous) [1,2].

Synchronous MPLC (sMPLC) was first described in 1924 [2]. It is characterized by at least two primary lung tumors simultaneously identified in ipsilateral or contralateral lung. With advances in imaging techniques especially in the area of computed tomography (CT) and PET-CT, there is an increasing number of sMPLCs being diagnosed; however, there remains limited evidence in the management and prognostication of MPLCs, and therefore provides huge challenges and uncertainties for both clinicians and patients [3].

In patients where there is a suspicion of sMPLCs, it is critical that the secondary tumor is determined on whether it is an independent primary tumor, a recurrence of the primary tumor, or a metastasis of the primary tumor, as this will influence the staging of the disease and how the cancer is managed [4–7].

Here, we describe a case of sMPLC, from initial diagnosis, treatment, to subsequent follow-up and recurrence.



Figure 1. Computed tomography chest from May 2016 showing 18 mm nodular lesion in the posterior aspect of the right upper lobe in contact with the pleura.

Case report

Initial clinical presentation

This 65-year-old male at the time of initial presentation was referred to the respiratory outpatient clinic in May 2016 by his general practitioner. He presents with a history of hoarseness for 12 months, and three episodes of small volume hemoptysis.

He has a past medical history of type 2 diabetes and ischemic heart disease with previous coronary artery bypass grafting in 1997 and stenting of his right coronary artery in 2014.

Medication history included metformin 500 mg twice daily, aspirin 75 mg once daily, omeprazole 20 mg once daily, atorvastatin 80 mg once daily, bisoprolol 2.5 mg once daily, isosorbide mononitrate 25 mg once daily, and salbutamol inhaler as required.

He is an ex-smoker of 40 pack-years, having stopped smoking 1 month prior to his clinic appointment. His exercise tolerance was 2–3 miles, and a functional performance status of 1 on the Eastern Cooperative Oncology Group scale. He is a retired telephone engineer and previously worked in the textile industry.

On examination, he had some inspiratory crackles at the left lung base on auscultation, with no evidence of digital clubbing or palpable lymphadenopathy. Oxygen saturation was measured at 96% on room air by pulse oximetry.

Initial investigations

Initial chest x-ray was unremarkable, and he proceeded to a CT chest which showed a 18 mm nodular lesion in the posterior aspect of the right upper lobe (Figure 1).

Pulmonary function tests showed a forced expiratory volume in 1 s of 1.65 l (60% predicted), functional vital capacity of 2.99 l (85% predicted), giving an obstructive ratio of 0.55 and a preserved transfer factor of 90%.

He proceeded to have a flexible bronchoscopy which did not reveal any endobronchial abnormalities in his right upper lobe, but showed a small endobronchial lesion at the left lingula. Biopsies of this showed squamous metaplasia and washings from the left lingula showed cells in keeping with a squamous cell carcinoma.

He proceeded to have a PET-CT, which showed the right upper lobe nodule to be fluorodeoxyglucose-avid, with no evidence of nodal or metastatic spread. (Figure 2) Discussion at the local lung multidisciplinary meeting (MDM) felt these two lesions represented two synchronous primaries, rather than metastatic disease given there was no evidence of nodal disease radiologically, as well as the absence of metastatic disease elsewhere. Referral to thoracic surgeons were made for resections of the two lesions.

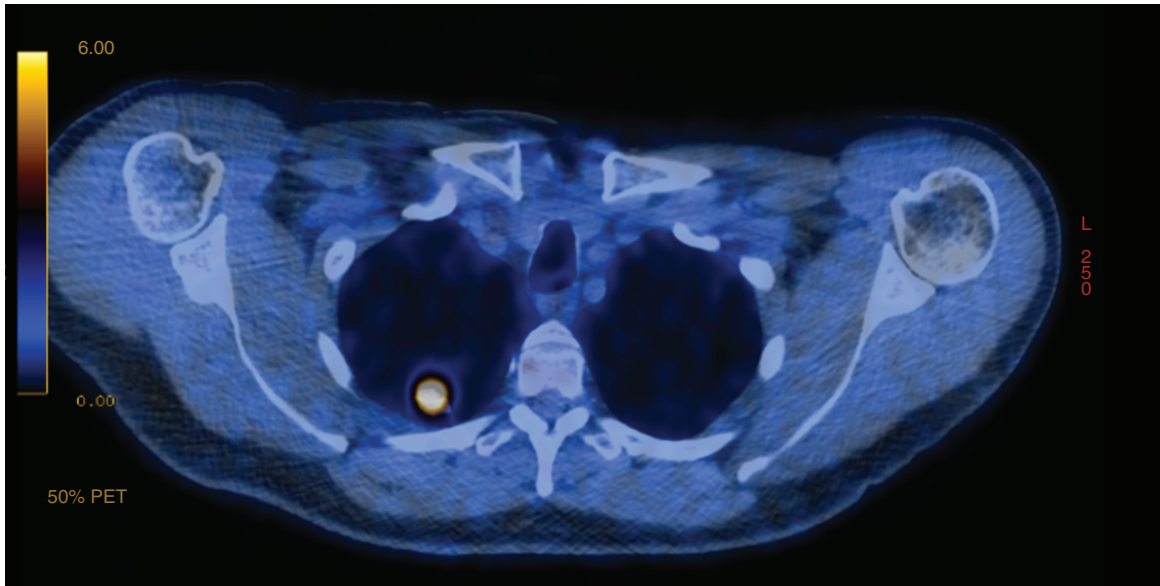


Figure 2. PET-computed tomography showing fluorodeoxyglucose-avidity of right upper lobe nodule shown in Figure 1 with no evidence of lymphadenopathy or metastatic disease.

A cardiopulmonary exercise test was performed in preparation for thoracic surgery. He was able to exercise for 11 minutes with a VO_2max of 16.4 l per minute (maximum rate of oxygen consumption attainable during physical exertion), indicating reasonably good fitness to proceed to thoracic surgery.

Initial treatment

The patient was assessed by the thoracic surgeons and proceeded to have a laser ablation of the left lingular endobronchial lesion via rigid bronchoscopy in the first instance in July 2016. Laser ablation was performed instead of surgical resection as it was felt by the MDM to be an endobronchial tumor only, due to its lack of visibility on CT. The option of a complete left upper lobe lobectomy was considered by the surgical team if laser does not treat this lesion adequately.

Four weeks later, he proceeded to have a wedge resection of the right upper lobe lesion via video assisted thoracoscopic surgery. On balance, a wedge resection was preferred instead of a segmentectomy by the surgical team due to the patient's chronic obstructive pulmonary disease and cardiac comorbidities. Histology from this confirms a 19 mm moderately differentiated squamous cell carcinoma, staged pT3 on the basis of infiltration of the parietal pleura. There was no evidence of local lymphovascular invasion. The stapled resection margin was free of tumor for 30 mm. He was not considered for adjuvant oncological therapy.

Surveillance post-resection

Following surgical management of both lung tumors, the patient underwent a period of clinical, radiological, and endoscopic surveillance over a number of years.

His initial CT follow-up in July 2017 suggests there may be excess soft tissue at the site of previous wedge resection at the right upper lobe, and a PET-CT was subsequently performed which did not suggest disease recurrence. His first surveillance bronchoscopy did not reveal any recurrence or new endobronchial lesions, however, bronchioalveolar lavage (BAL) specimen from the left main bronchus showed some atypical cells.

His follow-up bronchoscopy in February 2018 revealed evidence of malignant cells in keeping with an invasive squamous cell carcinoma from right upper lobe washings, however, repeat CT did not show evidence of disease progression which was confirmed with a PET-CT and he was re-discussed with the thoracic surgeons regarding the possibility of a right upper lobe completion lobectomy. Unfortunately, during 2018, he started to smoke cigarettes again, and his exercise tolerance began to deteriorate and was only able to exercise for 4 min for his repeat cardiopulmonary exercise test. He was considered not suitable for a completion right upper lobectomy due to this functional decline.

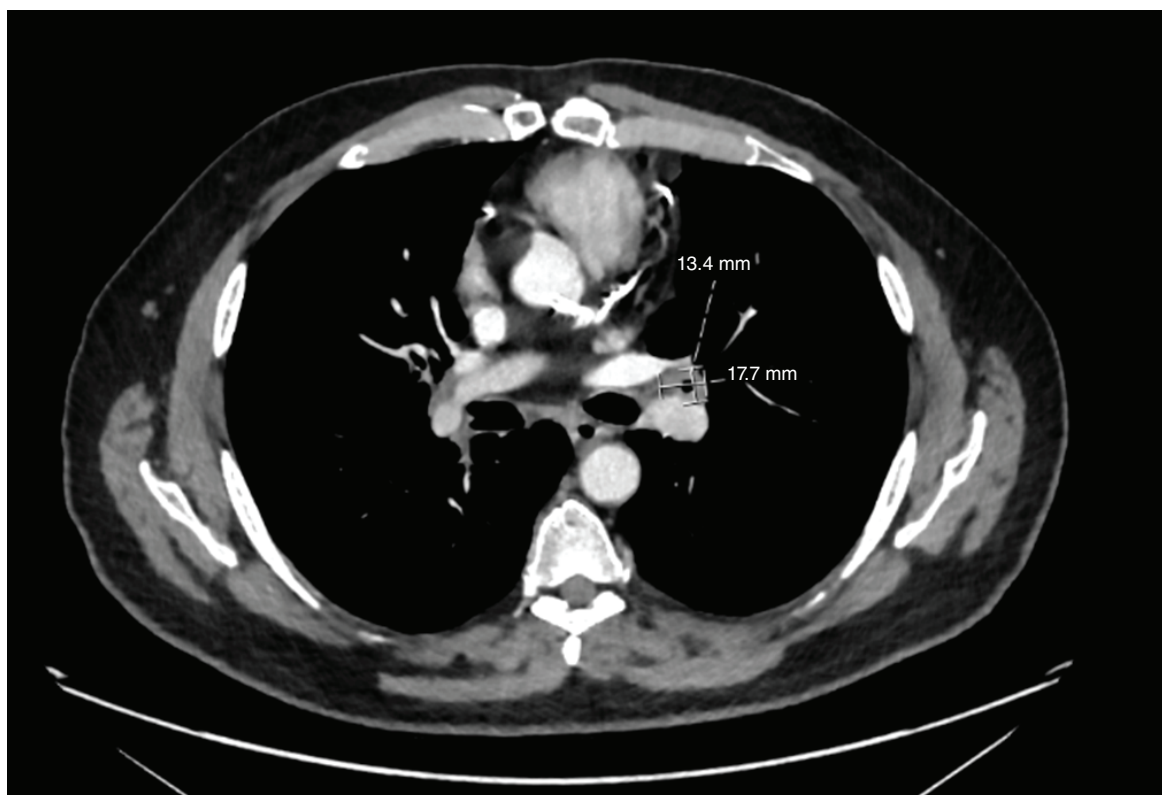


Figure 3. Computed tomography chest from May 2022 showing new proximal thickening of the left upper lobe.

He then had a hospital admission for a non-ST-elevation myocardial infarction (NSTEMI) in August 2018. He required further primary coronary intervention with stenting and commenced on dual antiplatelet therapy. Surveillance bronchoscopy was therefore delayed for a period of time.

After resumption of bronchoscopic surveillance, BAL samples from the left upper lobe continued to show atypical cells suspicious for malignancy, but no overt malignancy detected. Radiological appearances on CT continued to be unchanged in 2019.

At bronchoscopy in September 2019, there was a small mucosal abnormality at the left upper lobe, biopsies were taken from this which showed dysplasia, with a BAL from the right upper lobe showed malignant cells but no evidence of invasive malignancy and the MDM outcome was to continue to offer him ongoing surveillance with CT and bronchoscopy, as he was not fit for further surgical resection.

Unfortunately, due to service pressures from the COVID-19 pandemic, surveillance was not carried out from 2020 to 2021.

Cancer re-emergence & further treatment

On resumption of his clinical surveillance in 2022, he had become evidently more breathless with reduced exercise tolerance. The first CT surveillance during this period revealed some new bronchial wall thickening of the left upper lobe and he was planned for a bronchoscopy (Figure 3). However, he had a further episode of NSTEMI in June 2021 which required further stenting, and bronchoscopic surveillance became challenging as a result due to his antiplatelet therapy.

On bronchoscopy the area on the left upper lobe had edematous and hemorrhagic tissue. Subsequent washings and brushings were taken which revealed evidence of malignant cells. PET-CT performed in May 2022 was suggestive of bilateral recurrences of his lung cancer. (Figure 4) Given the deterioration of his performance status, the MDM consensus was to treat these both radically with radiotherapy.

Radical radiotherapy of 55 Grays in 20 fractions was delivered in August 2022 to both sites. Subsequent surveillance imaging in November 2022 and then February 2023 showed partial response with significant reduction of the bronchial wall thickening in the left upper lobe bronchus, with no evidence of metastatic disease.

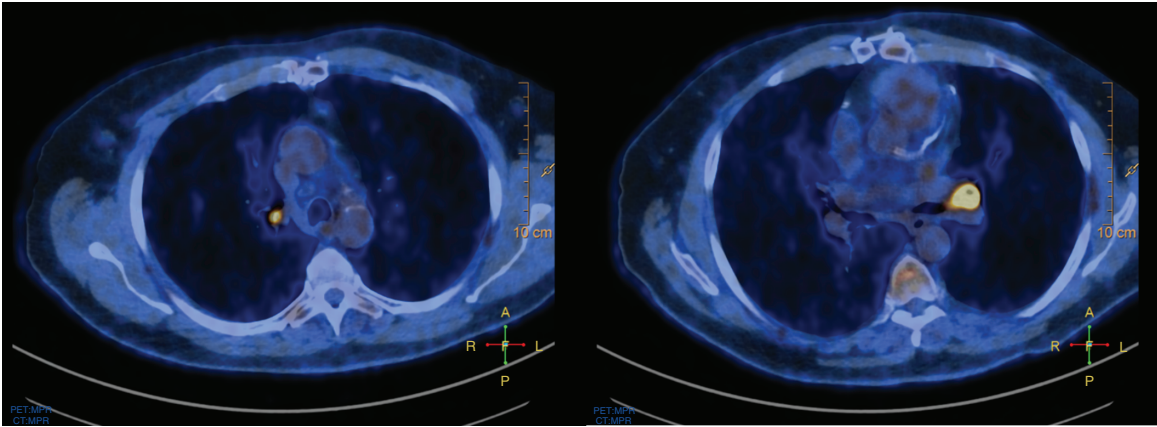


Figure 4. PET-computed tomography showing fluorodeoxyglucose avidity of both lesions of the left upper lobe lesion (right) as well as a right hilar lesion (left).

He remains under clinical follow-up from the oncology and respiratory teams.

Discussion

Epidemiology & risk factors

sMPLCs represent a minority of total lung cancers, with recent systematic reviews revealing they make up 2% of all primary lung cancers in the population which underwent surgical resection [2]. However, with advancements in CT and PET imaging, as well as the advent of lung cancer screening programmes, this number may rise in the coming years.

People who continue to smoke after their diagnosis of their primary lung cancer have an increased risk of developing a second lung cancer compared with those who do not use tobacco [8]. As observed in this case, the resumption of cigarette smoking may have been a major contributor in cancer recurrence.

Diagnosis & staging

Diagnostic criteria for sMPLCs were first described by Martini and Melamed in 1975 and have been adapted by several sources since [9]. Despite this, diagnosis of sMPLC remains challenging as it requires differentiation from metastasis of a primary neoplasm, therefore requiring clinical and pathological characterization of both lung tumors. A second lung tumor is generally presumed to be a metastasis, until proven otherwise. This usually involves careful staging of the mediastinum, usually with PET-CT to ensure absence of uptake on mediastinal lymph nodes, as well as the absence of extrathoracic metastases [4,7].

With bilateral sMPLCs such as our case, the absence of N2 and N3 disease is crucial in making a diagnosis of sMPLC, as shown on both CT and PET-CT imaging. Pathological exclusion of mediastinal disease may be challenging due to the lack of nodal disease, which means endobronchial ultrasound (EBUS)–transbronchial needle aspiration will likely be challenging and a risky procedure for the patient, but would otherwise be indicated if uptake was seen on PET or significant lymphadenopathy on CT. In this case, it was felt by the MDM that EBUS staging would not have any additional diagnostic value given lack of nodal uptake on PET-CT and would have delayed surgical management, so EBUS staging was not performed.

Conventional TNM staging for singular primary lung cancers may not be appropriate for sMPLCs [7]. Currently, the widely accepted sMPLC staging method is according to the location of separate tumor nodules relative to the main tumor, classifying as T3 in the same lobe, T4 in ipsilateral different lobe, and M1a in contralateral lung [7,9]. However, whether this classification could predict the prognosis of sMPLC remains unclear and differentiating sMPLC from intrapulmonary metastases is still a big challenge.

Tumors are considered metachronous if the histology is different, or if they are from the same histology and there is a four year or greater interval between the cancers with no evidence of systemic metastases [3]. Since the onset of histological recurrence was around 1 year after initial surgical management in this case, we have not classified this as also a mMPLC. This case highlights that defining “recurrence” may be difficult, as more atypical presentations such

as endobronchial predominant tumors such as in this case may present with histological recurrence a lot sooner than when it will recur radiologically, and will thus impact on its subsequent management.

Prognostication

MPLCs were found to have better overall survival than lung cancer patients with intrapulmonary metastasis from a systemic review, further emphasising the importance of differentiating between the two [3]. Stage is considered the most significant predictor of survival post-surgical resection. Consistently with non-small cell lung cancer (NSCLC) prognostic factors, there are also negative association between long-term survival with older age, male sex, smoking status and lower forced expiratory volume in 1 s in sMPLCs [3,10]. As highlighted in this case, with survival seven years on from initial diagnosis, the importance of differentiating MPLCs from intrapulmonary metastases must not be understated for prognostication, as despite carrying negative prognostic factors, this patient may have had a much poorer outcome if this were to be an intrapulmonary metastasis.

Therapeutic options

Provided there is adequate fitness, surgery of both lesions remains the preferred option for sMPLCs, with a significant proportion of patients who undergo successful surgical resection having survival greater than 60 months [10].

Certainly, limited pulmonary reserve was perhaps a deciding factor in proceeding with a wedge resection rather than a segmentectomy or a lobectomy in the first instance, and with further deterioration of pulmonary reserve upon disease recurrence, a completion right upper lobectomy in this case was not feasible. Of note, the initial left lingular lesion was felt to be endobronchial only, and was managed with laser ablation therapy via rigid bronchoscopy. The option for a completion left upper lobectomy was initially considered by the surgical team if there were to be recurrence at a later stage, however, similar to his right lung cancer, his deterioration in performance status meant further surgical management was not feasible.

The optimal surgical management in this case has been debated at previous MDMs. Laser ablation has been emerging as a suitable curative option for early stage, minimally invasive NSCLCs, with early studies demonstrating 90–100% success in regard to recurrence at 5 years [11]. However, these studies are largely based on cases which are not MPLC, and with knowledge that MPLCs have a higher recurrence rate than non-MPLCs, it can be argued that laser ablation in the context MPLCs do not have a strong enough evidence base. Further studies directly comparing laser ablation against surgical resection in the management of early-stage endobronchial lung cancers could be useful, however, applicability to MPLC cases might still remain difficult as they are relatively rare. There is, however, recent evidence at a meta-analysis level to suggest that lobectomy or segmentectomy for early-stage NSCLC had an overall better survival compared with patients who had a wedge resection [12]. Adding to existing data highlighting the higher recurrence rate with wedge resection compared with lobectomy in sMPLCs [6]. In this case, a wedge resection was chosen over lobectomy or segmentectomy largely based on the patient's comorbidities. Based on emerging evidence, however, it may be argued that major resection is still justifiable in early NSCLC.

Stereotactic ablative radiotherapy (SABR) is the preferred alternative for those who are not fit for surgical resection and have similar outcomes in survival compared with surgical resection, and have also reported greater local tumor control and overall survival compared with conventional radiation therapy [13,14]. With this case, SABR was not considered in the first instance as the patient was a surgical candidate, however, on its recurrence when the patient was no longer fit for surgery, its unique situation in its bilateral recurrence rendered it unsuitable for SABR and conventional radiation therapy was chosen instead.

Surveillance

A major challenge in this case was the ongoing surveillance following surgical management. Currently, there are no available guidelines for follow-up of MPLCs due to the lack of available data. Generally, sMPLCs are recommended to be followed up more aggressively compared with mMPLCs [6]. While frequent surveillance did occur in this case initially, there were major challenges in achieving this as the years went on. First, dual antiplatelet therapy following an NSTEMI limited bronchoscopic surveillance, and rather unfortunately, both radiological and bronchoscopic surveillance were halted as a result of the heavy resource depletion at the time during the COVID-19 pandemic. This case highlights that deciding on an optimal surveillance strategy may be difficult, as due to the heterogeneity of the presentation of MPLCs, surveillance options may differ. For endobronchial tumors, bronchoscopic surveillance proved to be extremely important in establishing the presence of cancer cells prior to the tumor becoming radiologically apparent.

Research & future directions

With the likely advent of lung cancer screening programmes in the future, MPLCs will likely become more prevalent. Development of updated diagnostic criteria and recommendations for therapy options, as well as standardization in post-treatment surveillance will be crucial to managing these challenging cases. Comprehensive genetic profiling and mutational testing trials to distinguish metastatic primary lung cancer with MPLCs are underway [5].

The regional recurrence rate of patients with sMPLCs was about twice as much as that of patients with single early-stage lung cancer [2]. With emerging studies in molecular biomarkers and genetic profiling underway, we hope to be able to answer important questions in how to differentiate MPLCs between intrapulmonary metastases and assess the potential for immunotherapy or targeted therapy for MPLC patients in the near future [15].

Conclusion

MPLCs pose a rising challenge in the current world of improved diagnostic imaging, with uncertainties in the optimal management strategies due to the lack of real-world data. Mapping molecular characteristics of MPLCs compared with that of intrapulmonary metastases is an evolving research field that aims to precisely differentiate between the two. Integrating radiological imaging with pathological and genomic data using artificial intelligence may promote more accurate diagnosis for MPLCs in the future. Immunotherapy and targeted therapy using molecular markers may be facilitated as an option for MPLCs once molecular profile mapping for MPLCs become more prominent in the future. While research is underway, close collaborative work of local lung MDMs are essential in ensuring the desired outcomes for patients diagnosed with MPLCs.

Summary points

- Synchronous multiple primary lung cancers (MPLCs) are characterized by at least two primary lung tumors simultaneously identified in ipsilateral or contralateral lung.
- Mediastinal staging with PET-computed tomography and/or endobronchial ultrasound–transbronchial needle aspiration with multidisciplinary meeting is crucial in the differentiation of synchronous MPLC from metastasis of a primary neoplasm.
- Where possible, surgical resection should be considered for both simultaneous lesions, with stereotactic ablative radiotherapy offering an adequate alternative.
- Close surveillance clinically, radiologically, and endoscopically (for endobronchial tumors) is crucial in detection of potential early cancer recurrence.
- MPLCs have a better overall survival compared with lung cancer with intrapulmonary metastases, therefore it is crucial to be able to differentiate between the two.
- Thoracic oncology research in this area remains limited and highlights the evidence gaps especially in the areas of clinical prognostic factors as well as the role for targeted and immunotherapy for MPLCs.

Author contributions

H Liu – conception of work, acquisition of data; drafting and revision; final approval for submission; agreement for accountability of accuracy of work. L Polley – conception of work, interpretation of data, drafting and revision; final approval for submission; agreement for accountability of accuracy of work.

Financial disclosure

The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

For investigations involving human subjects, informed consent has been obtained from the participants involved. Informed verbal consent has been obtained by the authors from the patient at their last clinic visit for the inclusion of their medical and treatment history within this manuscript.

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