

Molecular analysis driven video-assisted thoracic surgery resections in bilateral synchronous lung cancers: from the test tube to the operatory room

Sergio Nicola Forti Parri¹, Barbara Bonfanti¹, Alessandra Cancellieri², Dario De Biase³, Rocco Trisolini⁴, Stefania Zoboli⁵, Luca Bertolaccini⁶, Piergiorgio Solli¹, Giovanni Tallini⁷

¹Thoracic Surgery Unit, AUSL Bologna, Maggiore-Bellaria Hospital, Bologna, Italy; ²Pathology Unit, AUSL Bologna, Maggiore Hospital, Bologna, Italy; ³Department of Pharmacy and Biotechnology (FaBiT), Molecular Diagnostic Unit, AUSL Bologna, University of Bologna, Bologna, Italy; ⁴Interventional Pulmonology Unit, Policlinico Sant'Orsola-Malpighi, Bologna, Italy; ⁵Nuclear Medicine Unit, AUSL Bologna, Maggiore Hospital, Bologna, Italy; ⁶Department of Thoracic Surgery, AUSL Romagna Teaching Hospitals, Ravenna, Italy; ⁷Department of Medicine, Molecular Diagnostic Unit, AUSL Bologna, University of Bologna, School of Medicine, Bologna, Italy

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Correspondence to: Sergio Nicola Forti Parri, MD. Thoracic Surgery Unit, AUSL Bologna, Maggiore-Bellaria Hospitals, Largo Nigrisoli 2, Bologna 40133, Italy. Email: sergionicola.fortiparri@ausl.bo.it.

Abstract: Synchronous cancers are not such rare clinical conditions. Nevertheless, even after the 8th edition of the TNM classification of the lung cancer, the surgical approach for patients presenting with synchronous bilateral lung cancer is still under debate. The resection of both lesions in the case of synchronous bilateral lung cancer is reasonable, but, on the other hand, is the lobectomy the correct choice in the event of the single primary with a contralateral metastatic lesion? In this case report, we describe how the molecular analysis and the detection of the *EGFR*, *KRAS* and *TP53* mutations in both tumours have determined in a patient the two tumours as primary and both the right surgical approach. We also discuss how molecular analysis found differences in all the three genes examined in the two lesions and allowed to exclude the clonal nature of the two tumours. In conclusion, genetic studies help to offer a more radical surgical treatment to this patient.

Keywords: Lung cancer; oligometastatic; thoracic surgery; lung cancer classification

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Introduction

Synchronous cancers are not such rare clinical conditions (incidence around 1–8%) (1). Nevertheless, even after the 8th edition of the TNM classification of the lung cancer, the surgical approach for patients presenting with synchronous bilateral lung cancer is still under debate (2). The resection of both lesions in the case of synchronous bilateral lung cancer is reasonable, but, on the other hand, is the lobectomy the correct choice in the event of the single

primary with a contralateral metastatic lesion?

Herein, we describe how the molecular analysis and the detection of the *EGFR*, *KRAS* and *TP53* mutations in both tumours have determined the two tumours as both primary and the right surgical approach.

Case presentation

A 72-year-old male patient, with a smoking history (12 pack years) and without another substantial comorbidity,

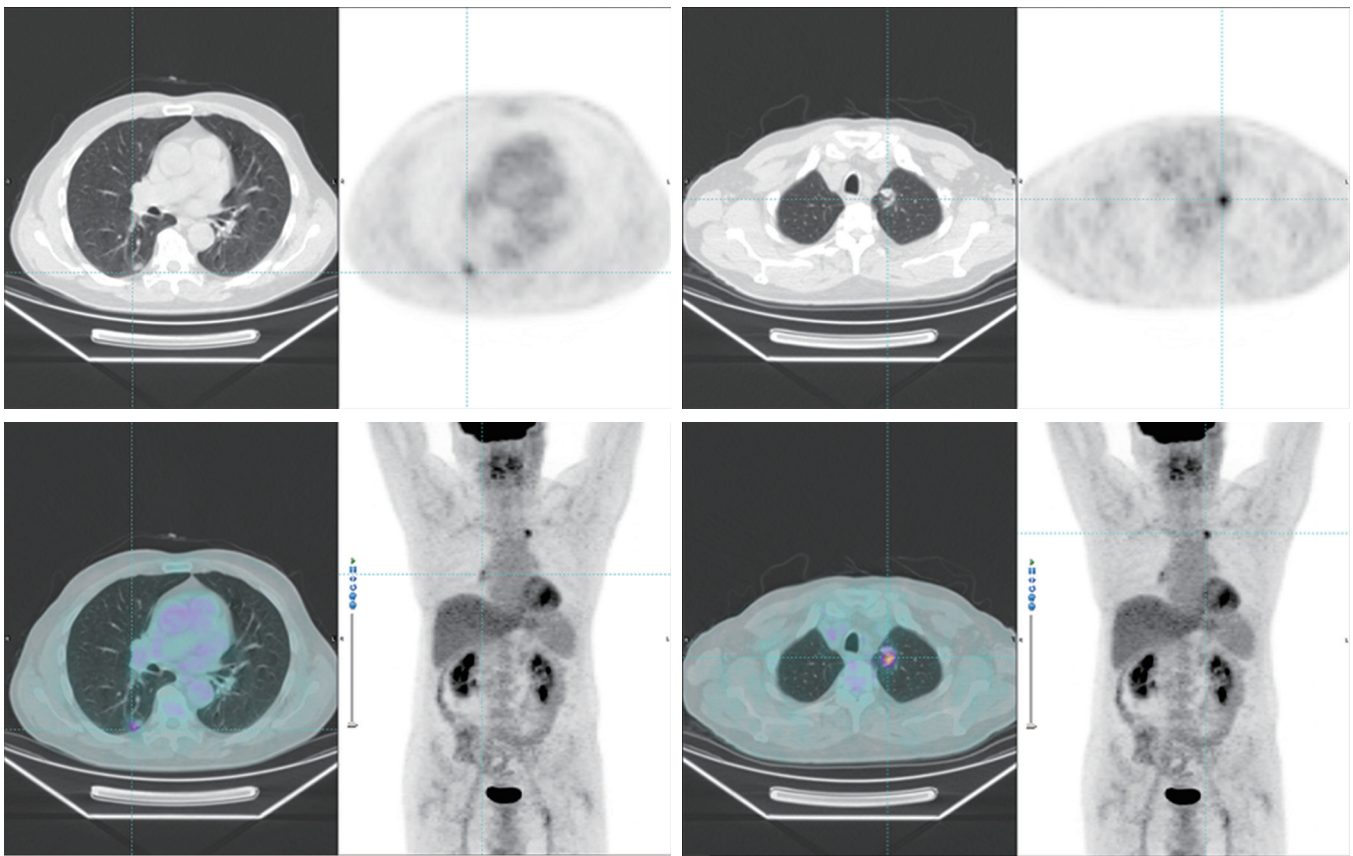


Figure 1 A 72-year-old male patient with a left upper lobe 2.5 cm nodule and a right lower lobe 1.2 cm nodule. The 18 FDG PET/CT scan was positive for both nodules (SUV for left nodule = 4.8, SUV for right nodule = 2.8).

was referred to our hospital with a left upper lobe nodule (diameter = 2.5 cm) and a right lower lobe nodule (diameter = 1.2 cm), both suggestive of malignancies. The 18 FDGPET/CT scan was positive for both nodules (SUV = 4.8 for the left nodule, SUV = 2.8 for the right one). No other positive areas were detected at the whole-body PET/CT scan (*Figure 1*). The left nodule was biopsied under bronchoscopy with rapid on-site evaluation, showing several aggregates of muco-secrent adenocarcinoma cells. Transthoracic fine needle aspiration of the right lobe nodule was performed twice, and both analyses were negative for neoplastic cells. The cardiorespiratory assessment did not show any relevant abnormality. A previous indeterminate surgery on the right chest at the age of 40 days and at 4 years old was the only relevant past medical history. Despite the negative cytological findings on the right nodule, the multidisciplinary team discussion suggested an anatomical resection to achieve the definitive diagnosis and to aid the approach of management regarding the left nodule. A video-thoracoscopic wedge

resection was performed on the right inferior lobe. No adhesences were found despite previous surgeries on that side, and the surgical procedure was uneventful. The histology revealed an adenocarcinoma with muco-secrent cells and signet ring cells, infiltrating the pleura. The resection margins were oncological radical with more than 2 cm from the tumour. The patient was discharged on postoperative day 3, and the recovery was uneventful.

At this point, we had not still determined whether the right lesion was a metastasis or a synchronous primary tumour, assumed the same histological aspects of the two lesions. Therefore, the major concerns were the following surgical indication: a left lung lobectomy for M1a cancer resected on the right side or a less invasive left upper wedge resection? To help us, we proceed to the molecular analysis of the two lesions. The *EGFR* (exons 18–21), *KRAS* (exons 2–3), and *TP53* (exons 4–9) genes were tested in both lesions to detect the similar clonal origin of the tumours, utilising the next-generation sequencing method (454 GS-Junior, Roche) (3-5). A mutation in the exon

Table 1 Molecular analysis of the two bilateral lung neoplasms

Gene [exon]	Left upper lobe lung cancer	Right lower lobe lung cancer
<i>EGFR</i> [18–21]	p.P753P (c.2259G>A); p.L782L (c.2346C>T)	WT
<i>KRAS</i> [2–3]	p.G12V (c.35G>T)	WT
<i>TP53</i> [4–9]	p.L308L (c.922C>T)	WT

WT, wild type.

2 of the *KRAS* [p.G12V (c.35G>T), in 17% of analysed alleles] was found in the left upper lesion, but not in the right lower cancer. Furthermore, the left lesion only had the following silent abnormalities: *EGFR* p.P753P (c.2259G>A) and *EGFR* p.L782L (c.2346C>T), *TP53* p.L308L (c.922C>T) (Table 1). The molecular analysis considered the lesions as two distinct primary tumours. Hence, the patient underwent a Video-Assisted left superior lobectomy with standard lymph nodes dissection 28 days after the first surgery. The postoperative recovery was uneventful, and the pathological stage was pT2(PL1)N0M0. The follow-up was regular without a sign of recurrences.

Discussion

The 7th edition of the TNM classification for lung cancer laid a focus on separating potentially curative stages without proven metastatic M1 disease from categories with positive M1 descriptors (M1a and M1b) where there was little chance of achieving relative rates of 5-year survival. First, the value of the above M1a descriptor definition was confirmed, including patients with contralateral or bilateral lung nodules (6). No significant differences were noted between the M1a descriptors, and there was also no effect observed of single versus multiple descriptors. It is not vibrant, whether these positive findings from clinical staging in comparison with the results of the previous TNM classification can be explained by stage migration effects or the possibility that some lesions are not actual sites of malignant involvement (2). Consequently, according to the newest TNM classification (8th edition), in the presence of two lesions from the same primary in the same lobe, the staging is T3, if in different lobes of the same lung is a T4, and in the bilateral nodules is an M1a (2).

Data from the Literature suggests that radical resection of two synchronous lesions offers better outcomes compared to the excision of metastatic disease, especially if N0 stage. All

the available studies on the different strategies to distinguish a metastasis from synchronous primaries are based on investigations performed after definitive treatment. Treatment of lesions with different histologies merely guided by the cardiorespiratory reserve of the patient (1). Synchronous surgery for bilateral tumours is considered an effective strategy for preventing disease progression. However, simultaneous bilateral lobectomy with lymph node dissection is related to increased risk and should only be performed in carefully selected patients and high volumes centres. Given the treatment outcomes in patients with the pN2 disease, if the N2 disease is perceived at the first stage of the two-steps resection, other treatment choices such as chemotherapy and stereotactic body radiotherapy should also be considered instead of performing lobectomy at the second step (7).

However, decision making on lesions with the same histology is more challenging, and currently, no research is available to inform the clinician on the best strategy to adopt. The Martini-Melamed criteria have been widely used for differential diagnosis (8). Tumours of the same histologic type that arise in the same segment of the lung are diagnosed as intrapulmonary metastasis. Even if different segments are involved, tumours of the same histologic subtype are diagnosed as intrapulmonary metastasis, if metastasis is originated at shared lymphatic pathways. The Martini-Melamed classification is currently used, even though it needs an histopathology exam of both lesions (8). In addition to these criteria, it is essential to assess other aspects of diagnosis. In multiple adenocarcinomas, the histologic subtypes of the tumours must be well-thought-out. The recently planned comprehensive histologic assessment has facilitated the differential diagnosis of multiple primary NSCLC and metastases (7). In our patient, the situation was challenging under some aspects. Using the Martini-Melamed classification after the right lung excisional biopsy, we could not define the two nodules as synchronous. No metastasis was shown, but neither histopathology analysis showed an in-situ origin. The slightly undefined histological subtype of both lesions suggested the possible clonal lesions.

According to international guidelines, an expert multidisciplinary team approach is the best option to define the individualised approach to patients with two bilateral lesions; in the case of two synchronous primaries, the surgical resections of both lesions is usually suggested (9).

It is evident that the differentiation between multiple primary lung cancers and intrapulmonary metastases is of first importance for disease staging and management, and

for patient prognosis. The arbitrary nature of the current histomorphological criteria already used often generates diagnostic dilemmas. Alternative approaches implementing genetic and/or molecular testing standards could provide more valid information for definite diagnosis in these doubtful cases. Surgical treatment is beneficial for selected patients with multiple primary lung lesions and might offer long-term survival, provided that the clinical stage of the second tumour and the patient's cardiopulmonary reserves permit it. The early stages of the second primary and the absence of extranodal involvement have been associated with a more favourable prognosis. Finally, postoperative surveillance with a medical history, physical examination, and imaging studies are mandatory to monitor for recurrence of the original tumour or screen for potentially curable, early-stage metachronous cancers (10).

The challenging questions remain whether a lobectomy was indicated for the left lesion considering that the disease could be a stage IV. On the other hand, a less invasive and less oncological surgical option, like a wedge resection, could not be acceptable to a healthy state patient with a possible stage I synchronous lesion without comorbidity.

In conclusion, the stage of the two lesions, as well as the deep cellular relation between, was not defined using only clinical and histological criteria. The molecular analysis found differences in all the three genes examined in both lesions and allowed to exclude the clonal nature of the two tumours. Therefore, the genetic studies help to offer a more radical surgical treatment to this patient.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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