

Multiple primary lung cancer: A literature review

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Abstract

Nowadays, lung cancer is a leading cause of death in both men and women worldwide. There is no clear explanation for its mortality rate. However, it is already known that genetic and environmental factors as well as oncological treatment are involved. As the incidence of lung cancer soars, the number of patients diagnosed with multiple primary lung cancers (MPLC) is also rising. While differentiating between MPLC and intrapulmonary metastasis of lung cancer is important for treatment strategy and prognosis, it is also quite complicated, particularly in the cases with similar histologies. It is also important not to delay the diagnosis. The aim of this paper was to discuss MPLC in general, and the differentiation between MPLC and intrapulmonary lung cancer metastasis in particular. Based on a review of statistical data and the current literature, we discuss the diagnostic criteria and the molecular, genetic and radiographic methods used to distinguish between MPLC and intrapulmonary metastases.

Key words: lung cancer, intrapulmonary metastasis, multiple primary lung cancer

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Introduction

Lung cancer is a leading cause of death in both men and women worldwide.¹ About 1.6 million people die of lung cancer each year and the overall 5-year survival rate is only 15%.^{1,2} Most lung cancers are detected at an advanced stage. During or after the treatment of one cancer, the patient may develop another one, including lung cancer. In patients with synchronous multiple primary lung cancer (MPLC) and contraindications to surgical treatment, the mean survival time is 31 months.³ Distinguishing between intrapulmonary metastases and a new primary cancer may be difficult (especially when the tumor histologies are similar). It is estimated that about 50.8–57.9% of MPLCs have similar histologies.^{4,5} It may be even more difficult to discriminate between a subsequent primary lung tumor and an intrapulmonary metastatic tumor if the former develops at a location previously treated with radiotherapy, due to the morphological changes that have taken place there.

Definition of multiple primary lung cancers

The first diagnostic criteria of MPLC were published by Martini et al. in 1975.⁶ According to these criteria, synchronous and metachronous MPLC can be distinguished. Synchronous cancers are separate neoplastic processes, histologically identical or different, but occurring in different segments, lobes, or lungs. If they originate from carcinomas in situ, they do not metastasize to the lymph nodes; moreover, extrapulmonary metastases are not present at the time of diagnosis. Metachronous cancers are neoplastic processes with identical or different histologies which develop at an interval of at least 2 years or which originate from carcinomas in situ, or in which the 2nd tumor is located in another lobe or lung, there is no evidence of lymph node metastases, and no extrapulmonary metastases are present at the time of diagnosis. The development of new diagnostic methods has led to modifications of these criteria. Since 1995, MPLC has been defined according to Antakli et al.⁴ A diagnosis of MPLC is established if the tumors have different or similar histologies and meet at least 2 of the following 5 criteria:

- different histological locations;
- premalignant lesion;
- no metastases;
- no mediastinal infiltration; or
- different DNA ploidy.

Metachronous lung cancers are the most common MPLC, accounting for 50–70% of all cases.⁷

A case of multiple primary cancers in a single patient was first reported in the literature by Billroth in 1898, while a report on the first case of MPLC was published by Beyreuther in 1924.^{8,9}

Various cancer registries have been created since then, enabling the collection of statistical data on the incidence

of multiple primary cancers and allowing the prediction of the most likely development of subsequent cancers. This may prove useful in guiding the diagnostic process and preventing the development of further tumors in patients already diagnosed with primary cancers. The registries include:

- the Vaud Cancer Registry, a cancer registry covering the Swiss canton of Vaud and designed to facilitate the risk assessment of the 2nd metachronous cancer;
- The Italian Association of Cancer Registries (AIRTUM), an Italian association of cancer registries providing data on the demographic situation, statistics, incidence, and mortality from cancer in Italy;
- European Cancer Registry (EUROCARE), a registry providing information on the survival of cancer patients based on data collected in population registries; and
- Surveillance, Epidemiology, and End Results Program (SEER), a National Cancer Institute (NCI) population analysis providing information on the statistics of cancer in the US population.

Epidemiology

The development of multiple cancers is determined by many different factors. The treatment administered for the initial cancer is thought to be the primary factor which affects the development of subsequent malignancies. The likelihood of developing the 2nd cancer increases with the duration of survival after the completion of treatment for the primary cancer. The risk is higher in patients diagnosed with the primary cancer below the age of 60 years and in patients with lower-stage primary cancers, in whom the chances of recovery are considerably higher. The process of subsequent neoplasia – apart from genetic factors – is largely determined by carcinogens, such as tobacco smoke and alcohol, which contribute to disseminated lesions in the tissues permanently exposed to these substances.

Smoking is one commonly known factor responsible for the development of cancer. It is particularly related to the direct exposure of the respiratory tract to carcinogenic substances. Many years of smoking may also contribute to the simultaneous development of several cancers at any point after resection of the primary cancer tumor.¹⁰ Despite considerable expenditure on the primary prevention of lung cancer (smoking cessation programs), this malignancy still ranks 1st in terms of incidence and cancer-related mortality worldwide.¹¹ In the vast majority of cases (85–90%), lung cancer is associated with smoking – including passive smoking by never-smokers.^{11,12} Moreover, in a large percentage of cases, lung cancer is diagnosed in former smokers, as the risk of this malignancy continues to increase for many years after smoking cessation.¹³

Retrospective studies have shown an increased risk of subsequent lung cancer after the diagnosis of the 1st lung

cancer. In patients with non-small-cell lung carcinoma (NSCLC), the risk of developing another cancer has been estimated at 1–2% per year, while the risk of another lung cancer in patients with successfully cured small-cell lung carcinoma (SCLC) has been reported at 2–14% per year.^{14,15}

In patients who have undergone primary surgical resection for lung cancer, the risk of MPLC is approx. 16%. The risk is obviously not very high, but this is explained by the fact that most patients diagnosed with primary lung cancer die before they develop another type of cancer. If we consider only those patients who survive more than 3 years after the diagnosis of the initial cancer, we can observe that 10–25% of them will develop another lung cancer.¹⁶

The effects of genetic factors on the development of lung cancer

Recent advances in the analysis of the lung cancer genome have profoundly changed our understanding of this disease on a molecular level. The most important genes responsible for the development of lung cancer are: *EGFR*, *KRAS*, *MET*, *LKB1*, *BRAF*, *PIK3CA*, *ALK*, *RET*, and *ROS1*.¹⁷

Mutations in *EGFR*, *KRAS*, and *ERBB2* have been demonstrated in adenocarcinoma of the lung.¹⁸ It is often the case that *EGFR* mutations are present in the primary lung cancer but not in its metastases.¹⁹ The *EGFR* gene was screened for mutation in exons 18, 19, 20, and 21 in a female patient with a recent diagnosis of lung adenocarcinoma and a previous lung adenocarcinoma. Mutation analysis of the *EGFR* gene revealed a different mutation in each tumor (on exon 19) confirming the diagnosis of 2 metachronous primary lung cancers.^{20,21} Both *EGFR* and *RAS* mutations contribute to the development of NSCLC.^{22,23}

KRAS mutations are rare in squamous cell carcinoma of the lung, but may be found in approx. 15–25% of lung adenocarcinomas.²⁴ In most cases, this is a missense mutation introducing an amino acid substitution at position 12, 13 or 61, which is associated with a poorer prognosis and resistance to erlotinib and gefitinib.²⁵ Yoon et al. described a case with synchronous triple primary lung cancers with wild-type *EGFR/KRAS* and anaplastic lymphoma kinase mutation.²⁶

The tyrosine kinase receptor c-Met plays a significant role in the development of many solid tumors, including SCLC, involved in the processes of neoplasia, cell motility, scattering, invasion, and metastatic spread.

Loss-of-function mutations in *LKB1* were initially only associated with Peutz-Jeghers syndrome, an autosomal dominant genetic disorder.²⁷ Sanchez-Cespedes et al., however, have demonstrated that *LKB1* mutation is also present in 1/3 of all lung adenocarcinomas.²⁸

In NSCLC, *BRAF* mutations have been identified in 1–3% of samples collected from patients. V600E mutations (50%) are the most common, followed by G469A mutations (39%) and D594G (11%).²⁹ An analysis of the *BRAF*

gene sequences in 127 patients with lung adenocarcinoma has shown 2 specific mutations: one in exon 11 (G465V) and the other in exon 15 (L596R).³⁰

Kawano et al., in a study of 135 patients with a diagnosis of lung cancer, showed that *PIK3CA* exon 9 mutation occurred in about 3.4% of the patients.³¹ This mutation was more common in squamous cell carcinoma of the lung than in adenocarcinoma (6.5% vs 1.5%), and its presence did not correlate with the patient's sex or smoking history.

Less frequent mutations, such as *ROS1* and *RET* mutations in patients with NSCLC, have been reported to occur at a rate of 2% and 1%, respectively.^{32,33} *ROS1* mutations are almost always exclusively concomitant with *KRAS*, *EGFR*, and *ALK* mutations.^{34,35}

Oncogenetic lung cancer research will lead to new considerations, such as diagnostic tools and therapies. In the near future, more research is needed to more accurately characterize lung cancer mutations in order to generate information that can significantly change the future clinical management of this disease. This can contribute to reducing the incidence of MPLC and improving its detectability. Based on the difference in the expression of the mutated genes, a new primary tumor can be differentiated from an intrapulmonary metastasis, as discussed below.

Screening tests

Preventing lung cancer is much more important than screening for it. Randomized clinical trials have shown that obtaining a chest radiograph does not increase the survival of patients diagnosed with lung cancer. Recent studies, however, have demonstrated that annual screening for lung cancer with chest computed tomography (CT) decreases mortality in patients with a history of strong nicotine dependence.³⁶ The efficacy of intensive surveillance by means of annual chest CT scanning to detect subsequent lung cancers or lung cancer metastases has not been formally demonstrated, although subsequent annual CT scans are often performed and recommended by the National Comprehensive Cancer Network (NCCN) guidelines. This data, however, is insufficient to conclusively support this common practice. More sensitive diagnostic measures, such as lung imaging fluorescence endoscopy (LIFE), are being investigated to establish their usefulness for the detection of synchronous tumors.³⁷

How to differentiate multiple primary lung cancers from disseminated primary tumor

The incidence of synchronous or metachronous lung cancers has been increasing over the past few years. This has been due to technological progress and the increasing

availability of novel diagnostic methods, such as computed tomography and positron emission tomography. What continues to be challenging is the differentiation of a subsequent lung cancer from intrapulmonary metastases of the 1st lung cancer. According to the current TNM classification (8th edition) for lung cancer, in the event that the tumor nodules are found in the same lobe as the main tumor, the tumor is categorized as T3; if the tumor is found in a different lobe but on the same side – T4; and if it is located on a contralateral side – M1a.³⁸ When multiple primary lung tumors are present, it is quite difficult to distinguish multicentric lung cancer from a primary cancer in a different organ.³⁹ Currently, based on histopathology, many of the subsequent lung cancers are erroneously diagnosed, especially if the patient develops a multiple lung malignancy that is histologically impossible to differentiate.³ Such differentiation, however, is possible using genetic and immunohistochemical methods, and a correct diagnosis is necessary for the selection of suitable treatment. Many studies have reported differences in certain cancer gene mutations, chromosome aberrations, and microsatellite alterations between different MPLCs.^{40,41}

A study of 19 metachronous and 11 synchronous multiple lung tumors investigated the overexpression and genetic abnormalities of the *p53* gene.⁴² The results have shown that some of the multiple tumors were of different clonal origins, although their histological type was the same. Mitsudomi et al. analyzed the phenotypes in 16 patients with *p53* gene mutation using polymerase chain reaction (PCR) and single-strand conformation polymorphism (SSCP).⁴³ At least one *p53* gene mutation in the lung tumor was demonstrated in 9 of these patients. The *p53* mutation statuses were incongruent in these patients. This suggested a different clonal origin, even though 6 of them had nearly identical histological features. In lung cancer, the *p53* gene has so far been considered one of the most commonly mutated genes, with mutations present in 50% of NSCLC patients and in nearly all SCLC patients.⁴⁴ Another advantage offered by testing for *p53* gene mutation is that the mutation can be demonstrated relatively early in the course of lung cancer, especially its squamous cell variety, because the mutation plays a role in developing the malignant phenotype.⁴⁵ Once acquired, this phenotype is well-preserved during progression and metastasis.⁴⁶ In addition to the *p53* gene mutation, several other molecular methods are currently available for clonal analysis of lung tumors. The analysis of X-chromosome inactivation, which occurs in the early phase of lung cancer development, is interesting. It is only possible, however, to investigate it in females.⁴⁷ In addition, testing for the loss of heterozygosity (LOH) in certain arms of chromosomes, such as 3p, 5q, 9q, 11p, 13q, 17p, or 18q, or for *RAS* mutations is currently being performed.

Many studies have shown that phenomena based on microsatellite instability (MSI) and on LOH can be used to differentiate between a disseminated primary tumor

and a subsequent primary tumor, both in the early and late stages of the disease.^{48–50} Both of these phenomena, MSI and LOH, represent molecular abnormalities acquired by the cell during neoplastic transformation. Shen et al. carried out a molecular analysis of 2 lung tumors in a single patient (one tumor located in the right lower lobe and the other in the right upper lobe) based on microsatellite allele D2S1363, which was detected in the 1st tumor, but not in the other. In both tumors, the same allelic background for 5 microsatellite markers was established, although it did differ in 1 microsatellite marker – D2S1363 – which was detected in the 1st, but not in the other tumor.⁵¹ This finding was concluded to substantiate the fact that the 2nd lesion was indeed a metastatic lesion originating from the 1st tumor, which was histologically confirmed.

Wang et al. investigated genetic material from 70 lung tumors in 30 patients.⁵² In each of the 30 patients, LOH was demonstrated in 1–4 of the 6 microsatellite markers. Twenty-three of the 30 patients (77%) were shown to have identical genetic abnormalities consistent with a monoclonal origin of different tumors.

Molecular analysis of different alleles and microsatellite polymorphic markers can therefore be used to differentiate metastatic tumors from MPLCs.

Differential diagnosis of tumors can also be carried out on the basis of *EGFR* mutations.⁵³ Takuwa et al. published a case report on the simultaneous presence of 2 adenocarcinomas, each at a different location.⁵⁴ One tumor, located in the middle lobe, showed the L858R mutation in *EGFR* exon 21, which was identical to the mutation in the cells sampled from the subcarinal lymph nodes. No such mutation, however, was detected in the other tumor, located in the upper lobe. Based on that, a diagnosis of dual primary lung cancer was established. This is a known hotspot mutation and accounts for more than 40% of *EGFR* mutations reported in Asian lung adenocarcinoma patients.⁵⁵

In the area of low-dose CT screening for lung cancer, though, the search for a non-invasive tool to differentiate primary lung cancer and granulomatous nodules has intensified.^{56,57}

Positron emission tomography (PET) can be used to differentiate multiple primary synchronous tumors from disseminated primary tumors. Dijkman et al. conducted a study in 37 patients in which they demonstrated a significantly higher Δ SUV (difference between standardized uptake values) in those with the 2nd primary tumor compared to those with a metastatic tumor (58% vs 28%, $p < 0.001$).⁵⁸ Furthermore, Hsu et al. showed that tumor size itself may have a strong influence on potential local progression or metastasis, and that the combination of SUV_{max} and size together identified a subgroup of patients at higher risk for recurrence after surgical resection.⁵⁹ The SUV values from images acquired using ¹⁸F-FDG PET can therefore be useful in differentiating metastatic tumors from other primary tumors in patients with synchronous lung cancer.⁶⁰

Summary

Patients diagnosed with their 1st lung cancer should be carefully monitored in order to allow the early detection of a subsequent malignancy. The diagnosis of MPLC may be delayed or incorrect in patients with lung cancer with intrapulmonary spread. Novel methods of differential diagnosis of the intrapulmonary spread of a primary tumor vs MPLC may provide valuable diagnostic clues. Undoubtedly, molecular methods in the near future will have a growing role and will optimize the management of patients with multiple neoplasms. However, the current knowledge about MPLC oncogenetics is still insufficient. We hope that future studies will provide a deeper understanding of this problem, and thus contribute to better prevention and earlier diagnosis. Precise determination of the clonal origin of MPLC might help rationalize the treatment and improve the prognosis of patients.

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