Metachronous and Synchronous Primary Lung Cancers: Diagnostic Aspects, Surgical Treatment, and Prognosis

Angeliki A. Loukeri,[1] Christos F. Kampolis,[2] Anna Ntokou,[3] George Tsoukalas,[3] Konstantinos Syrigos[3]

Abstract

The average lifelong rate of developing a new primary lung cancer approximates 1% and 6% per year after radical therapy for non–small-cell lung cancer and small cell lung cancer, respectively. The frequency of recorded synchronous and metachronous lung cancers has been increasing in the recent years because of the development of early detection techniques and advances in cancer therapy. The distinction between multiple synchronous or metachronous primary lung cancers and intrapulmonary metastases is based on established clinicopathological criteria, however it is often difficult, although of great importance for the management and prognosis of these patients. Newly developed molecular and genomic methods are expected to contribute to a more solid and clear differentiation. Surgical treatment, whenever feasible, is considered the modality of choice for the management of patients with second primary lung cancers, as opposed to those with metastases. The type and extent of surgery are under discussion. The prognosis of patients with second primary lung cancers largely depends on the time of detection and the stage and location of the second cancer, thus surveillance after surgical resection of the initial tumor is mandatory.

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] Unfortunately, despite advances in the detection and treatment of lung cancer, incidence is high and prognosis remains poor (overall 5-year survival rates are < 20%).[2] After radical therapy with curative intent, a structured surveillance program is required to detect early recurrences of the primary lung tumor or the development of a second lung cancer. Recurrences are more frequent within the first 2 years after surgery. The average lifelong rate of developing a new primary lung cancer approximates 1% and 6% per year after radical therapy for non–small-cell (NSCLC) and small cell lung cancer (SCLC), respectively.[3]

[1]Respiratory Intensive Care Unit, Athens Chest Hospital "Sotiria," Athens, Greece
[2]Second Department of Propaedeutic Surgery, University of Athens, Medical School, "Laiko" General Hospital, Athens, Greece
[3]Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, Athens, Greece

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Address for correspondence: Konstantinos Syrigos, MD, PhD, Sotiria General Hospital, Athens School of Medicine, Oncology Unit GPP, 152 Mesogeion Ave, 115 27 Athens, Greece
Fax: +30-210-7781035; e-mail contact: ksyrigos@med.uoa.gr

The distinction between multiple synchronous primary lung cancers and intrapulmonary metastases is often difficult, but of great importance for the therapeutic management and prognosis of these patients. The estimated incidence of synchronous lung cancers, as reported in various clinical series, ranges from 0.2% to 8% (3.5%-14% in autopsy studies).[4] The frequency of recorded synchronous or metachronous lung cancers has been increasing in the recent years because of the development of early detection techniques, such as computed tomography (CT) and positron emission tomography (PET), and advances in cancer therapy, thus resulting in a longer period of patient survival.

The purpose of this narrative review is to gather all relevant information and present the various clinicopathological and genetic aspects of diagnosis, management strategies, and prognostic factors in patients with synchronous or metachronous primary lung cancers. A search was performed using the PubMed and Medline databases using the keywords, "metachronous," "synchronous," "primary lung cancer," "diagnosis," "surgery OR surgical treatment," and "prognosis OR prognostic factors." Relevant articles, cited articles, and references were extracted and included in the study. An effort will be made to elucidate this complicated issue and draw some useful conclusions regarding optimal diagnostic and

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management strategies of patients with synchronous or metachronous lung cancer.

Definitions—Clinicopathological Criteria

The first case of 2 distinct primary lung cancers was published in a German journal by Beyreuther in 1924.[5] Clinicopathological criteria for the diagnosis of multiple independent primary lung tumors were initially introduced by Martini and Melamed in 1975 (Table 1).[6-8] According to the these criteria, a second tumor of different histological type can be safely classified as metachronous, even though most studies concerning surgically treated patients with multiple primary lung cancers (either synchronous or metachronous) have reported an identical histological type between the 2 tumors in > 50% of cases (Table 2).[9-29] When histology is identical to that of the first lesion, at least 1 of the following conditions should be met to differentiate a new primary cancer from recurrence: a disease-free interval between the 2 lesions of at least 2 years, development of the new neoplasm from an in situ carcinoma, or occurrence of the second tumor in a different lobe or lung, provided that extrapulmonary metastases and lymphatic involvement common in both tumors have been excluded. A revised set of criteria was subsequently proposed by Antakli et al,[7] and afterward by Colice et al,[30] who extended the required disease-free interval up to 4 years. All groups[6,7,30] have emphasized, however, that it is more important to determine whether the tumor can be treated with curative intent than whether it is a new cancer or recurrence of the first cancer. The criteria were further extended by the American College of Chest Physicians (ACCP) guidelines (2007 edition).[8]

Table 1 Criteria for the Definition of Second Lung Cancers

Martini and Melamed Criteria[6]
Synchronous MPLC:
A. Tumors physically distinct and separate
B. Histological type:
1. Different
2. Same, but in different segment, lobe or lung if:
a. Origin from carcinoma in situ
b. No carcinoma in common lymphatics
c. No extrapulmonary metastases at the time of diagnosis
Metachronous MPLC:
A. Histologically different
B. Histologically identical, if:
1. Free interval between cancers ≥2 years, or
2. Origin from carcinoma in situ
3. Second cancer in different lobe or lung, but:
a. No carcinoma in common lymphatics
b. No extrapulmonary metastases in at time of diagnosis
Antakli et al Modifications[7]
A. Different histological conditions
B. Same histological condition with two or more of the following:
1. Anatomical distinct
2. Associated premalignant lesion
3. No systemic metastases
4. No mediastinal spread
5. Different DNA ploidy
Shen et al Modifications[8]
A. Same histology, anatomically separated
1. Cancers in different lobes
2. And no N2, 3 involvement
3. And no systemic metastases
B. Same histology, temporally separated
1. ≥4-year interval between cancers
2. And no systemic metastases from either cancer
C. Different histology
1. Different histologic type
2. Or different molecular genetic characteristics
3. Or arising separately from foci of carcinoma in situ

Abbreviation: MPLC = multiple primary lung cancer.

Coexisting lung cancers are called synchronous when detected or resected simultaneously with the first lesion. According to Martini and Melamed, the 2 tumors are physically distinct and separate and may be either of different or the same histologic type.[6] In the case of identical histology, tumors located in different segments, lobes, or lungs should originate from carcinomas in situ without evidence of extrapulmonary metastases or lymphatic spread at the time of diagnosis.[6,7,30] Alternative approaches using histomorphological or molecular testing criteria have been proposed by more recent reports.[6,31,32]

Pathogenesis—Genetic Evidence of Tumor Independence

The multifocality of independent lung tumors has been linked to the "field cancerization" process, a concept initially introduced by Slaughter et al in 1953.[33] According to this theory, smoke-related carcinogenic insults affect different susceptible cells of the bronchial tree and result in invasive tumors of the lung, that can occur either simultaneously or sequentially. Smoking-induced cellular atypias in multiple areas of the bronchial mucosa have been previously reported in smokers with or without lung cancer.[34] In addition, diffuse allele-specific imbalance and genetic changes, which most likely represent alterations caused by cigarette-contained substances, have been observed in the entire bronchial tree surrounding a primary bronchial squamous carcinoma.[35] Several follow-up studies confirm these previously mentioned observations in long-term SCLC[36] or NSCLC[20,37] survivors; the results of these studies incriminate continued smoking as a factor associated with the development of a second primary lung cancer.[20,36,37] Thus, it might be presumed that the development of metachronous primary lung cancer results from the continuous exposure to carcinogenic stimuli of several areas of the lung with a different risk for cancer development. In addition, it should be noted that there must be a sufficient time interval between surgical excision of the first lesion and occurrence of the second tumor to consider various insults as contributors and promoters of the carcinogenesis process. Most lung cancer patients survive < 3 years after diagnosis and the time interval between curative intent treatment of the original lesion and development of metachronous lung cancer ranges from a few months to 17 years.[12,30,37] Many subclinical second lung tumors