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# Synchronous, Metachronous or Metastases?

Celalettin İbrahim Kocatürk
Department of Thoracic Surgery, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

**ABSTRACT**
Multiple primer lung cancer (MPAK) satellite tumors (accessory tumor of the same type with the same tumor in the same lobe) synchronous tumors (at the time of diagnosis, or at the same site within 3 months or with other tumors in the opposite lung) and metachronous tumors (a newly developed tumor in a patient with a definitively treated tumor). Satellite tumors are synchronous tumors also. It may be difficult to understand whether MPAC is primer tumors originating from different areas of the lung, or whether they are metastases from each other. If the histopathological types of the tumors are different from each other, it can be said that they are generally MPAK. However, if histopathological types are the same, histopathological, molecular, genetic and clinical data are needed. It is useful to demonstrate histopathologically that the detailed analysis of tumors (subtype, dominant type, especially in adenocarcinomas) and carcioma insitu background. Genetic and molecular tests are still a matter of debate. It is both very expensive and can be performed in a small number of centers, and not at the expected activity. Because the cancer cells are very complex and constantly undergoing mutation and change. The clinical criteria, especially the Martini-Melamed criteria have been used for a long time. It is still valid. If the histopathological types are different for metachronous tumors, there is no problem, but if they are the same, the second tumor is defined according to the development time. However, it may be more accurate to evaluate these patients independently from time to time. The best survival data is obtained with surgery even if it is second cancer or local recurrence or metachronous cancer Therefore, if patients with synchronous or metachronous cancer are considered to have no distant metastasis or mediastinal involvement, surgical treatment should be the priority.
**Keywords:** Multiple primary lung cancer, non-small cell lung cancer, metachronous lung cancers, satellits tumors

## INTRODUCTION

Multiple primary lung cancer (MPLC) is a tumor that develops in the lungs and originates from the bronchial epithelium. It can be classified into three main types:

- Satellite tumors
- Synchronous lung cancer
- Metachronous lung cancer

Multiple primary lung cancer (MPLC) is being seen frequency increasingly in parallel with the developments in diagnosis-treatment methods.

### Satellite Tumors

This refers to the presence of one or more tumor nodules with the same histopathological type within the same lobe. Although there are descriptions based on clinicopathological data to distinguish between satellite tumors and especially synchronous lung cancer (SLC), there is still no clear definition. The American College of Chest Physicians (ACCP) considers tumors that have the same histopathological type found in the same lobe as satellite tumors regardless of their T and N status and the segment in which they are located, without taking into account whether these tumors were detected by surgeons, radiologists or pathologists (1). This type of tumor was first described by Deslauriers in 1989 and defined as a criterion of poor prognosis (2). The prevalence of satellite lesions has been reported to be 5.9-16%, and they are expected to become more familiar due to the developments in imaging modalities (3-5).

Due to the uncertainties concerning the definition of satellite tumors in most of the studies in the literature, some cases have been assessed as SLC and some as metastasis and it is seen that the patients in these studies were not homogeneous (3, 6, 7). Despite this, almost all studies conducted after Deslauriers et al. (2) work showed that ST has a satisfactory survival time and its position in the staging system was thus changed from M1 to T3 in time (2, 8).

In practice, it is not necessary to diagnose additional nodules if the diagnosis of the main tumor is known. If the tumors have the same histopathology, then the diagnosis is satellite tumor with a good prognosis. If the tumors have different histopathological types, the diagnosis is synchronous tumor and resection is recommended as these tumors also have good survival times (1, 4, 9).

Many surgeons use the Martini and Melamed (10) and Antaklı et al. (11) criteria for diagnosis. However, these criteria exhibit uncertainties regarding satellite tumors. According to these criteria tumors with the same cell type located in different segments are considered as SLC (if other criteria match). On the other hand, Detterbeck et al. (9) stated that the possibility of such tumors being SLC is low and the possibility of them being satellite tumors is very high as their survival time is generally good (Table 1). At

**Corresponding Author:** Celalettin İbrahim Kocatürk **E-mail:** celalettinkocaturk@hotmail.com
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Table 1 Martini and Melamed (10) and Antakli et al. (11) criteria were explained.

Regarding the oncologic treatment in the postoperative period, NCCN guidelines recommend cisplatin-based chemotherapy after surgery for N0 or N1 patients with satellite tumors (12). According to our study conducted in 2010 involving patients with satellite tumors, 5-year survival rate was found to be 52%, the main tumor and satellite tumor characteristics and the distance between tumors did not affect survival, while postoperative adjuvant treatment affected survival positively (p=0.0043) (13).

Today, there are still unanswered questions regarding satellite tumors; is a satellite nodule intraparenchymal metastasis? Is the distance between two tumors important? Does it matter if tumors are in the same segment/different segments? How should patients that have a satellite tumor with N1 and/or N2 involvement evaluated?

**Synchronous Lung Cancer**

Synchronous lung cancer (SLC) is the presence of second primary lung cancer in a lung cancer case at the time of diagnosis (1, 9). In 1924, two different cancer foci were incidentally detected in a tuberculosis case by Beyreuther et al. (14). The prevalence of SLC was reported as 2-14.5%. However, the population of SLC patients is gradually expanding due to the developments in diagnosis methods (15-17).

Although the definition states "second tumor at the time of diagnosis", there are publications that report second tumors diagnosed within 2 months, 6 months and even 2 years after the diagnosis of the first tumor that can be accepted as synchronous lung cancer (18-22).

**Table 1.** Martini and Melamed (10) and Antakli et al. (11) criteria

| **Martini and Melamed Criteria** |
|---|
| I. Tumors' being distant from each other and separated |
| II. Histological types |
| a. Different histology |
| b. Same histology Located in different segments, lobes or lungs and; |
| i. Originates from carcinoma in situ |
| ii. No carcinoma is detected in common lymphatic drainage pathways |
| iii. There is no extrapulmonary metastasis at the time of detection |
| **Antakli Criteria** |
| I. Different histology |
| II. Same histology |
| a. Located in different anatomical areas |
| b. Associated with premalignant lesion |
| c. There is no systemic metastasis |
| d. There is no mediastinal lymph node involvement |
| e. Possesses different DNA ploidy |
| At least 2 of these 5 criteria should be satisfied |

The literature regarding the approach to synchronous lung cancer patients is not sufficiently extensive and there are variable results in terms of survival (1). The possible causes of this variability could be the challenges in diagnosing SLC, the inclusion of bronchoalveolar carcinoma cases, N2 tumor cases, carcinoid tumor cases and satellite nodule cases in some studies, the shortcomings in evaluation due to the limited number of cases, or the fact that the second cancer is actually metastasis in some patients (23-26).

Synchronous lung cancer can be seen in the same lung (same lobe; satellite tumor?) in a different lobe or in the other lung. It is easy to make a diagnosis when they are different histopathological types. On the other hand, it is nearly impossible to make a definitive diagnosis when they are the same histopathological types.

Tumors with the same histopathology are more likely to be considered as metastasis. However, the development of tumors with the same histopathological type is possible in an individual who has the same genetic structure and is exposed to the same etiologic factors. Until recently, it was thought that immunity and genetic studies could be guiding in the differentiation of tumors with the same histopathological type. However, recent studies have shown otherwise. Various methods can be used in order to determine the genetic characteristics of tumors. However, none of these methods have worked completely as of yet. Tumors are much more complicated structures than predicted. Tumor mutations are very commonly and frequently seen. In other words, the first tumor cell is not the same as the 100,000$^{th}$ or the 1,000,000$^{th}$ tumor cell. Therefore, there may even be differences between the main tumor and its metastasis in terms of histopathological type. Cancer cells continuously undergo mutations and modifications. This is more frequently seen in patients who receive chemotherapy. Hence, it is not possible to make a definitive diagnosis with genetic or molecular studies. In addition, these studies are quite expensive and are conducted in few centers (27).

Detailed histopathological evaluation of the tumor is easier than mutation and molecular analyses and it can be guiding (28). Showing that tumors originate from carcinoma in situ, conducting immunohistochemistry workup, and determining the subtype and predominant pattern in adenocarcinomas in particular may be helpful for differential diagnosis.

The study conducted by Girard et al. (29) also supports this notion. The survival results, molecular studies, and detailed histopathological evaluations of patients who were differentiated in terms of synchronous/metastasis using clinical criteria [Martini and Melamed (10)] were shown to have no significant differences.

Each case of suspected synchronous lung cancer should be evaluated by a multidisciplinary team and a decision should be made using clinical data. The most commonly used criteria today are Martini and Melamed (10) criteria. Although it has been

more than 30 years since these criteria were first defined, they are still valid. In 1991, Ichinose showed the difference of tumors with the same cell type in DNA ploidy studies conducted using flow cytometry (28). Antakli et al. (11) modified the Martini and Melamed (10) criteria in 1995. These criteria are based on showing that distant metastasis and involvement of common lymphatic pathways are not present. Although not very widely known, Warren and Gates successfully defined synchronous tumors a long time ago in 1932 (30).

In the 8th edition of the staging system, SLC has not been studied under a separate title and there have been no amendments. However, it has been reported that the predominant pattern and subtype can be guiding in tumors that are classified as adenocarcinomas in terms of histopathological type (31). In the 8th edition of the staging system (as in the 6th and 7th editions), an evaluation has been made by considering one tumor as the metastasis of another (8, 32). Tumors in the same lung but in different lobes have been accepted as T4. However, this evaluation was made considering 180 cases, some of whom were bronchoalveolar cancer patients. Nodules in the other lung were classed as M1a. The evaluation was made considering 369 bilateral SLC cases and only 7 patients among those received surgical treatment on both sides [8]. Therefore, the place of SLC cases in the staging system is debatable.

There are significantly different results regarding survival in synchronous tumors[11,15]. The possible cause of this variability is the heterogenicity of patient populations and treatment methods. However, almost all of the studies conducted in recent years have satisfactory survival results and the patients concerned benefit from surgical treatment (33, 34). At the Table 2. A comparison of publications in the literature on MPLC.

The second lesion is incidentally detected during surgery in nearly one-third of synchronous lung tumors. Resection can be performed in patients that do not have mediastinal and distant metastases postoperatively using aggressive methods if both tumors are resectable, and also if the patient is already faced with thoracotomy morbidity. The absence of mediastinal involvement and distant metastasis should be proven before surgical treatment. Patient's respiratory reserve determines the extent of the surgical procedure (1). Patients should undergo PET-CT and cranial MRI and mediastinoscopy should be performed before surgery. It has been reported that patients with mediastinal lymph node involvement should be treated using nonsurgical methods (1). However, Detterbeck et al. (8) estimated that one-third of patients with mediastinal lymph node involvement may have no metastasis (according to tumor stage, time of tumor occurrence, metastasis properties, and survival rates). In other words, a NSCLC with N2 involvement and another concomitant NSCLC can be present. Still, the general opinion is in favor of accepting patients with mediastinal involvement and the same histopathological type as metastasis instead of SLC and not performing resection on these patients (1).

**Table 2.** Publications in the literature related to Multiple Primary Lung Cancer

| Author | Year | n | Survival (5 years) |
|---|---|---|---|
| Roberts et al. (35) | 2003 | 14 | 64 |
| Mun et al. (25) | 2007 | 18 | 75.8 |
| Chang et al. (36) | 2007 | 92 | 35.3 |
| Trousse et al. (22) | 2007 | 125 | 34 |
| Riquet et al. (37) | 2008 | 118 | 26 |
| Rostad et al. (26) | 2008 | 94 | 27.6 |
| Voltolini et al. (38) | 2010 | 43 | 34 |
| Fabian et al. (39) | 2011 | 67 | 69 |
| Kocaturk et al. (40) | 2011 | 26 | 49.7 |
| Shimada et al. (36) | 2015 | 67 | 53.6 |

In cases with bilateral synchronous lesions, surgery should be performed on the side that has the more advanced stage (14). In cases with bilateral synchronous lesions with the lesion on one side definitively diagnosed with cancer and one on the other side not diagnosed, priority should be given to the undiagnosed side. If one side requires pneumonectomy, the order of priority may be changed to be able to perform segmentectomy on the side with the smaller tumor, as resection on the other side can only be limited if the side that requires pneumonectomy is operated on first. Similarly, both sides requiring sleeve resection might change the order of priority. Briefly, it would be appropriate to evaluate each patient individually instead of obeying the rules at this point (24).

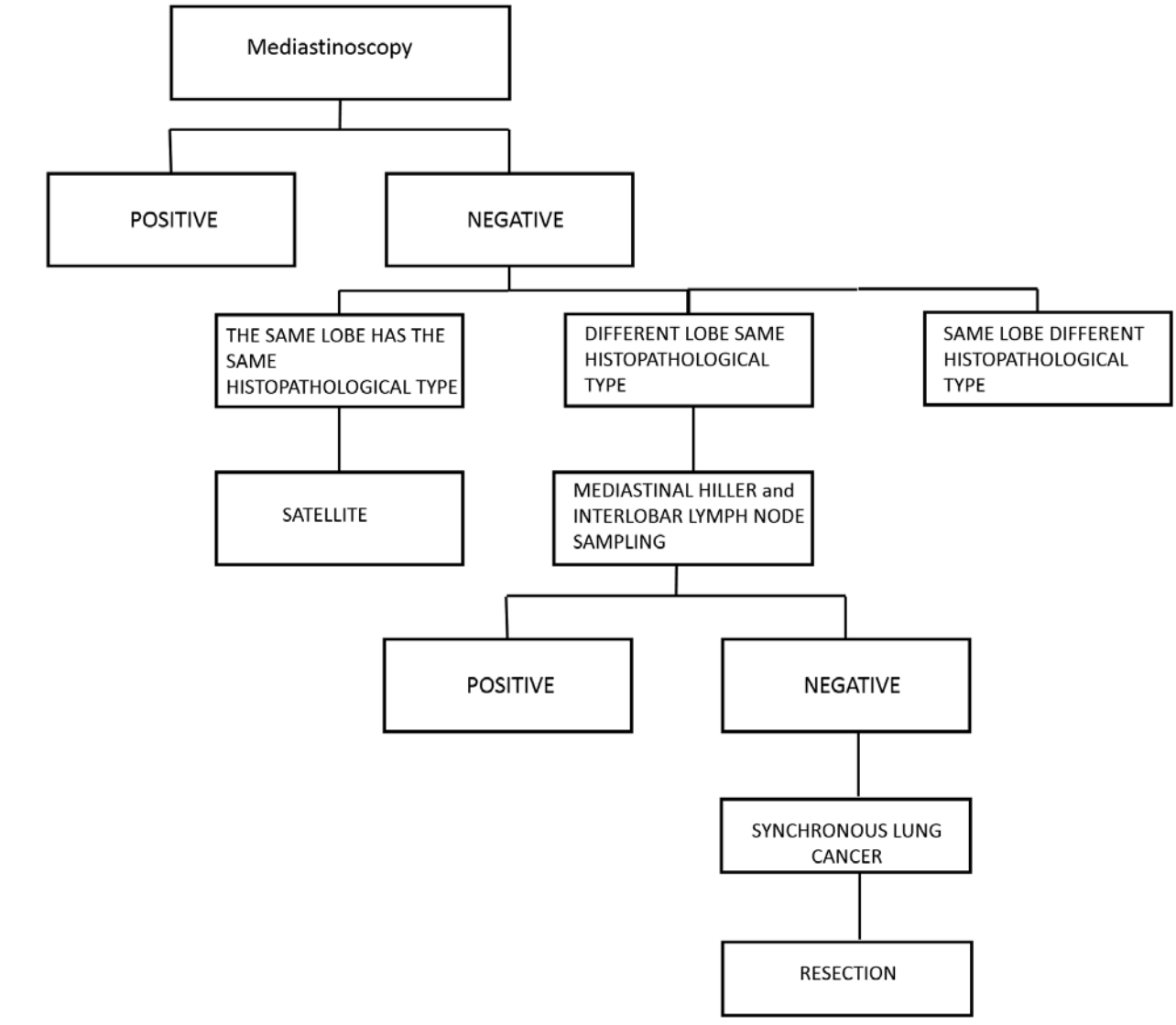
Successive thoracotomy is the generally preferred surgical approach. Recently, VATS has also frequently been used. As palpation is not possible during VATS, cases with suspected additional nodules should be approached carefully. The recommended time period between two surgeries is 4-6 weeks. However, a patient's performance, the morbidities developing after the first surgery, and the surgeon's opinion might change this time period (24, 25, 41).

According to our study conducted in 2010 regarding synchronous lung cancer, the 5-year survival rate was found to be 49.7%; 40.6% in unilateral cases and 62.8% in bilateral cases. It was found that pneumonectomy was a factor of poor prognosis and receiving adjuvant chemotherapy was a factor of good prognosis in terms of survival (40). The recommended treatment approach for cases with suspected unilateral and bilateral synchronous lung cancer is shown in Figure 1, 2 (40).

In the literature, it has been reported that female gender, bilateral localization, no lymph node involvement, complete resection, and postoperative adjuvant therapy were factors of good prognosis, whereas N1-2 involvement, advanced age and performing pneumonectomy were factors of poor prognosis (33, 38, 39, 42, 43). The most important prognostic factor in many studies is the N status (4).

The average morbidity of surgeries has been reported as 10.5-37% (38-40, 45). The average mortality rate is around 5%.

Figure 1. Approach to suspected unilateral SLC cases




In a pooled analysis (467 patients) conducted with a group of authors studying MPLC in 2012, we found the median survival to be 52 months. Male gender, advanced age, unilateral tumor localization and nodal status were found to be factors of poor prognosis (46).

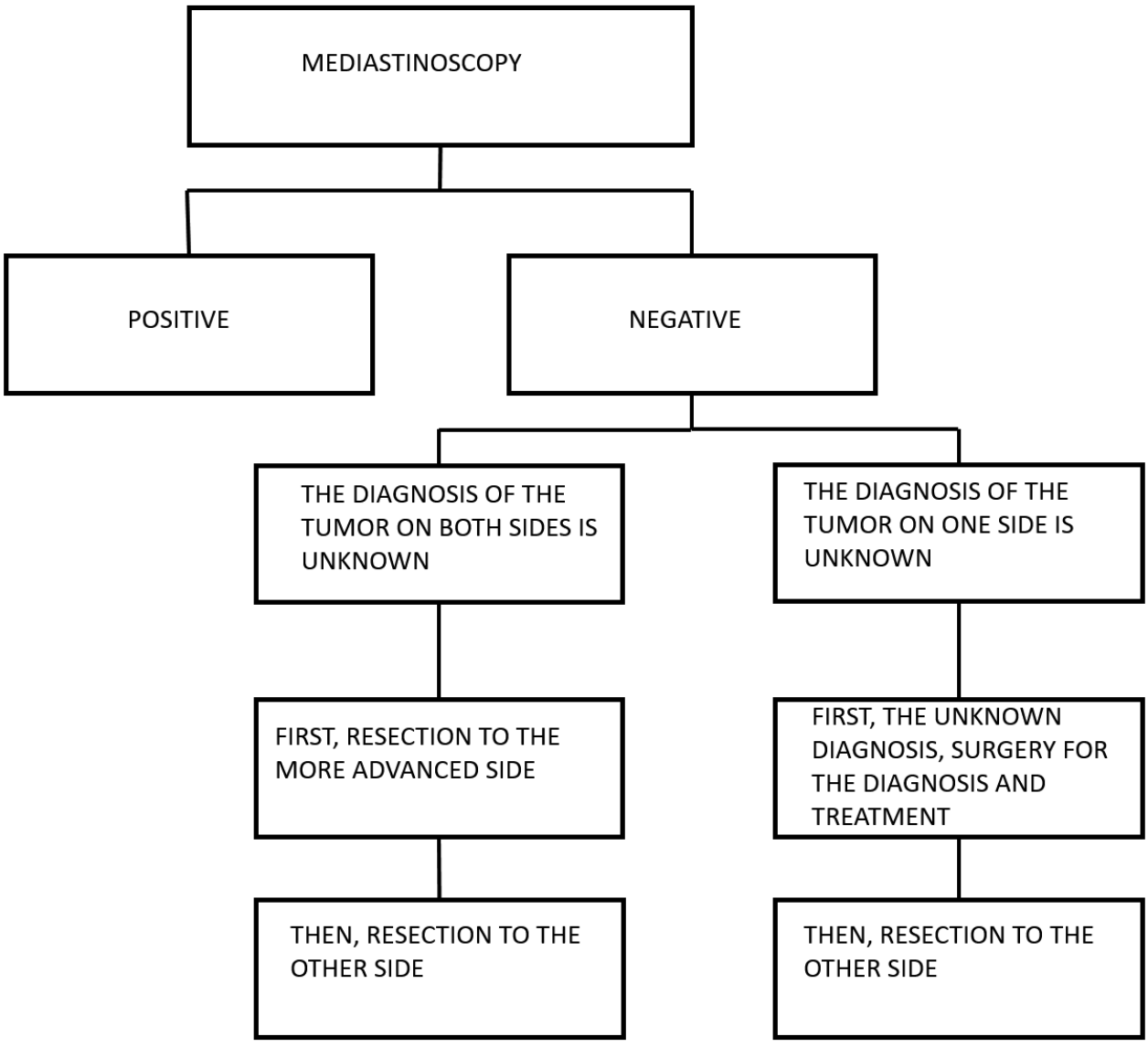
In another study conducted with the same group in 2015, we found that the best survival was observed in the adenocarcinoma patient group without N involvement and we tried to predict survival with a nomogram which we developed (21).

**Metachronous Lung Cancer**

Detection of a new lung cancer during the period following curative treatment for primary lung cancer implies metachronous lung cancer (MLC) (47). In every patient receiving curative treatment for primary lung cancer, recurrence may be seen as well as metachronous lung cancer. Therefore, patients receiving treatment for lung cancer should be followed up regularly. Metachronous lung cancers constitute 55-65% of multiple primary lung cancers (18). Many of them are detected during routine PA and 75% of these are in Stage 1 (48).

It is easy to make a metachronous cancer diagnosis when the histopathological type of the newly developed cancer is different. However, the newly developed lung cancer is usually on the same side and has the same cell type in nearly two-thirds of cases (generally squamous cell carcinoma). Some clinical parameters can be used in evaluating such patients (10). According to the ACCP guidelines, in a patient with a detected second tumor which is the same histopathological type as the previous one and without systemic metastasis, the second tumor is accepted as MLC if the time period between the occurrence of the two tumors is more than 4 years, and as the metastasis of the first cancer if the same is less than 2 years. The time period between two-four years is called the "gray zone" and it is very hard to make a differential diagnosis precisely (47, 48). According to Martini and Melamed (10), MLC diagnosis can be made if the disease-free pe-

Figure 2. Approach to suspected bilateral SLC cases




riod after the first tumor is more than 2 years, the second tumor originates from carcinoma in situ, the second tumor has developed in a different lobe or in the other lung, there is no carcinoma in the common lymphatic drainage pathways, and there is no extra-thoracic metastasis (10).

As shown above, these criteria are based on showing that distant metastasis and involvement of common lymphatic pathways are not present. In patients with suspected metachronous lung cancer, invasive mediastinal staging and extra-thoracic imaging (whole body PET-CT or abdominal CT and bone scintigraphy, as well as cranial CT/MRI) are recommended (47, 48). Resection is contraindicated in the presence of mediastinal lymph node involvement or metastatic disease (2).

Curative surgical resection is recommended for metachronous lung cancer patients. Surgical treatment of metachronous lung cancer depends on the side of the newly developed tumor, the extent thereof, the surgical procedure performed for the first tumor, and the patient's pulmonary function capacity (5). Resection can be performed in 65% of the cases, wherein one-third of the patients that undergo resection receive sub-lobar resection (49). The 5-year survival rate is 20% in all patients who have metachronous lung cancer, whereas the average 5-year survival rate in patients who undergo resection is 36% (20-50) (2, 5). The indication of adjuvant therapy after surgical resection is the same as with other patients (12). Operative mortality has been reported as 2-7% in metachronous tumors (50). However, in patients with tumor development on the same side and who need complementary pneumonectomy, this rate can be as high as 20%. The risk is higher in patients who have received adjuvant treatment (especially RT) after the first surgery (50).

Although the second tumor with the same histopathological type developing within less than 2 years is accepted as metasta-

sis, the possibility of the newly detected tumor being metachronous lung cancer should be remembered.

Recurrence after the primary lung cancer is most frequently seen within the first 1-2 years. Recurrence can be local, locoregional and in the form of distant metastasis. Recurrence in patients who have received surgical treatment and have negative surgical margins and no mediastinal lymphatic involvement is generally in the form of distant metastasis. In these patients, the possibility of metachronous tumor is higher, although the second tumor in the lungs is the same histopathological type as the first tumor.

In a patient who has previously received treatment for lung cancer, the recurrence of cancer in resection margins (bronchi, vascular structures, chest wall, pericardium, etc.) is called "local recurrence", the recurrence of cancer in the lymph nodes within the same-sided hemithorax is called "regional recurrence", and the recurrence of cancer in other areas of the body is called "systemic recurrence" (21).

In patients with resected Stage-1 NSCLC, the rate of local or regional recurrence is around 7% and the rate of systemic recurrence is around 20% (51, 52). The prevalence of recurrence increases with advanced stage[49]. When all cases who have undergone resection are considered, local, regional or systemic recurrence is seen almost in half of patients (49). Recurrence most commonly occurs in the same hemithorax (50% of cases) and second most commonly in the other hemithorax (49). The risk of recurrence is the highest in the first year after surgery and decreases in the following years (51). The survival rates of patients with recurrence is low (nearly 50% one-year survival and 20% two-year survival). The worsening of survival is more remarkable in patients who develop systemic recurrence (49, 51-53).

The ratio of reoperation in the treatment of patients who develop recurrence is very low (54, 55). Therefore, there is limited information concerning the results of reoperation in patients with local recurrence. It has been reported that the 2-year survival rate after reoperation for local recurrence is approximately 20%, whereas patients who have local recurrence detected in the early stage had nearly 50% five-year survival rate after complementary pneumonectomy (51, 56). Therefore, it is recommended to follow-up all patients who have been operated on for primary lung cancer closely so as to detect a potential local recurrence in the early stage. For the treatment of local recurrence in these patients, surgical resection should be preferred if the tumor is resectable (57).

Surgical treatment of local recurrence was found to be more effective especially in the Stage-1 NSCLC patients who underwent resection in comparison to the patients treated with CT and/or RT 8 (53). As a matter of fact, the contribution of CT to survival could not be demonstrated in patients who developed local recurrence[58]. RT should be preferred in patients who have not undergone surgery in the treatment of local recurrence (12). Although information regarding the treatment of regional recurrence is lacking, it is recommended to administer concomitant chemoradiotherapy instead of surgical treatment (12).

If there is isolated metastasis (brain or adrenal metastasis), satisfactory survival may be achieved by surgical treatment in patients with systemic recurrence (12, 49, 59). RT can be applied in patients who have isolated metastasis (brain or adrenal metastasis) and who cannot be operated on. Systemic CT should be added to the local treatment (surgical or RT) of patients with isolated metastasis. In patients with generalized metastasis or patients who have multiple metastases in one organ, RT and systemic CT should be administered based on local symptoms (12).

The prevailing debate on metachronous lung cancers regards tumors that develop within the first 2 years and between 2-4 years and that have the same histopathological type. We would like to share one of our analyses that is awaiting publication. We conducted a study on patients on which complementary pneumonectomy was performed due to a newly developed tumor on the same side and we found that the survival of patients with the same histopathology was good regardless of the time when the second tumor developed. In this study, we evaluated 32 NSCLC patients who underwent complementary pneumonectomy between January 2000 and December 2015. The five-year survival rate of the patients operated on with the same histopathology was found to be as follows: surgery time <2 years 62.5%, 2-4 years 63%, >4 years 75% (p=0.54).

## CONCLUSION

In light of this information, in patients who previously received curative treatment and developed a new lung cancer within 2-4 years, if the new tumor is the same histopathological type as the first one, a decision that it is inoperable should not be made immediately, and the tumors that develop within the first 2 years should be considered after the first operation with the same histopathological type as the metastasis. One may act more boldly and administer surgical treatment especially in the treatment of tumors that develop in the same hemithorax. For lung cancers that develop in the other hemithorax, it may be appropriate to act on a case-by-case basis and choose limited resection.

Briefly, the following question needs an answer: is it necessary to make a definitive diagnosis in suspected synchronous and metachronous tumor cases?

If the patient has sufficient cardiopulmonary capacity, no mediastinal and distant metastasis, no multiple tumor nodules (more than 2), and is suitable for complete resection, the preferred treatment method in these patients should be surgical. If the patient has synchronous tumors or metastasis, then there is no problem. It is possible to evaluate this metastasis as oligometastasis. These patients also benefit more from surgical treatment in comparison to other treatment options.

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