Review Article



# Second surgery for metachronous primary lung cancer

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**Abstract:** As curative surgeries for early-stage non-small cell lung cancer (NSCLC) increase and longer postoperative survival becomes possible, metachronous primary lung cancer (MPLC) have become more common in recent years. Lung cancer survivors have a high risk of MPLC for the rest of their lives, so long-term follow-up and close surveillance are needed. MPLC is often detected relatively early by routine surveillance after the initial surgery, and 64.7% to 85.2% of the cases reported to date have been stage I. Operative mortality after resection of MPLC has been reported to be 0% to 13.0%. Operative morbidity has been reported to be 19.7% to 36.2%. The Five-year overall survival from second surgery was recently reported to be 42% to 78.7%. If the new lesion is solitary and cardiopulmonary function is preserved, complete surgical resection should be considered, regardless of the duration of disease-free survival from initial surgery. Lung-sparing surgery such as segmentectomy or wedge resection and lobectomy have been often reported to have comparable outcomes. Sublobar resection would be acceptable depending on the tumor size and location of the tumor. Because residual pulmonary function is the most important factor for decision-making regarding surgical resection of MPLC, lung preservation should be attempted as much as possible at the time of initial surgery.

**Keywords:** Metachronous primary lung cancer (MPLC); second surgery; non-small cell lung cancer (NSCLC)

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## Introduction

Surgery for primary lung cancer in Japan is increasing year by year (1); computed tomography (CT) imaging is becoming more common, and surgeries for early-stage lung cancer are also increasing. CT scans are now commonly performed every six months to a year after surgery, and long-term postoperative survival can be expected, which is expected to increase the chances of encountering metachronous primary lung cancer (MPLC). However, there are only retrospective and small case reports on MPLC, and no solid evidence exists for the diagnosis and treatment of MPLC. This paper summarizes the current understanding of MPLC, from its definition to surgical resection, based on previous reports.

## Incidence of MPLC

The incidence of MPLC has been reported to be 1% to 7%, fourfold or sixfold higher than in those with no history of lung cancer (2-8). It has been reported that the risk of recurrence after resection for early-stage non-small cell lung cancer (NSCLC) reached a plateau at 2 years, but it remained elevated for up to 4 years before decreasing (9). On the other hand, the risk of second primary lung cancer ranged from 3% to 6% per person per year and did not decrease over time (9). Moreover, the cumulative incidence at 10 years for MPLC was reported to be 20.3% for never-smokers and 18.2% for ever-smokers (10). Yang *et al.* also reported that 22.4% of MPLCs developed more than 5 years after first resection and 15.7% after more than 10 years (8).

Bae analyzed their cohort of 1,852 patients who underwent resection for NSCLC and reported that the cumulative risk of developing a second lung cancer after the initial operation increases to 4.7% at 5 years and 12.6% at 10 years after the initial surgery (6). Recently, the American Association for Thoracic Surgery recommended that annual low-dose CT scan for detection of MPLC in lung cancer survivors should continue for the rest of the patient's life as long as the patients has the functional status and pulmonary reserve needed for treatment of a new lung cancer (11). The Mayo Clinic also recommended lifelong close follow-up of patients who have undergone resection of NSCLC, because MPLC developed in 33.6% of patients more than 5 years after their first operation and in 6.9% of patients more than 10 years later (12). These data suggest that patients who survive the first operation have a higher risk of developing a second primary lung cancer, so long-term follow-up and close surveillance are prudent.

## Definition and clinical diagnosis of MPLC

The criteria for the diagnosis of MPLC that have been used so far are the 1975 Martini-Melamed criteria (13), which require (I) different histology; or (II) same histology, if (i) the disease-free interval was more than 2 years, or (ii) the origin was carcinoma in situ, or (iii) the second cancer arose in a different lobe or lung, other than carcinoma involving lymphatics common to both sides, and no extrapulmonary metastases were present at the time of diagnosis. Many reports of MPLC have been reported according to these Martini-Melamed criteria. However, a single-institution study analyzing 2,107 patients who underwent pulmonary resection for NSCLC reported that there was no difference in survival between patients who underwent resection of a metachronous lesion within 2 years and those patients whose interval between resections was greater than 2 years (5). The Mayo Clinic also reported that the disease-free interval was not associated with survival, and they proposed that a disease-free interval of at least 2 years should not be used as a strict criterion to distinguish metachronous lung cancer from more advanced states of disease (12). More recently, the American College of Chest Physicians (ACCP) guidelines (14) revised their criteria so that the second focus can be reliably defined as a second primary if there is no evidence of systematic metastases and at least a 4-year interval between the two. An interval of 2 to 4 years represents a grey area, where it is difficult to determine whether a new lesion is a second primary. In the future, it will be possible to distinguish by histological similarity or genetic investigation. However, whichever criteria are used for diagnosis, the most important matter is whether it can be treated with curative intent. If the newly appearing pulmonary nodule is solitary, has no lymph node metastases or extrapulmonary involvement, and if cardiopulmonary function is preserved and the patient can tolerate surgery, surgical resection should be considered to avoid losing the opportunity to cure.

## Is sublobar resection feasible?

The extent of resection for MPLC is still controversial. The selection of surgical procedure is affected not only by the condition of the tumor, but also by many factors such as age, residual cardiopulmonary function, performance status, comorbidities, and whether MPLC is ipsilateral or contralateral to the initial surgery. In previous reports, completion pneumonectomy was performed in 2.6% to 31%, lobectomy in 22.4% to 45%, and the remaining were segmentectomy and wedge resection (2-8,15,16). Some reports stated that completion pneumonectomy should be avoided due to its high morbidity and low survival rates (8,15). Although lobectomy has been considered the standard surgical procedure for early-stage NSCLC (17), the standard treatment for patients with clinical stage IA NSCLC (tumour diameter ≤2 cm; consolidation-to-tumour ratio >0.5) is likely to change, based on the findings of a randomized controlled trial confirming the noninferiority of segmentectomy to lobectomy (JCOG0802/WJOG4607L) (18). Considering that most MPLCs were found by chance on regular surveillance while remaining asymptomatic (9,19), many of them are detected at earlier stages, and sublobar resection could be an alternative.

Many previous reports have demonstrated that sublobar resection and lobectomy were equivalent (3,5-8). Bae and colleagues demonstrated in their 40-patient cohort who underwent resection for MPLC that when comparing the anatomical resection group with the sublobar resection group, there was no significant difference in survival, and furthermore, there was no mortality, complications or death during the observation period in the sublobar resection group (6). Yang and colleagues reported about the surgical treatment of 143 patients with MPLC, and there was no significant difference in 5-year survival between lobectomy and sublobar resection (77.1% and 56.7%, P=0.203) (8). Hamaji and colleagues similarly reported that the extent of surgical resection was not associated with survival, and tumor size >2 cm and number of pack years of smoking were the

only independent predictors of shorter survival (7). They also found in their meta-analysis of resected MPLC that there was no significant difference in survival between lobectomy and sublobar resection, although there was a relatively small number of patients, and there was heterogeneity between studies (12). Sato *et al.* also reported that, in 61 patients who underwent surgery for ipsilateral MPLC, five-year overall survival rates in patients who underwent anatomic resection and wedge resection after second surgery were 75.8% and 75.8%, respectively (P=0.738), and 5-year recurrence-free survival rates were 54.2% and 67.6%, respectively (P=0.368) (20). On the other hand, a retrospective study base on the Surveillance, Epidemiology, and End Results database using propensity score matching concluded that lobectomy was associated with significantly better survival (P=0.023), and subgroup analyses showed that lobectomy achieved a significantly better prognosis if the previous lung cancer was stage I (16). Similar results have been reported by Zhang and colleagues with lobectomy and thorough lymph node evaluation as favorable prognostic factors (21). At the present time, it is difficult to draw conclusions about the optimal surgical procedure for MPLC due to the small number of cases and the retrospective nature of all of the studies. However, since tumor size >2 cm was found to be a significant prognostic factor in some reports (7,8,20), limited resection for tumors less than 2 cm is considered acceptable. Since lymph node dissection is often omitted or reduced for MPLC surgery, especially on the ipsilateral side, the possibility of underestimating the N factor should be considered. Therefore, it is reasonable to use tumor size for decision making.

## Morbidity, mortality, and prognosis

Operative mortality after resection of MPLC has been reported to be 0% to 13.0% (3,4,6-8,20,21). In these reports, all cases of operative mortality occurred in the completion pneumonectomy or lobectomy group and not in the sublobar resection group. Operative morbidity has been reported to be 19.7% to 36.2% (4,5,7,8,20,21). Frequently reported complications were prolonged air leaks, supraventricular arrhythmia, and pneumonia. Independent predictors of postoperative complications were reported to be age older 70 years (7), a low percent forced expiratory volume in the first second, and ipsilateral surgery (6). Hattori and colleagues investigated the surgical outcomes of 104 cases of repeated pulmonary resection for ipsilateral MPLC (22). The 3-year overall survival of repeat anatomical resection was equivalent to the other procedures (P=0.816), whereas repeat anatomical resection was a significant predictor of severe postoperative morbidity (P=0.036), which was found in 41%.

MPLC is often detected relatively early by routine surveillance after the initial surgery, and 64.7% to 85.2% of the cases reported to date have been stage I (2-8,20,23). Five-year overall survival from second surgery was reported to be 26% to78.7%, broken down into 26% to 33.4% reported from 2001 to 2008 (2-4,23) and 42% to 78.7% reported since 2009 (5-8,20). Prognostic factors for survival after resection of MPLC included TNM stage (3,5,8), tumor size (7,8,20), smoking status (7,8,20), age (4), performance status (20), and N factor (4). Many reports showed that histology was not associated with survival (3-5,7).

## Conclusions

In conclusion, surgical resection for MPLC can be performed safely with acceptable mortality and morbidity. The reported survival rate is good, and if the new lesion is solitary and cardiopulmonary function is preserved, complete surgical resection should be considered, regardless of the duration of disease-free survival from initial surgery. Sublobar resection would be acceptable depending on the tumor size and location of the tumor (peripheral or near the hilum). Because residual pulmonary function is the most important factor for decision-making regarding surgical resection of MPLC, lung preservation should be attempted as much as possible at the time of initial surgery. Long-term follow-up and close surveillance are prudent after the initial surgery.

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## References

1. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery; Shimizu H, Okada M, et al. Thoracic and cardiovascular surgeries in Japan during 2017 : Annual report by the Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg 2020;68:414-49.
2. van Rens MT, Zanen P, de la Rivière AB, et al. Survival after resection of metachronous non-small cell lung cancer in 127 patients. Ann Thorac Surg 2001;71:309-13.
3. Battafarano RJ, Force SD, Meyers BF, et al. Benefits of resection for metachronous lung cancer. J Thorac Cardiovasc Surg 2004;127:836-42.
4. Riquet M, Cazes A, Pfeuty K, et al. Multiple lung cancers prognosis: what about histology? Ann Thorac Surg 2008;86:921-6.
5. Lee BE, Port JL, Stiles BM, et al. TNM stage is the most important determinant of survival in metachronous lung cancer. Ann Thorac Surg 2009;88:1100-5.
6. Bae MK, Byun CS, Lee CY, et al. The role of surgical treatment in second primary lung cancer. Ann Thorac Surg 2011;92:256-62.
7. Hamaji M, Allen MS, Cassivi SD, et al. Surgical treatment of metachronous second primary lung cancer after complete resection of non-small cell lung cancer. J Thorac Cardiovasc Surg 2013;145:683-90; discussion 690-1.
8. Yang J, Liu M, Fan J, et al. Surgical treatment of metachronous second primary lung cancer. Ann Thorac Surg 2014;98:1192-8.
9. Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg 2013;145:75-81; discussion 81-2.
10. Ripley RT, McMillan RR, Sima CS, et al. Second primary lung cancers: smokers versus nonsmokers after resection of stage I lung adenocarcinoma. Ann Thorac Surg 2014;98:968-74.
11. Jaklitsch MT, Jacobson FL, Austin JH, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg 2012;144:33-8.
12. Hamaji M, Ali SO, Burt BM. A meta-analysis of resected metachronous second non-small cell lung cancer. Ann Thorac Surg 2015;99:1470-8.
13. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12.
14. Kozower BD, Larner JM, Detterbeck FC, et al. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e369S-e399S.
15. Zuin A, Andriolo LG, Marulli G, et al. Is lobectomy really more effective than sublobar resection in the surgical treatment of second primary lung cancer? Eur J Cardiothorac Surg 2013;44:e120-5; discussion e125.
16. Yang X, Zhan C, Li M, et al. Lobectomy Versus Sublobectomy in Metachronous Second Primary Lung Cancer: A Propensity Score Study. Ann Thorac Surg 2018;106:880-7.
17. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
18. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet 2022;399:1607-17.
19. Gregoire J. Guiding Principles in the Management of Synchronous and Metachronous Primary Non-Small Cell Lung Cancer. Thorac Surg Clin 2021;31:237-54.
20. Sato S, Shimizu Y, Goto T, et al. Surgical outcomes of ipsilateral metachronous second primary lung cancer. Interact Cardiovasc Thorac Surg 2021;32:896-903.
21. Zhang R, Wang G, Lin Y, et al. Extent of resection and

 

lymph node evaluation in early stage metachronous second primary lung cancer: a population-based study. Transl Lung Cancer Res 2020;9:33-44.
22. Hattori A, Matsunaga T, Watanabe Y, et al. Repeated anatomical pulmonary resection for metachronous ipsilateral second non-small cell lung cancer. J Thorac Cardiovasc Surg 2021;162:1389-1398.e2.
23. Doddoli C, Thomas P, Ghez O, et al. Surgical management of metachronous bronchial carcinoma. Eur J Cardiothorac Surg 2001;19:899-903.

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