

## Case Report

# Successful Treatment of Synchronous Solitary Ipsilateral Axillary Lymph Node Metastasis from Non-Small Cell Lung Cancer with Radical Resection and Perioperative Chemotherapy

Yuan-Hao Yang<sup>1,2,3</sup>, Lin-Kun Lee<sup>1,3\*</sup>, Cheng-Hwai Tzeng<sup>1,3</sup>

<sup>1</sup>Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

<sup>2</sup>Department of Medicine, National Yang-Ming University Hospital, Yilan, Taiwan

<sup>3</sup>School of Medicine, National Yang-Ming University, Taipei, Taiwan

### Abstract.

Lung cancer is the leading cause of death from cancer worldwide. Almost 60% of patients with non-small cell lung cancer present with metastasis at the time of diagnosis. Without treatment, the median survival for patients with metastatic non-small cell lung cancer is only 3-4 months. While targeted therapy has improved median overall survival to 12 months and even longer in patients with driver mutations, most patients with initial response to targeted agents ultimately develop disease progression. On the other hand, several studies have shown resection of solitary brain or adrenal metastases may achieve long-term survival in selected patients. However, in patients with solitary extra-cranial, extra-adrenal metastases, the results of metastasectomy have rarely been reported. Herein, we report a case of synchronous solitary axillary lymph node metastasis from non-small cell lung cancer. Surgical resection of both the primary lung tumor and metastasis combined with perioperative chemotherapy achieved prolonged disease-free survival in this case. To date, the optimal treatment strategy for patients with solitary distant lymph node metastases and resectable primary lung tumors has not been established. The addition of metastasectomy to primary lung cancer surgery may provide a chance for long-term survival for such patients.

**Keywords :** non-small cell lung cancer, solitary metastasis, axillary lymph node metastasis, metastasectomy

## 病例報告

# 經根除性手術合併手術前後化學治療成功之非小細胞肺癌併同側腋下淋巴節同時性單一轉移

楊元豪<sup>1,2,3</sup> 李霖昆<sup>1,3\*</sup> 曾成槐<sup>1,3</sup>

<sup>1</sup> 台北榮民總醫院 內科部血液腫瘤科

<sup>2</sup> 國立陽明大學附設醫院 內科

<sup>3</sup> 國立陽明大學 醫學院

## 中文摘要

肺癌位居全世界癌症死亡原因之第一位。約 60%非小細胞肺癌病患診斷時已發生轉移。轉移性非小細胞肺癌病患未治療的中位數存活期僅約 3 至 4 個月。即使標靶治療用於部分具有突變基因的病患可延長總存活期至 12 個月甚至更長，但多數起初對於標靶治療有反應的病患最終疾病仍惡化。另一方面，部分研究指出手術切除轉移病灶對於單一腦部或腎上腺轉移的病患可能達成長期存活。但對於其它位置單一轉移的病患，轉移病灶切除的效果很少被提及。我們在這裡提出一個非小細胞肺癌合併同時性單一腋下淋巴節轉移的臨床案例。經同時手術切除原發性肺腫瘤及轉移病灶後，這個案例達到延長的無疾病存活。目前針對非小細胞肺癌原發處可切除但併有單一遠端淋巴節轉移的最佳治療策略尚未確定。轉移病灶切除配合原發肺腫瘤手術有機會延長此類病患的存活期。

**關鍵字:** 非小細胞肺癌、單一轉移、腋下淋巴節轉移、轉移病灶切除

## INTRODUCTION

It is recognized worldwide that lung cancer is the leading cause of cancer death [1]. Approximately 80% of lung cancers are non-small cell lung cancers (NSCLC) [2], and almost 60% of patients with NSCLC present with metastatic disease at diagnosis [3]. Metastatic NSCLC used to be considered as an incurable disease. Conventional cisplatin-based chemotherapy was shown to result in modest benefit with a median overall survival of 8-11 months [4]. Previous studies have shown that subgroups of patients with metastatic NSCLC benefit from novel targeted agents, such as epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors, and inhibitors against anaplastic lymphoma kinase (ALK) gene rearrangement or ROS-1 gene rearrangement products, and therefore achieve improved survival [5,6]. Most patients with initial response to targeted agents, however, ultimately develop disease progression [7]. Long-term survival for patients with metastatic NSCLC remains elusive in the era of novel targeted therapy. Therefore, it is worth noting that selected patients with solitary metastases may benefit from surgical resection. A grow-

ing size of literature has shown selected patients with primary resectable NSCLC and solitary brain metastases can achieve long-term survival following metastectomy [8-10]. Similarly, local radical therapy of solitary adrenal metastasis from NSCLC has produced long-term survivors when radical resection of the primary lung tumor is possible [11-14]. However, in patients with solitary extra-cranial, extra-adrenal metastases from NSCLC, the results of surgical resection have rarely been reported. Herein, we report a case of synchronous solitary axillary lymph node metastasis from NSCLC, who achieved prolonged disease-free survival of at least 24 months after surgical resection combined with perioperative chemotherapy.

## CASE REPORT

A 63-year-old man with a smoking history of 20 pack-years presented to our hospital with fatigue and right axillary lymphadenopathy. The patient had been well until approximately 3 months before presentation. He had a common cold, fatigue and a fixed, non-tender nodule in the right axilla. Over the next two months, the nodule gradually enlarged and fatigue persisted. Two weeks prior to presentation, he visited a local hospital, where ultrasonography showed an irregular-shaped, hypoechoic and homogeneous nodule, approximately 1.5 cm in diameter, in the right axilla. There were no abnormal lymph nodes in the cervical or supraclavicular region. Excisional biopsy

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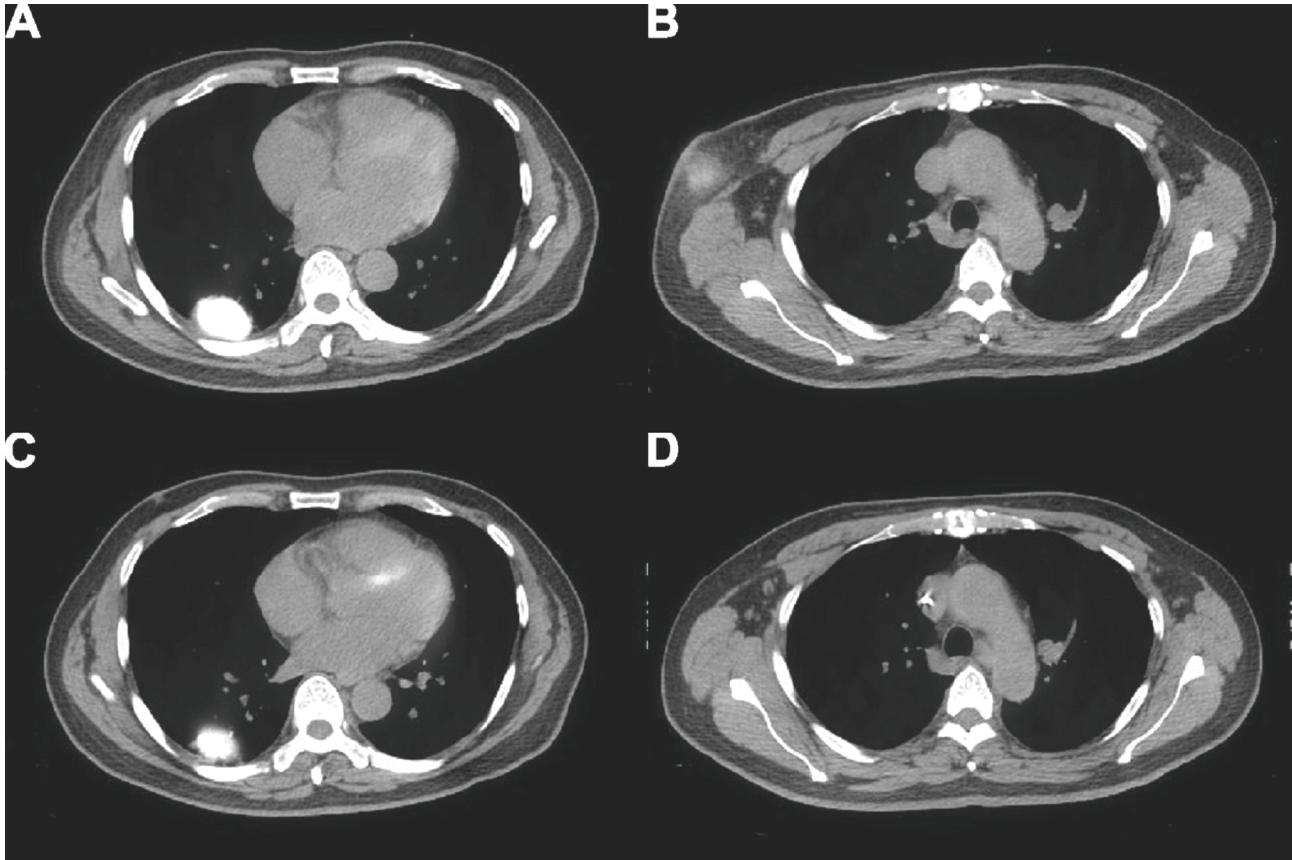
\*Corresponding author: Lin-Kun Lee M.D.

\*通訊作者：李霖昆醫師

Tel: +886-2-28757529

Fax: +886-2-28757762

E-mail: parniber@yahoo.com.tw



**Figure 1.** Positron-emission tomography/computed tomography at diagnosis (A and B) and after preoperative chemotherapy (C and D)

of the right axillary lymph node was performed, and the specimen reportedly showed metastatic adenocarcinoma. Immunohistochemical staining results were positive for CK7, but negative for ER, PR, HER2/neu, CDX-2, CK20, TTF-1 and PSA. The patient was then referred to our hospital for further survey.

He reported no history of fever, weight loss, or chronic cough. On physical examination there was a firm, tender lump in the right axilla. The serum level of carcinoembryonic antigen (CEA) was normal (1.36 ng per milliliter). Whole-body positron-emission tomography (PET) in conjunction with computed tomography (CT), performed 2 weeks after excisional biopsy of the right axillary lymph node, revealed a tumor, 4.3 cm in diameter, with intense uptake of fluorodeoxyglucose (FDG) in the lower lobe of the

right lung, with pleural traction (Figure 1A); and a nodule with peripheral uptake of FDG in the right axilla (Figure 1B). The magnetic resonance imaging (MRI) of the brain showed no tumors. CT-guided fine needle aspiration and core biopsy of the lung tumor was performed. Pathological examination of the biopsy specimens showed lung parenchyma with infiltrating adenocarcinoma cells in acinar (40%) and solid (60%) growth patterns, poorly differentiated. The tumor cells were immunoreactive for CK7, but non-reactive for CK20, TTF-1 and CDX-2 stains. Furthermore, the tumor cells were negative for EGFR gene mutations or ALK gene rearrangement. The diagnosis was adenocarcinoma of the lung, clinical stage IV, T2aN0M1b, according to the American Joint Committee on Cancer (AJCC) 7th edition of staging

system for lung cancer.

After multidisciplinary team planning, the patient was treated with chemotherapy consisting of cisplatin (75 mg per square meter) and pemetrexed (500 mg per square meter) every three weeks. After three courses of chemotherapy, a restaging PET/CT study showed the tumor in the lower lobe of the right lung with reduction in size and FDG avidity as compared with the result of the previous study (Figure 1C); and the right axillary node was also apparently decreased in size and FDG avidity (Figure 1D). Approximately four months after diagnosis, the patient underwent video-assisted thoracoscopic surgery (VATS) lobectomy of the lower lobe of the right lung, as well as intrapulmonary, ipsilateral peribronchial, ipsilateral hilar, ipsilateral mediastinal, subcarinal and ipsilateral axillary lymph node dissection. The pathological examination of the specimens revealed R0 resection of adenocarcinoma of the lower lobe of the right lung; there were no malignant cells in all dissected lymph nodes. Consequently, after preoperative chemotherapy and radical resection, the pathologic staging for the patient became ypT2aN0M0, stage Ib. After surgery, the patient received additional three courses of adjuvant chemotherapy with cisplatin and pemetrexed, the same regimen as the preoperative one. The patient remained disease-free for more than 24 months after radical surgical resection.

## DISCUSSION

Metastatic NSCLC is generally associated with a poor prognosis. Without treatment, the median survival is only 3-4 months [15]. Treatment with systemic chemotherapy has been the gold standard, although the efficacy is only modest. For patients with specific driver mutations, such as EGFR gene mutations, ALK gene rearrangement or ROS-1 gene rearrangement, targeted therapy has improved median overall survival to 12 months and even longer in clinical studies [16]. Nevertheless, the development of resistance to targeted therapy hampers the achievement of long-term sur-

vival. On the other hand, since surgery provides the best opportunity for cure for patients with early-stage NSCLC, it has been proposed that metastasectomy may be beneficial for patients with solitary metastases if the primary lung tumors are also resectable. Indeed, several studies have shown a survival benefit from resection of solitary brain or adrenal metastases [8-14,17-19]. However, there is limited clinical evidence of the benefit of metastasectomy in patients with solitary extra-cranial, extra-adrenal metastases.

Our patient presented with a T2aN0, resectable primary lung tumor with solitary axillary lymph node metastasis. The diagnosis and staging were confirmed by the whole-body PET/CT and pathologic examination of the specimens from the axillary lymph node and the primary lung tumor. Axillary lymph node metastases are occasionally seen in patients with NSCLC [20]. However, it is unusual for a primary NSCLC to metastasize to a distant lymph node without involving regional ones. Le Pimpec Barthes F et al. [21] reported a patient with right axillary lymph node metastasis observed 4 months after a right lower lobectomy performed for a T2N0 NSCLC. The patient subsequently underwent surgical excision and adjuvant radiotherapy, and survived for more than 6 years afterward. Similarly, reported in a case series [22], a patient with a T3N1 NSCLC and solitary ipsilateral axillary lymph node metastasis underwent surgical resection of both the primary tumor and solitary metastasis, and survived more than 8 years without disease recurrence. In addition, another case series [23] including 3 patients with synchronous axillary lymph node metastases who underwent surgical resection also reported prolonged survival. Although the number of cases was small, surgical resection of the primary tumors and solitary metastases seemed to provide a chance for long-term survival for selected patients with solitary axillary lymph node metastases and resectable primary NSCLC. It is still controversial, however, whether the long-term survival actually resulted from metastasectomy. A retrospective study [24] analyzed 94 patients

presenting with extrathoracic synchronous solitary metastases amenable to resection of the primary lung cancer. Of all patients, 69 (73%) underwent metastasectomy. The result showed that induction therapy for adenocarcinoma, N0 staging and lobectomy were predictive of a better prognosis, but metastasectomy was not.

It is important, but may be difficult, to identify the favorable subgroup who will benefit from metastasectomy. Several factors may influence the outcome of patients with a solitary metastasis from NSCLC who undergo surgical resection of both the primary lung tumor and metastasis. Retrospective analyses have shown the intra-thoracic disease status is the most important predictor of overall survival after surgical resection [25-28]. More specifically, T1 or T2 disease, N0 disease, and stage I or II disease have been reportedly associated with superior outcome [26-28]. Other potential prognostic factors include other baseline patient characteristics, the site of metastasis, R0 resection of the metastasis and the primary lung tumor, and the use of adjuvant therapy, such as perioperative chemotherapy or radiotherapy [27]. The roles played by these factors in patients with solitary metastatic NSCLC remain inconclusive and need to be further studied.

There are certain unsolved issues in our case. First, the presence of residual metastatic lymphadenopathy after excisional biopsy was only determined by the radiologic evaluation. However, the modest FDG uptake of the right axillary lymph node shown on the PET/CT might be due to post-traumatic inflammation after biopsy. Second, to date, there have been no established principles of lymph node dissection for patients with NSCLC and distant lymph node metastases. We are not sure that the extent of lymph node dissection was adequate.

In conclusion, we have reported a patient with successful treatment and prolonged survival who presented with synchronous solitary axillary lymph node metastasis from a T2aN0 NSCLC and underwent re-

section of both the primary lung tumor and the metastasis in combination with perioperative chemotherapy. While the optimal treatment strategy for patients with solitary distant lymph node metastases and resectable primary lung tumors has yet to be achieved, the addition of metastasectomy to primary lung cancer surgery may provide a chance for long-term survival for selected patients.

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