

We should be done in such a way that patients with stage IV non-small cell lung cancer who would benefit from surgery are not overlooked

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The standard treatment for stage IV non-small cell lung cancer (NSCLC) is systemic chemotherapy; however, survival rates are poor (1). Furthermore, most patients with NSCLC have stage IV disease at the time of diagnosis (2). As oncologists, we should consider using the best treatment strategies for stage IV NSCLC patients.

Recently, systemic chemotherapy such as platinum-based chemotherapy, including pemetrexed, angiogenesis inhibitors, including bevacizumab, as well as targeted kinase inhibitors, and immune checkpoint inhibitors (ICIs) have been rapidly evolving with advances in new drug development (3-6). Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend that select stage IV patients (such as those with oligometastases (7) and primary tumors that are otherwise T1-2, N0-1, or T3, N0) are treated with local therapy for their metastasis, followed by resection of the lung lesion in combination with chemotherapy either before or after lung resection (8). There have been a few reports, including prospective and retrospective studies, which have suggested that even for stage IV NSCLC, appropriately selected patients may benefit from surgical treatment (9-15). However, in these previous studies, patient numbers were small.

In a large retrospective study based on data from the National Cancer Database (2004–2013), published in the May 2018 issue of *Lung Cancer* by Yang and coworkers (16), an elegant analysis of the 5-year survival rates of all stage IV

NSCLC patients who underwent surgical resection (n=3,098) was presented. Previous reports involving stage IV NSCLC patients who underwent surgical resection were based on data from much smaller numbers of patients, approximately 100 or less (9-12,14,15). Numbers of patients in prospective studies are even lower, about 50 patients at most (11,15). In the study by Yang *et al.*, the 5-year survival rate for all stage IV patients who underwent surgical resection was 21.1%. For patients with primary tumors, increasing stage was generally associated with decreased survival. These data are similar to results from previous reports (9-12,14,15). This study also found that both tumor lesion and surgical procedure were independent variables that influenced prognosis. Furthermore, tumor location was found to be associated with prognosis; patients with tumors in the right lower lobe (RLL) had a poorer prognosis compared with those with tumors in other lobes, especially the right upper lobe. However, other reports have found that patients with tumors in the right middle lobe or left lower lobe had a poorer prognosis (17,18), and that tumor location was not an independent prognostic factor in early stage disease (19). In this study, the surgical procedure was a prognostic factor; lobectomy was associated with a better prognosis compared with pneumonectomy, segmentectomy, or wedge resection. In previous studies in which patients had early stage disease, the surgical procedure was similarly found to be a prognostic factor (20). Previous reports concerning surgical resection for stage IV

NSCLC described patients with oligometastases (11-15), but unfortunately, these data were not included in the Yang *et al.* study. One of the independent subjects is that extracted cohort of cT1-2, N0-2 and cT3, N0 disease who receive the following: (I) surgery with or without chemotherapy and with or without radiation; (II) chemotherapy alone; (III) radiation alone; or (IV) chemoradiation. These were based on NCCN guidelines, which recommend that selected stage IV patients (such as those with oligometastases (7) and primary tumors that are otherwise T1-2, N0-1 or T3, N0) are treated with local therapy for their metastasis, followed by resection of the lung lesion in combination with chemotherapy either before or after lung resection (8). In the Yang *et al.* study, patients who had surgery, chemoradiation, only chemotherapy, or radiation alone demonstrated 5-year survival rates of 25.1%, 5.8%, 5.9%, and 3.2%, respectively. In this study, surgical procedure was the best strategy for the above cohorts. However, which treatment (surgery and other treatment) resulted in a better prognosis in advanced cases such as N2 was not studied. The effect that surgical treatment in advanced cases such as N2 has on disease outcome is of interest because treatment strategies without surgery lead to a poorer prognosis.

The Yang *et al.* study had important limitations. First, detailed information on the nature and distribution of patient metastatic disease was not available. Second, the NCDB does not explicitly record how stage IV disease was established. Some patients with early-stage disease may have been overstaged as stage IV, based on radiographic images without pathologic confirmation. Moreover, in this study, staging was based on clinical and not pathologic stage, which could have improved the accuracy of staging of the disease. In fact, staging of the primary tumor might be overstaged, especially those with N status. Third, a small percentage of patients in the study did not have stage IV disease as classified according to the AJCC 7th edition, because the study duration was from 2004 to 2013. During this period, there were changes made to the AJCC 7th edition compared with the 6th. Fourth, a significant limitation was that selection bias may have impacted results. However, in such a large patient database, it seems that the above limitations are unavoidable. Despite the above limitations, we will use this study as a reference for designing future treatment strategies for stage IV NSCLC patients because of the large dataset on which this study was based.

Last year, we reported our data on stage IV NSCLC patients (12) in our institution. The 5-year survival rate was 29.0%, which was similar to the findings of Yang *et al.*

However, T and N factors, which were significant factors in the study by Yang *et al.*, showed no statistically significant effect on survival ($P>0.05$) in our report. In our report, NSCLC patients without squamous cell carcinomas, as determined histologically, had a statistically significant beneficial effect on survival ($P=0.01$). Conversely, NSCLC patients with large-cell lung cancer had significantly worse survival ($P<0.05$) in the study by Yang *et al.* Therefore, the study by Yang *et al.* presented persuasive data involving a large number of patients. We have reported that whether or not local therapy (such as complete resection or radiotherapy) was administered, including metastatic sites was more important. This was also similar regarding treatment of NSCLC M1a, in that it was important to perform complete macroscopic resection to improve disease outcomes. The study by Yang *et al.* pointed out that in the AJCC 7th edition some cases that were classified as NSCLC T4 would have been classified as M1 disease in the 6th edition; however, it seems that this was only a minor obstacle.

Recently, prognosis of stage IV NSCLC patients has been improving because of the discovery of key drugs, e.g., pemetrexed, bevacizumab, targeted therapy (tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase inhibitors), as well as immune check point inhibitors (3-6). Furthermore, salvage surgery for stage IV NSCLC is being actively performed (15,21) based on retrospective and prospective studies and case reports (22,23). In the future, it will be important to investigate which strategy will be most beneficial: local therapy or systemic chemotherapy. It is difficult to perform a prospective phase III clinical trial, because stage IV NSCLC patients are a heterogeneous group. However, there is no doubt that there are stage IV NSCLC patients whose survival period is improved by surgery. Therefore, we should carefully select appropriate surgical candidates among patients with stage IV NSCLC, and this should be done in such a way that patients who would benefit from surgery are not overlooked. Thus, more evidence will need to be obtained from both small and large retrospective studies.

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Footnote

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to declare.

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