Letter to the Editor

Heterogeneity of stage IIIA leads to difficulty in determining optimal treatment

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A recent PACIFIC trial shows that patients with clinical stage IIIA non-small cell lung cancer who can't have surgical resection have an overall survival rate of 66% at 24 months with chemoradiation therapy followed by immunotherapy. The addition of immunotherapy provides a significantly better survival rate compared to chemoradiotherapy alone (1). This trial has led to the approval of immunotherapy followed by chemoradiation therapy for stage IIIA diseases. Moreover, a recent study of resectable clinical stage IIIA non-small cell lung cancer shows that neo-adjuvant chemo/immunotherapy leads to an 80% overall response and a 60% complete response (2). These trials, along with other randomized controlled trials, show that the addition of immunotherapy in the treatment of locally advanced and metastatic non-small cell lung cancer provide improved long term survival, with some patients being cured of lung cancer (3). Immunotherapy's ability to cure patients once thought to have a fatal stage of lung cancer raises a key question: should surgery play a role in patients with a clinical stage IIIA disease?

Our current paradigm for patients with a clinical stage IIIA disease has been either initial treatment with chemotherapy followed by surgery followed by radiation therapy, or initial treatment with chemoradiation therapy followed by surgery (4-7). The 8th edition of the American Joint Committee on Cancer (AJCC) staging guidelines shows that patients with pathologic stage IIIA diseases have a 5-year survival rate of 41% (8). While the advance stage equates with a poor survival rate, there is heterogeneity within the stage IIIA disease: patients with tumor metastatic to the station N2 lymph node (IIIA-N2) have different degree of the disease in the mediastinal lymph nodes. Patients with microscopic stage IIIA-N2 diseases have different survival rates compared to patients with bulky, multi-station stage IIIA-N2 diseases. In the randomized controlled trial of pathologically proven unresectable stage IIIA-N2 patients, the induction chemotherapy followed by either radiation therapy or surgery showed no difference in overall survival (9). The 5-year overall survival rate for patients who underwent surgical resection was 15.7%, while it was 14% for patients who underwent definitive radiation therapy after induction chemotherapy. These results stand in stark contrast to those of our study of occult stage IIIA-N2 diseases at the MD Anderson Cancer Center. We found that patients with microscopic stage IIIA-N2 diseases with positron emission tomography (PET)/computed tomography (CT) and CT negative mediastinum have a 5-year survival rate of 54%, with a median survival of 74 months; most of the patients received adjuvant chemoradiation therapy (10). This difference in the overall survival outcome points to the heterogeneity of the stage IIIA-N2 disease.

Our current staging system does not further classify the N2 disease according to the lymph node, which may be either the bulky N2 disease or the microscopic N2 disease. Furthermore, the current staging system does not account for single-station N2 disease versus the multi-station N2 disease. Multiple studies have shown that patients

with multi-station N2 diseases have worse survival rates compared to those with single-station N2 diseases (11-13). The current treatment guidelines for patients with pathologically proven stage IIIA-N2 diseases recommend either initial chemotherapy followed by surgery and adjuvant radiation therapy or initial chemoradiation therapy followed by surgery with possible adjuvant therapy. Some studies, however, show that there is no difference in survival in patients with chemoradiation with or without surgery (14,15). The inefficacy of surgery stems from our current treatment recommendations, which fail to take into account that the microscopic N2 disease may have different behavior than the bulky N2 disease.

Should we, then, have different treatment paradigms for patients with the bulky multi-station N2 disease and those with the microscopic N2 disease? Patients with the former may have a better overall survival rate with initial chemoradiation therapy followed by immunotherapy, while patients with the latter may benefit from surgery followed by adjuvant therapy. Is it possible, though, to distinguish between the bulky multi-station N2 disease and the microscopic N2 disease? This distinction may be made by a PET/CT and CT of the chest. For patients with ultimate pathologic stage IIIA-N2 diseases, if there is a PET/CT negative N2 station with all of the lymph nodes <1 cm on the CT scan, then the patient likely has the microscopic N2 disease. If there is a positive multi-station PET/CT N2 disease or a lymph node >1 cm, then the patient should have an invasive mediastinal staging with endobronchial ultrasound (EBUS) or mediastinoscopy to confirm the stage. This personalized treatment strategy will change the staging paradigm for performing invasive mediastinal staging in patients with T1 or T2 cancer only with positive PET or CT N2 disease criteria. Perhaps patients with pathologic stage IIIA-N2 diseases who have clinical normal PET and normal CT may have a minimal amount of disease in the mediastinum—an amount that could be cleared locally with surgery followed by adjuvant therapy; and perhaps patients with multi-station bulky diseases or positive uptake on PET scans may be best treated with definitive chemoradiation therapy followed by immunotherapy. Ultimately, the personalized treatment paradigm based on the amount of N2 disease may provide an optimal treatment strategy for patients with stage IIIA diseases.

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Footnote

Conflicts of Interest: Dr. Kim has taught courses for Intuitive Surgical, Veran and Medtronics. Another author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342-50.
2. Provencio M, Nadal E, Insa A, et al. OA01.05 phase II study of neo-adjuvant chemo/immunotherapy for resectable stages IIIa non-small cell lung cancer-nadim study-SLCG. J Thorac Oncol 2018;13:S320.
3. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol 2019;37:537-46.
4. Roth JA, Atkinson EN, Fossella F, et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. Lung Cancer 1998;21:1-6.
5. Rosell R, Gómez-Codina J, Camps C, et al. Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. Lung Cancer 1999;26:7-14.
6. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J Clin Oncol 2002;20:247-53.
7. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Lancet 2007;369:1929-37.
8. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the

TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016;11:39-51.
9. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442-50.
10. Kim MP, Correa AM, Hofstetter WL, et al. Occult stage IIIA-N2 patients have excellent overall survival with initial surgery. J Thorac Dis 2018;10:6670-6.
11. Misthos P, Sepsas E, Kokotsakis J, et al. The significance of one-station N2 disease in the prognosis of patients with non-small-cell lung cancer. Ann Thorac Surg 2008;86:1626-30.
12. Cho HJ, Kim SR, Kim HR, et al. Modern outcome and risk analysis of surgically resected occult N2 non-small cell lung cancer. Ann Thorac Surg 2014;97:1920-5.
13. Funakoshi Y, Takeuchi Y, Kusumoto H, et al. Which subgroup of patients with pathologic N2 non-small cell lung cancer benefit from surgery? J Cancer Res Clin Oncol 2012;138:1027-33.
14. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.
15. Eberhardt WE, Pöttgen C, Gauler TC, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). J Clin Oncol 2015;33:4194-201.

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