Preponderance of High-Grade Histologic Subtype in Autologous Metastases in Lung Adenocarcinoma

To the Editor:

In 2015, the World Health Organization's new classification of lung tumors characterized lung adenocarcinoma (ADC) as a heterogeneous mixture of histologic subtypes (1). Both predominance and presence of histologic subtypes in early-stage lung ADC have been reported to aid in prognostic stratification and therapeutic choice (2–5). Despite the increasing use and therapeutic significance of histologic subtypes in primary lung ADC, their incidence in metastatic tumors and relation to primary tumors remains unknown. Our study aimed to investigate the presence, distribution, and predominance of histologic subtypes of primary and autologous metastatic lung ADC tumors. This study was presented at the 17th World Conference on Lung Cancer, Vienna, Austria, December 4–7, 2016 (6).

Methods

We performed a retrospective review of our prospectively maintained Thoracic Surgery Service database of 4,093 patients who had undergone surgical resection for primary lung ADC at Memorial Sloan Kettering Cancer Center between January 1995 and December 2012. Of these, patients who had undergone surgical resection for pathologic stage I–III solitary primary lung ADC without induction therapy were eligible for inclusion. We excluded patients with 1) no recurrence identified during the follow-up period, 2) no available pathology specimens of either primary or autologous metastatic tumors, 3) tumors <5 mm, or 4) local recurrence.

All recurrences were confirmed by cytologic or histologic evaluation. All available hematoxylin and eosin–stained tumor slides were reviewed by two experienced pathologists (S.L. and W.D.T.). Both primary and metastatic tumors were characterized according to the World Health Organization classification as lepidic, acinar (ACI), papillary, micropapillary (MIP), solid (SOL), and colloid in 5% increments (1).

Second primary lung ADC was excluded from our study population and was defined as a tumor that meets one of the following three criteria: 1) histologically different from the index tumor; 2) similar histologic appearance to the index tumor but diagnosed more than 2 years after primary tumor diagnosis; or 3) similar histology to the index tumor and diagnosed within 2 years of treatment of the index tumor, but in a different lobe or segment without intervening positive lymph nodes and no evidence of metastatic disease. Cases in which the primary and secondary

lesions were morphologically different or had differing gene mutation status were considered separate histologies (7). Data were compared using the Pearson chi-squared test with SPSS Statistics v24.0 (IBM Corporation).

Results

Our study cohort included 117 patients who had undergone surgical resection for metastatic tumors with adequate histology slides available for analysis (Figure 1). Median age at the time of primary tumor surgery was 67.8 years (range, 38.9–86.1 yr), 76 patients (65%) were women, and 96 patients (82%) were either former or current smokers. The pathologic stage of the primary tumor was stage I in 61 (52%) patients, stage II in 38 (33%) patients, and stage IIIA in 18 (15%) patients. Resected metastatic sites included the brain (44 patients; 38%), lung (28 patients; 24%), lymph nodes (13 patients; 11%), pleura (10 patients; 9%), bone (8 patients; 7%), adrenal gland (5 patients; 4%), and other organs (9 patients; 8%).

Among the 117 patients, the most frequent predominant histologic subtype in their primary tumors was ACI in 53 (45%) patients, followed by SOL in 29 (25%) patients and papillary in 21 (18%) patients (Figure 2). The most frequent predominant histologic subtype in autologous metastases was SOL in 61 (52%) patients, followed by ACI in 34 (29%) patients and MIP in 15 (13%) patients. As shown in Figure 2, analysis of the percentage of histologic subtypes in primary tumors and autologous metastases in each case revealed an increasing incidence of the SOL histologic subtype in metastatic tumors. The presence of the SOL subtype was identified in 87 (74%) metastatic tumors. Metastases more frequently exhibited SOL predominance than the primary tumors ($P < 0.001$).

Discussion

To date, this is the largest series examining primary and matched metastases of lung ADC. The majority of autologous metastases exhibited SOL predominance, which was more frequent than in the primary tumors. As the majority of patients with lung ADC metastases do not undergo resection and are diagnosed only by fine-needle aspiration or needle biopsy, available tissue to perform histologic subtyping is limited. When comparing the SOL component percentage between primary and metastatic tumors, the majority of the patients ($n = 98$; 84%) had an increase in the percentage of the SOL pattern at the metastatic site compared with the primary site (SOL pattern-increased). The proportion of *EGFR* mutant tumors was lower in these SOL pattern-increased patients compared with those patients with SOL pattern decrease at metastatic sites (19% vs. 33%). By contrast, the proportion of *KRAS* mutant tumors was higher in the SOL pattern-increased patients than in the SOL pattern-decreased patients (38% vs. 17%). Distant metastatic sites frequently showed SOL predominance (55–80%), whereas lung metastases were more frequently ACI predominant (57%). Additionally, in patients with an ACI-predominant tumor at their primary site ($n = 53$), the predominant subtype at the metastatic site was usually ACI (45%, $n = 24$) or SOL (40%, $n = 21$). Even when the SOL subtype represented a small percentage of the primary lung ADC tumor composition, the majority of subsequent metastases demonstrated SOL predominance. This is suggestive of the aggressive nature of the SOL subtype and that this subtype may contribute to the metastatic process (8). Clay and colleagues showed that the SOL

Supported by grants from the NIH (P30 CA008748), the U.S. Department of Defense (BC132124 and LC160212), the Derfner Foundation, the Joanne and John DallePezze Foundation, Mr. William H. Goodwin and Mrs. Alice Goodwin, the Commonwealth Foundation for Cancer Research, and the Experimental Therapeutics Center of Memorial Sloan Kettering Cancer Center.

Author Contributions: Y.T.: acquisition of data, analysis of data, and writing of manuscript; T.E., S.L., and W.D.T.: acquisition of data and review of manuscript; R.J.D. and D.R.J.: review of manuscript; and P.S.A.: study design, analysis of data, writing of manuscript, and review of manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201705-0924LE on September 1, 2017

Figure 1. Between January 1995 and December 2012, 4,093 patients underwent surgical resection for primary lung adenocarcinoma (ADC) at Memorial Sloan Kettering (MSK) Cancer Center. We identified 877 patients who had developed recurrence after complete resection without induction therapy. Among them, 760 patients had either no available pathologic specimens or had metastatic tumors <5 mm in size and were excluded. The remaining 117 patients were included in our study cohort.

subtype in metastatic tumor biopsy specimens was associated with a poor prognosis in stage IV lung ADC (9). Patients with MIP- and SOL-predominant primary tumors reportedly showed better disease-free survival among patients with lung ADC who had undergone adjuvant chemotherapy after surgical resection compared with those who had not (10). This implies that tumor histologic subtypes can influence chemotherapeutic efficacy. Additionally, Zhang and colleagues reported that SOL-predominant lung ADC showed a

Figure 2. The graph demonstrates the percentage of each histologic subtype in the primary and matched metastatic tumor for each case. One data point represents one patient. (When consecutive patients have the same percentage of a specific histologic subtype, the colors may extend across different patients and may display a wedge shape.) This graph shows that most of the metastatic tumors had the solid (SOL) subtype present at a higher percentage compared with matched primary tumors. In addition, the SOL subtype was identified in 87 (74%) metastatic tumors. The pie chart shows the predominant histologic subtype in tumors at primary sites and autologous metastases. The acinar (ACI) subtype, which was present in 53 (45%) patients, was the most common histologic subtype in primary tumors. The most common predominant histologic subtype in autologous metastases was the SOL subtype, which was present in 61 (52%) patients, followed by the ACI subtype in 34 (29%) patients and the micropapillary (MIP) subtype in 15 (13%) patients. COL = colloid; LEP = lepidic; PAP = papillary.

higher immunopositivity for programmed cell death ligand 1 (11). Given the difference in therapeutic efficacy according to histologic subtype, our observations based on a thorough analysis of primary and matched metastases may have clinical significance.

Our data suggests that the presence, even at a low percentage, of the SOL subtype in resected primary tumors should raise suspicion for the presence and/or predominance of the SOL subtype in metastatic tumors; this may, in turn, affect the choice of chemioimmunotherapies. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The authors thank Alex Torres of the Memorial Sloan Kettering Cancer Center Thoracic Surgery Service for his editorial assistance.

Yusuke Takahashi, M.D., Ph.D.
Memorial Sloan Kettering Cancer Center
New York, New York
and

Keio University School of Medicine
Tokyo, Japan

Takashi Eguchi, M.D., Ph.D.
Memorial Sloan Kettering Cancer Center
New York, New York
and
Shinshu University School of Medicine
Matsumoto, Japan

Shaohua Lu, M.D., Ph.D.
Memorial Sloan Kettering Cancer Center
New York, New York
and
Fudan University
Shanghai, China

Robert J. Downey, M.D.
David R. Jones, M.D.
William D. Travis, M.D.
Prasad S. Adusumilli, M.D.
Memorial Sloan Kettering Cancer Center
New York, New York

ORCID ID: 0000-0002-1699-2046 (P.S.A.).

References

1. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JH, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, *et al*.; WHO Panel. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 2015;10:1243–1260.
2. Eguchi T, Kadota K, Park BJ, Travis WD, Jones DR, Adusumilli PS. The new IASLC-ATS-ERS lung adenocarcinoma classification: what the surgeon should know. *Semin Thorac Cardiovasc Surg* 2014;26:210–222.
3. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol* 2013;31:992–1001.
4. Takahashi Y, Ishii G, Aokage K, Hishida T, Yoshida J, Nagai K. Distinctive histopathological features of lepidic growth predominant node-negative adenocarcinomas 3–5 cm in size. *Lung Cancer* 2013;79:118–124.
5. Nitadori J, Bograd AJ, Kadota K, Sima CS, Rizk NP, Morales EA, Rusch VW, Travis WD, Adusumilli PS. Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2cm or smaller. *J Natl Cancer Inst* 2013;105:1212–1220.
6. Takahashi Y, Eguchi T, Lu S, Downey R, Jones D, Travis W, *et al*. Histological subtyping of matched primary and metastases sites in lung adenocarcinoma: significance of solid predominance. *J Thorac Oncol* 12:S414–S415.
7. Ripley RT, McMillan RR, Sima CS, Hasan SM, Ahmad U, Lou F, Jones DR, Rusch VW, Rizk NP, Huang J. Second primary lung cancers: smokers versus nonsmokers after resection of stage I lung adenocarcinoma. *Ann Thorac Surg* 2014;98:968–974.
8. Ujiie H, Kadota K, Chaft JE, Buitrago D, Sima CS, Lee MC, Huang J, Travis WD, Rizk NP, Rudin CM, *et al*. Solid predominant histologic subtype in resected stage I lung adenocarcinoma is an independent predictor of early, extrathoracic, multisite recurrence and of poor postrecurrence survival. *J Clin Oncol* 2015;33:2877–2884.
9. Clay TD, Do H, Sundararajan V, Moore MM, Conron M, Wright GM, McLachlan SA, Dobrovic A, Russell PA. The clinical relevance of pathologic subtypes in metastatic lung adenocarcinoma. *J Thorac Oncol* 2014;9:654–663.
10. Tsao MS, Marguet S, Le Teuff G, Lantuejoul S, Shepherd FA, Seymour L, Kratzke R, Graziano SL, Popper HH, Rosell R, *et al*. Subtype classification of lung adenocarcinoma predicts benefit from adjuvant chemotherapy in patients undergoing complete resection. *J Clin Oncol* 2015;33:3439–3446.
11. Zhang Y, Wang L, Li Y, Pan Y, Wang R, Hu H, Li H, Luo X, Ye T, Sun Y, *et al*. Protein expression of programmed death 1 ligand 1 and ligand 2 independently predict poor prognosis in surgically resected lung adenocarcinoma. *Oncotargets Ther* 2014;7:567–573.

Copyright © 2018 by the American Thoracic Society

Differentially Culturable Tubercule Bacilli Are Generated during Nonpulmonary Tuberculosis Infection

To the Editor:

Mycobacterium tuberculosis (*Mtb*) is a major global cause of death from infectious disease (1). Rarely contagious, extrapulmonary tuberculosis (EPTB) is neglected in tuberculosis (TB) control strategies. Nonetheless, EPTB contributes significantly to the burden of disease, is frequently difficult to diagnose, and inflicts significant morbidity (2).

After the establishment of infection in the host, it is believed that heterogeneous populations develop, distinguishable by specific growth requirements (3–5), metabolic features (6, 7), and differential susceptibility to antimicrobial agents (3, 8). The application of limiting

The PreDiCT-TB project is funded by European Commission the Innovative Medicines Initiative (No. 115337), a joint undertaking of the European Union Seventh Framework Program and The European Federation of Pharmaceutical Industries and Associations (O.T. and G.V.M.); Biotechnology and Biological Sciences Research Council grant BB/K000330/1 (G.V.M.); the Dowager Countess Eleanor Peel Trust (A.R. and G.V.M.); and National Institute for Health Research grant PDF-2015-08-102 (M.P.). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

Author Contributions: Conception and design: A.R., M.P., O.T., M.J.W., and G.V.M.; analysis and interpretation: A.R. and G.V.M.; drafting the manuscript for important intellectual content: A.R., M.P., and G.V.M.

Originally Published in Press as DOI: 10.1164/rccm.201705-1048LE on September 7, 2017