Commentary

Say goodbye to Martini and Melamed: genomic classification of multiple synchronous lung cancer

Brendon M. Stiles

Division of Thoracic Surgery, Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY, USA

Correspondence to: Brendon M. Stiles, MD. Department of Cardiothoracic Surgery, Suite M404, Weill Medical College of Cornell University, 525 East 68th Street, New York, NY 10021, USA. Email: brs9035@med.cornell.edu.

Provenance: This is an invited Commentary commissioned by the Editorial Board Member Yoshihisa Shimada (Department of Thoracic Surgery, Tokyo Medical University, Shinjuku-ku, Tokyo, Japan).

Comment on: Liu Y, Zhang J, Li L, *et al.* Genomic heterogeneity of multiple synchronous lung cancer. Nat Commun 2016;7:13200.

Submitted Dec 13, 2016. Accepted for publication Dec 27, 2016.

doi: 10.21037/jtd.2017.01.48

View this article at: http://dx.doi.org/10.21037/jtd.2017.01.48

It is said that all good things must come to an end. The paper "Genomic heterogeneity of multiple synchronous lung cancer" by Liu *et al.* may finally close the book on the Martini and Melamed criteria for establishing whether multiple synchronous lung cancers (MSLC) represent distinct primary tumors or intrapulmonary metastases (1). These empirical criteria, although first published in 1974, to this day are discussed at tumor boards around the country when multiple lung nodules are discovered in patients by computed tomography (CT) or by other radiologic imaging studies (2). Yet modern pathology and molecular techniques have moved well beyond Martini and Melamed. The manuscript by Liu *et al.* is a striking example of that. In it, the authors describe lung tumors in several patients that, despite meeting classic criteria for intrapulmonary or hematogenous metastases, in fact carry distinct mutations. Even more notable, the authors describe a marked absence of shared mutations in individual patient tumors and instead assert that distinct lung tumors in the same individual are "no more similar to each other than are lung adenocarcinomas of different patients" (1). These findings have marked implications for the treatment of patients found to have multiple pulmonary nodules.

As the basis for their study, Liu *et al.* examined 16 lung tumors removed from 6 patients with multiple lung adenocarcinomas. Four of the six patients were never-smokers. The median tumor size was 1.9 cm with three tumors being pure ground glass opacities (GGO) on CT, five being part-solid, and the remaining eight being solid nodules by preoperative imaging. According to 2007 American College of Chest Physicians (ACCP) guidelines and presumably when evaluated by Martini and Melamed criteria, all cases were either classified as satellite nodules or as hematogenous spread of a primary cancer (2,3). The authors performed whole-genome sequencing (WGS) or whole-exome sequencing (WES) to determine the genetic make-up of these tumors and to assess possible clonal relationships between different tumors. Among the 16 tumors (which included one lymph node metastasis), 1,127 nonsynonymous coding and splice site mutations were detected, of which 92% were validated. Remarkably, shared mutations between tumors in the same patient were exceedingly rare. Four patients had no shared mutations at all among their different lung tumors. Curiously, EGFR mutations seemed to perhaps occur in more of a "field" pattern. One patient had three tumors, all of which shared an EGFR p.L858R mutation, while another patient had two out of three tumors which shared an EGFR p.L858R mutation. Nevertheless, these tumors shared no other mutations, suggesting that they were independent events. Distinct primary tumors were also suggested by clear differences in copy number variation and in indels in tumors taken from individual patients. Perhaps even more remarkable was that when the sharing of one exonic mutation was compared in patient matched tumors to the sharing of mutations in different individual tumors from the TCGA (matched for size and smoking status), MSLCs from the same patient were no more similar to each other than to tumors from unrelated patients. As the authors point out, this finding suggests that multiple unique mutational processes may be at play in an individual patient despite his or her own personal exposure history and genetic make-up.

Such findings have important clinical implications for patients found to have multiple lung nodules, a clinical scenario that is increasingly encountered. Indeed, although the incidence of MSLCs is reported to be between 0.2–8%, that incidence obviously depends upon how rigorously CT detected synchronous nodules are investigated (1,4). A study by our group reported that over 50% of patients presenting with a newly diagnosed lung cancer will have at least one secondary nodule (5). Many of these patients could be mistaken as having intrapulmonary T3 metastases at best, and at worst as having distant metastatic disease. For instance, all six of the patients in the study by Liu *et al.* were defined as clinically metastatic based upon ACCP guidelines (1). In the real world, such patients run the risk of being under-treated by not being offered surgery and of being over-treated with systemic therapy for what is in reality, curable multifocal local disease.

The study has several caveats when applied to clinical practice. First, the sample number is quite small and contains a majority of never smokers. A larger previous study has suggested that multifocal lung cancers may indeed have a clonal origin based upon commonality of TP53 mutations and loss of heterozygosity (4). However, the WGS and WES techniques performed in the current study are much more comprehensive than the technique used by Wang *et al.* and provide convincing evidence of genomic heterogeneity between MSLCs in their study. It is curious however that among all the mutations analyzed, there did seem to be concordance of EGFR mutations in two of the six patients studied. In these Asian never-smokers, L858R mutations can be expected to be common. This does however raise the question of whether limited clinical mutation testing for "actionable" mutations alone will provide enough information to reliably distinguish MSLCs in larger patient data sets. Some emerging evidence on this topic has suggested that even in patients with high rates of EGFR mutations, genomic heterogeneity is the rule rather than the exception (6). Finally, the question arises as to how best to determine tumor heterogeneity clinically. Certainly, it is not practical to perform WGS or WES on every tumor. Readers should take note of the authors' assertion that they were able to accurately classify 5 of the 6 patients as having distinct tumors by performing retrospective comprehensive histologic assessment of adenocarcinoma subtypes. Clearly such pathological assessment is critical for the accurate classification and prognosis of lung adenocarcinoma, has supplanted Martini and Melamed, and should be universally performed. Similarly, radiologic evaluation has come a long way since the time of Martini and Melamed's initial classification scheme. It would seem unlikely that ground glass lesions or even part-solid lesions could represent metastatic spread from another primary tumor, as evidenced in the paper by Liu *et al.* of which 8 of 16 tumors had such an appearance on CT. I expect that in the current era, radiographic classification combined with histologic and molecular characterization should be able to accurately classify most MSLCs as either individual primary tumors or as metastases. In the appropriate context of multiple nodules with radiographic disease confined to the lungs, it increasingly seems that the former is much more likely.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Liu Y, Zhang J, Li L, et al. Genomic heterogeneity of multiple synchronous lung cancer. Nat Commun 2016;7:13200.
2. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12.
3. Shen KR, Meyers BF, Larner JM, et al. Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:290S-305S.
4. Wang X, Wang M, MacLennan GT, et al. Evidence for common clonal origin of multifocal lung cancers. J Natl Cancer Inst 2009;101:560-70.
5. Stiles BM, Schulster M, Nasar A, et al. Characteristics and outcomes of secondary nodules identified on initial computed tomography scan for patients undergoing resection for primary non-small cell lung cancer. J Thorac Cardiovasc Surg 2015;149:19-24.
6. Liu M, He WX, Song N, et al. Discrepancy of epidermal growth factor receptor mutation in lung adenocarcinoma presenting as multiple ground-glass opacities. Eur J Cardiothorac Surg 2016;50:909-13.

Cite this article as: Stiles BM. Say goodbye to Martini and Melamed: genomic classification of multiple synchronous lung cancer. J Thorac Dis 2017;9(1):E87-E88. doi: 10.21037/jtd.2017.01.48

