Synchronous, Separate, and Similar

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This issue of *Journal of Thoracic Oncology* includes two separate articles that have a lot of similarities.[1,2] Both address the issue of what to do with patients that present with the synchronous finding of a primary lung cancer and an additional separate, yet similar lesion. The article by Finley et al.[1] restricts its analysis to patients who were proven to have synchronous primary lung cancers, whereas the article by Kim et al.[2] addresses patients who have one or more additional ground glass opacities (GGO), and the task of determining which of these additional lesions is malignant. These articles present a good opportunity to discuss the topic of how we should think of synchronous, separate nodules in patients with lung cancer.

The article by Finley et al.[1] has several unique features, starting with a new definition of what should be considered a second primary lung cancer. The widely used criteria proposed by Martini and Melamed[3] in 1975 were empirically derived and have never been validated. An analysis of data suggests that for metachronous second primary lung cancers, a 4-year interval is better than the traditional 2-year interval.[4,5] Finley et al. have added definitions to distinguish synchronous tumors, accepting them as second primary cancers if they are either of a different histologic type or subtype of adenocarcinoma. Because most of adenocarcinomas are of mixed subtypes, distinct tumors are defined by differing proportions of the subtypes. This distinction has been shown to correlate with genetic differences but has the advantage of being apparent by light microscopy.[6] I believe that this definition will become the new standard, at least for synchronous tumors. Distinguishing tumors on the basis of genomic signatures remains costly, available only in research laboratories, is sometimes plagued by conflicting results,[7–9] and, in fact, genetic features correlate quite well with details apparent by light microscopy.[6,10]

The study by Finley et al. also used careful staging of the patients to avoid considering patients as having synchronous second primary cancers if in fact they had evidence of metastases to distant sites or mediastinal nodes although full details are not explicit. Not all centers reporting on second primary lung cancers have used such a thorough evaluation, although this is recommended in the American College of Chest Physicians Lung Cancer guidelines.[4,5]

The survival observed in this study (5-year overall survival ~55%) is better than most series of synchronous primary lung cancers (average 5-year survival ~30%).[11] Is this because of better patient selection (e.g., more careful staging)? Is this due to a changing spectrum of disease, with a greater proportion of more indolent tumors (e.g., due to computed tomography screening, increasing proportion of women or nonsmokers)? Or is this because we are seeing more of a different kind of non-small cell lung cancer that has a propensity for multifocal disease?

Unfortunately, there is no information on recurrence patterns. This could shed light on whether we are dealing with "regular" lung cancers that have been carefully selected, in which case we should see primarily distant metastases among those patients that develop recurrent disease. However, if we are dealing with tumors that have a propensity to multifocal disease in the lungs, we would expect a high proportion of "local recur-

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rences" among those who have a recurrence. Of course, if a new pulmonary focus of malignancy becomes apparent, it is difficult to distinguish a local recurrence from a new primary tumor.

The second article, by Kim et al.,[2] reports on patients with a bronchioloalveolar carcinoma (BAC) who have additional GGO lesions, realizing that some of these may be (or may become) synchronous or metachronous foci of malignancy. It seems intuitively easier in the case of a GGO to think of this as a separate process, as opposed to a metastasis. Consistent with this sentiment, the authors do not dwell on describing how metastases are excluded (other than using the classic criteria of Martini and Melamed). BAC was found in 25% of the additional GGO lesions that were biopsied. These results are not limited only to BAC, as evidenced by another study from this same group,[12] involving patients with a dominant lung cancer who have additional GGO. Lesions that were lobulated, and especially, lesions larger than 10 mm had a relatively high chance of being recognized as additional foci of malignancy (45 and 67%, respectively).

But how should we think about these additional foci of malignancy? Are they synchronous second primary cancers that are the same as in the first article by Finley et al (which were almost all solid lesions without a significant GGO component)[1]? Or is there something different about these second primary cancers that arise from a GGO? It should be noted that on average there were three GGOs per patient—so are many of these patients exhibiting multiple primary cancers? Are we dealing with a different type of tumor that has a propensity to develop multifocal disease in the lungs? Multifocal disease is well recognized for BAC,[13–15] but the large majority of both the dominant initial tumor and the secondary cancers were adenocarcinomas and not BAC.[2] However, the distinction between adenocarcinoma and BAC is becoming increasingly indistinct, and in the near future, the official pathologic nomenclature may no longer include BAC (instead, pure BAC will be referred to as adenocarcinoma in situ).[16] The fact that some GGOs eventually grow, develop a solid component, and are classified histologically at this point as an adenocarcinoma has long been recognized.[14,17,18] Furthermore, many clinical and pathologic studies have suggested that BAC may be a precursor to invasive adenocarcinoma.[14,15,19–21]

If we assume that a form of lung cancer exists that is prone to multifocal disease, what etiologic factors play a role? Is this a manifestation of field cancerization? Is this due to infection, perhaps by an unknown oncogenic virus? Or is this due to an alteration in the host, for example resulting in a favorable microenvironment in the lung or in altered immune recognition?

The new International Association for the Study of Lung Cancer (IASLC) staging system does not make it clear how to think about these patients. The new staging system has defined nomenclature for additional nodules of the same histologic type,[22] but in fact most of patients that have been defined as having synchronous primary cancers have had tumors of the same histologic type. Synchronous second primary tumors were excluded from the IASLC analysis, but the definition of this was left to each center that submitted data. The new staging system has viewed these additional nodules primarily as isolated pulmonary metastases, but, in fact, the survival is much better that for isolated metastases at any other site (1-year survival 45% versus 23% for cM1a-contralateral nodule versus cM1b-single site).[23] Hence, what is the nature of these "additional nodules"? This confusion is apparent in the discussion by Finley et al., who argue that their data on synchronous primaries support the IASLC reclassification of additional nodules.[1]

Of note, the IASLC analysis of additional nodules was dominated by data from Asia (just like the origin of the patients in the article by Kim et al.).[2] Is there a subset of patients in Asia that are fundamentally different, with a predisposition to multifocal disease, usually arising from a GGO? Most of articles discussing multifocal cancers or GGOs have come from Asia. Is this due to a heightened awareness or recognition of this phenomenon? Or is this due to a more widespread use of computed tomography as a screening tool for lung cancer?

Are the patients considered in the articles by Finley et al. and Kim et al. the same, with only a slight difference in the point during the natural history of the disease at which they are studied? Or is there an inherent biologic difference in the type of patients and tumors between these studies? Are solid, spiculated tumors biologically different than those that appear radiographically as a GGO? Are tumors in North America biologically different than tumors in Asia?

Although clear answers to these questions are not available, we have to try to draw what conclusions we can from the data available. First, I believe that the system of defining synchronous primary lung cancers in the article by Finley et al. should become the new standard. I also believe that we should adopt the ACCP definition of metachronous lung cancers,[4,5] rather than continue to rely on the criteria of Martini and Melamed[3]) that were derived empirically 35 years ago.

Second, we should be carefully, thoughtfully aggressive in treating patients that may have synchronous primary lung cancers. I would define this as patients who have solid masses that fit the appearance of traditional lung cancers (i.e., spiculated). These patients should undergo very careful investigation for distant or mediastinal metastases, but if this is negative, they should undergo definitive treatment with curative intent. The second lesion should be thought of as a pulmonary metastasis only if the histologic type and subtype is exactly the same and there are distant or mediastinal metastases.

Third, we certainly should be aggressive in treating the primary tumor in patients that harbor an additional GGO. It is reasonable to follow these additional lesions if they are pure GGO and less than 10 mm in diameter. If the additional focus exceeds 10 mm or develops a solid component, it should be biopsied or resected. The size cutpoint that should trigger intervention has been arbitrary, but the study by Kim et al. provides reasonable data to justify 10 mm.[12]

Fourth, I believe that we need to maintain an open mind about the nature of multiple foci of pulmonary malignancy, especially when these have a ground glass component. This

may be a different kind of lung cancer that has a propensity for multifocal involvement. There are some data to suggest that these tumors have a decreased propensity to metastasize,[14,19,24,25] making them good candidates for parenchymal sparing local therapy with curative intent. However, research is needed to substantiate or refute this impression.

Finally, we need to develop a set of criteria to distinguish a synchronous second primary cancer from an isolated pulmonary metastasis, an "additional nodule" and multifocal disease. A definition would at least allow us to assemble some data to guide this process. We need this both to define how to approach the patients addressed in the two articles that are the focus of this editorial and prospectively to understand the additional nodule category of the new IASLC staging system.

REFERENCES

1. Finley D, Yoshizawa A, Travis W, et al. Predictors of outcomes after surgical treatment of synchronous primary lung cancers. *J Thorac Oncol* 2010;5:197–205.
2. Kim H, Choi Y, Kim J, et al. Management of multiple pure ground-glass opacity lesions in patients with bronchioloalveolar carcinoma. *J Thorac Oncol* 2010;5:206–210.
3. Martini N, Melamed MR. Multiple primary lung cancers. *J Thorac Cardiovasc Surg* 1975;70:606–612.
4. Detterbeck FC, Jones DR, Kernstine KH, et al. Special treatment issues. *Chest* 2003;123:244S–258S.
5. 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.
6. Motoi N, Szoke J, Riely GJ, et al. Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. *Am J Surg Pathol* 2008;32:810–827.
7. Wang X, Wang M, MacLennan GT, et al. Evidence for common clonal origin of multifocal lung cancers. *J Natl Cancer Inst* 2009;101:560–570.
8. Hiroshima K, Toyozaki T, Kohno H, et al. Synchronous and metachronous lung carcinomas: molecular evidence for multicentricity. *Pathol Int* 1998;48:869.
9. Chang Y-L, Wu C-T, Lin S-C, et al. Clonality and Prognostic implications of p53 and epidermal growth factor receptor somatic aberrations in multiple primary lung cancers. *Clin Cancer Res* 2007;13:52–58.
10. Girard ND, Lau C, Finley D, et al. Comprehensive histologic assessment helps to differentiate multiple lung primary non-small cell carcinomas from metastases. *Am J Surg Pathol.* In press.
11. Detterbeck FC, Jones DR, Funkhouser WK Jr. Satellite nodules and multiple primary cancers. In Detterbeck FC, Rivera MP, Socinski MA, et al. (Eds.), Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician. Philadelphia, PA: W. B. Saunders, 2001. Pp. 437–449.
12. Kim H, Choi Y, Kim K, et al. Management of ground-glass opacity lesions detected in patients with otherwise operable non-small cell lung cancer. *J Thorac Oncol* 2009;4:1242–1246.
13. Arenberg D. Bronchioloalveolar lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:306S–313S.
14. Garfield D, Cadranel J, Wislez M, et al. The bronchioloalveolar carcinoma and peripheral adenocarcinoma spectrum of diseases. *J Thorac Oncol* 2006;1:344–359.
15. Detterbeck FC, Jones DR, Funkhouser WK Jr. Bronchioloalveolar carcinoma. In Detterbeck FC, Rivera MP, Socinski MA, et al. (Eds.), Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician. Philadelphia, PA: W. B. Saunders, 2001. Pp. 394–407.
16. Travis W, Brambilla E, Noguchi M, et al. The new IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification. Presented at the 13th World Conference on Lung Cancer San Francisco, CA, 2009.
17. Kakinuma R, Ohmatsu H, Kaneko M, et al. Progression of focal pure ground-glass opacity detected by low-dose helical computed tomography screening for lung cancer. *J Comput Assist Tomogr* 2004;28:17–23.
18. Nakata M, Sawada S, Yamashita M, et al. Surgical treatments for multiple primary adenocarcinoma of the lung. *Ann Thorac Surg* 2004; 78:1194–1199.
19. Travis WD, Garg K, Franklin WA, et al. Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma. *J Clin Oncol* 2005;23:3279–3287.
20. Sakuma Y, Matsukuma S, Yoshihara M, et al. Epidermal growth factor receptor gene mutations in atypical adenomatous hyperplasias of the lung. *Mod Pathol* 2007;20:967–973.
21. Takashima S, Maruyama Y, Hasegawa M, et al. CT findings and progression of small peripheral lung neoplasms having a replacement growth pattern. *AJR Am J Roentgenol* 2003;180:817–826.
22. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the T descriptors in the forthcoming (7th) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2007;2:593–602.
23. Postmus P, Brambilla E, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2007;2:686–693.
24. Trousse D, Barlesi F, Loundou A, et al. Synchronous multiple primary lung cancer: an increasing clinical occurrence requiring multidisciplinary management. *J Thorac Cardiovasc Surg* 2007;133:1193–1200.
25. Battafarano RJ, Meyers BF, Guthrie TJ, et al. Surgical resection of multifocal non-small cell lung cancer is associated with prolonged survival. *Ann Thorac Surg* 2002;74:988–994.