

Approach to the Patient with Multiple Lung Nodules

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KEYWORDS

- Non–small cell lung cancer • Adenocarcinoma in situ • Minimally invasive adenocarcinoma
- Lepidic-predominant adenocarcinoma • Ground-glass opacity • Multifocal lung cancer
- Synchronous primary lung cancer

KEY POINTS

- Typical solid, invasive non–small cell lung cancer (NSCLC) behaves much more aggressively than lepidic-predominate adenocarcinoma with a small invasive focus, and thus these disease processes must be managed differently, in cases of both single and multiple tumors.
- Patients with pure ground-glass opacities (GGOs) less than 1 cm in diameter likely do not require surgical resection.
- Minimally invasive adenocarcinomas and pure GGOs less than 2 cm in diameter may be managed by sublobar resection, preferably anatomic segmentectomy.
- Patients with an invasive adenocarcinoma and as many as approximately 10 synchronous, pure GGOs should be approached by anatomic resection of the primary tumor, wedge resection of accessible, ipsilateral GGOs, and serial computed tomography follow-up.

INTRODUCTION

When Bob Ginsberg was at the peak of his practice, a patient with more than 1 pulmonary nodule in separate lobes would have been considered to harbor stage 4 disease with a presumed attendant extremely poor prognosis. That patient would therefore more than likely not have been considered for surgical resection. In recent years, however, data have accumulated that even with standard, solid, invasive, cigarette-smoking–associated non–small-cell lung cancer (NSCLC), a patient with a single malignant nodule in a separate lobe actually does not have such a dire prognosis with resection. Our staging system, in fact, has been changed to reflect this, rendering such a tumor T4 (potentially stage IIIB) rather than stage IV, and this does not even take into consideration the real possibility of the 2 tumors representing separate primaries. In short, many of these patients are now clearly candidates for surgical resection.

Furthermore, in the past decade entirely new types of NSCLC have emerged, namely minimally invasive adenocarcinoma (MIA) and adenocarcinoma in situ (AIS). The unique clinical behavior of these tumors has enormous importance for how we approach patients with multiple nodules of these subtypes. These adenocarcinomas, frequently occurring in nonsmokers, are very often multifocal at presentation, and yet early data on this tumor type would suggest that this multifocality should not dissuade us from operating on these tumors once one or more of the lesions appear to have developed an invasive phenotype.

This article reviews the data underlying the recommended approach to each of these tumor-types when they present with more than a single nodule, and discusses the overall clinical approach to patients with each of these types of multifocal tumors.

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HISTORICAL NOTES

- 1975: Martini and Melamed report the seminal series of 50 patients with synchronous and metachronous NSCLC, and propose criteria for differentiating metastases from separate primary tumors.¹
- 1997: Revision of the of American Joint Cancer Committee/International Union Against Cancer (AJCC/UICC) International System for Staging Lung Cancer is published²; separate tumor in ipsilateral lobe is specifically classified as M1 and thus generally considered nonsurgical.
- 2007: Seventh edition of AJCC/UICC staging system is published³; separate tumor in ipsilateral lobe reclassified as T4 (IIIB if N0).
- 1995: Noguchi publishes his classification of small pulmonary adenocarcinomas that includes the first clear description of in situ tumors, with their extremely good prognosis.⁴
- 2011: Publication of joint International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) Classification of Lung Adenocarcinoma that eliminates term bronchioloalveolar carcinoma (BAC) and proposes 5 categories, including AIS and MIA (Box 1).⁵

THE PATIENT WITH MULTIPLE FOCI OF "SOLID" NSCLC

As suggested in the introduction, it is very important to differentiate between solid tumors and tumors that are in part nonsolid (or "ground glass"), when discussing the approach to multifocal lung cancer. First discussed are tumors that are predominately solid on CT imaging, upon which our current official staging system is based. These tumors are presumed to represent invasive NSCLC, with substantial potential for lymph node metastasis and distant metastasis; they may represent squamous cell carcinomas or invasive adenocarcinomas, and are highly associated with cigarette smoking.

Two Solid Tumors in Separate, Ipsilateral Lobes

Before the 2007 revision of the AJCC/UICC lung cancer classification, tumors with an NSCLC in one lobe and a second tumor in a separate, ipsilateral lobe were classified as stage IV. However, this classification failed to take account of several important issues. First, it is usually not at all clear in these situations if the 2 tumors represent a single primary tumor with a site of metastasis within the lung, or whether they in fact represent 2 separate

Box 1

The IASLC/ATS/ERS classification of lung adenocarcinoma

Preinvasive Lesions

Atypical adenomatous hyperplasia (AAH): a pure in situ tumor ≤ 5 mm diameter

Adenocarcinoma in situ (AIS): a pure in situ tumor >5 mm and ≤ 3 cm

Mucinous (may also be invasive in some cases)

Nonmucinous

Mixed

Minimally Invasive Adenocarcinoma: a lepidic-predominant tumor ≤ 3 cm with ≤ 5 mm invasive focus

Invasive Adenocarcinoma

Lepidic predominant: a lepidic-predominant tumor with >5 mm invasive focus

Acinar predominant

Papillary predominant

Micropapillary predominant

Solid predominant with mucin

Variants of Invasive Adenocarcinoma (4; not listed here)

Adapted from Travis W, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244–85.

primary tumors. Although one can have a suspicion that the smaller lesion is a metastasis that has spread from the larger one if that smaller lesion has a well-circumscribed, "punched-out" appearance, this is far from being a reliable indicator. Even if a biopsy of each tumor suggests the same basic histology (eg, squamous or adenocarcinoma), they still may represent separate primary tumors. And of course a patient with a true metastasis to another lobe of the lung will have a far poorer prognosis than a patient with 2 separate primaries, at least 1 of which is likely to be a very early, stage I tumor with a very high cure rate.

For these reasons, many surgeons, even before the 2007 revision of the lung cancer classification that restaged tumors with a concurrent lesion in a different ipsilateral lobe as T4, would consider these patients for surgical resection. This approach was proved, in retrospect, to be appropriate by the survival curves used to create the 2007 revision.⁶ These curves showed that a T4 tumor of this type

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