Editorial

Multifocal ground-glass opacities: multifocal origin versus intrapulmonary metastasis

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Multifocal origin or intrapulmonary metastasis; that is the question (1).

Introduction of low-dose computed tomography (LDCT) of the chest for lung cancer screening has facilitated the detection of many lung nodules, including ground-glass opacity nodules (GGNs). Most GGNs have only been detected using LDCT. More than one GGN were found in a patient. There are no existing correct data; however, more than 10% of patients with GGNs harbor more than one GGN.

Whenever we encounter patients with multiple GGNs, it is not easy to determine whether multiple GGNs indicate intrapulmonary metastasis or multifocal origin. For example, the stage of lung cancer would differ if a patient harbors a GGN with solid portion of 1.5 cm in the right upper lobe and another GGN of 0.8 cm solid portion in the left upper lobe. If the two GGNs occurred independently, the T stages would be T1b and T1a, respectively, and overall stages would be IA2 and IA1, respectively. However, they would be staged as M1a and IVA if the two GGNs were intrapulmonary metastases.

Two major mechanisms have been proposed by which histologically similar multifocal tumors arise: (I) a single clonal event resulting in a tumor that subsequently spreads within one or both lungs (aerogenous intrapulmonary metastasis) and (II) multiple tumors arising independently in a carcinogen-damaged field (field cancerization, multiclonality) (2).

Traditionally, the determination of multiple tumors or metastases was followed by the Martini and Melamed criteria (3). They defined multiple tumors as either (I) tumors showed different pathologies, or (II) those that showed the same pathologies when the following criteria were met: the origin was from a carcinoma *in situ*, with no lymph node involvement in the common lymphatic pathways, and no extra-thoracic metastasis.

According to Martini and Melamed's criteria, multiple GGNs would be multifocal in origin. However, whether these criteria are still valid in cases of multiple GGNs remains unclear.

Most GGNs are atypical adenomatous hyperplasia, adenocarcinoma in situ, or pathological adenocarcinoma, and arise from the alveolar membrane with no lymph node involvement and no extra-thoracic metastasis. This issue has been investigated extensively with modern technology, such as genetic analysis. Most GGNs are basically adenocarcinomas, even though there are minor differences in subtype, and numerous genetic alterations have been proven to be involved in the carcinogenesis of adenocarcinoma. Therefore, the status of genetic alterations of GGNs could be a marker of clonality (4).

My group has already investigated alterations in epidermal growth factor receptor (EGFR) and *K-ras* in multiple GGNs among 24 patients, and found that a high frequency of discordant EGFR mutations (17 of 24, 70.8%)

Table 1 Summary of selected papers on clonality of multifocal GGNs or lung nodules

Author (ref)	Total number of GGNs (or nodules)/total patients	Target gene	Methods of analysis	Result (% of multiclonality)
Chung *et al.* 2009 (5)	56/24	*EGFR, K-ras*	Direct sequencing	17/24 (70.8%) multiclonality
Takamochi *et al.* 2012 (6)	82/36	*EGFR, K-ras*	Peptide nucleic acid clamping-PCR	30/36 (83%) multiclonality
Wu *et al.* 2015 (7)	60/35	*EGFR, K-ras, BRAF, PIK3A, ALK, ROS1, RET*	Sequencing (ADX mutation detection kit)	80% multiclonality
Liu *et al.* 2016 (8)	15/6	*Multiple*	WGS/WES	100% multiclonality
Liu *et al.* 2016 (9)	159/78	*EGFR*	Real time PCR-sequencing	35/38 (92.1%) multiclonality
Saab *et al.* 2017 (10)	52/18	*EGFR, K-ras, MET, TP53, BRAF, PIK3A, ALK* etc.	Targeted NGS/ALK FISH	10/11 multiclonality (synchronous)
Li *et al.* 2018 (11)	14/2	Multiple	WES	12/14 multiclonality 2/14 intrapulmonary metastasis

WGS, whole-genome sequencing; WES, whole-exome sequencing; NGS, next-generation sequencing.

could discriminate different tumor clonalities (18 of 24, 75%) of multiple lung neoplastic nodules presenting as GGNs (5). Many reports have supported the theory of multiple clonalities of multiple GGNs and are summarized in *Table 1*.

Therefore, the theory of different clonalities of multiple GGNs in patients was generally accepted.

Recent modifications of T staging of multiple GGNs in the 8th tumor-node-metastasis (TNM) classification of the International Association for the Study of Lung Cancer (IASLC) were also based on multiclonality rather than intrapulmonary metastasis. It proposed that T staging of multifocal GGNs was determined by high T lesions, with either the number of tumors or *m* in parentheses to denote the multifocal nature (12). According to multifocal origin, surgery for dominant GGNs by lobectomy or, more preferably, limited resection is recommended and then close follow-up of remaining GGNs is warranted (13).

However, there may be a possibility of intrapulmonary metastasis of small multifocal GGNs.

When we examined the pathological specimens of resected GGNs, small tumor nests in alveolar sacs or in bronchial lumen were frequently observed. This finding strongly suggests the potential of intrabronchial spread of GGNs. Kadota *et al.* (14) reported that tumors spread through air space (STAS), which were defined as tumor cells—micropapillary structures, solid nests, or single cells—spreading within air spaces in the lung parenchyma beyond the edge of the main tumor, was a significant risk factor of recurrence in small lung adenocarcinomas treated with limited resection. This finding could be clinical evidence of early metastasis of small GGNs.

Recent introduction of next-generation sequencing (NGS) enables us to complete analysis of tumor clonality easily by measuring whole-genome, exome, or target gene sequences (8,10).

Li *et al.* (11) analyzed the clonalities of multiple GGNs with matched blood samples in two patients using exome sequencing and found that two GGNs in each patient shared multiple nonsynonymous and synonymous mutations, which strongly suggested intrapulmonary metastasis, and remaining GGNs showed different clonalities. This finding has great impact on the management of multiple GGNs. I believe that the strategy of resection of dominant GGNs and close follow-up of remaining nodules would be optimal; however, complete analysis of genetic mutations using NGS would be necessary for the management of patients in the future. From these reports, it is reasonable to conclude that multiple GGNs are multifocal in origin, however, small portion of GGN might be the result of intrapulmonary metastasis.

The cause of GGNs may be a major issue that remains unresolved. Smoking—a major cause of lung cancer—may not be a causative factor in GGNs as most patients are non-smokers. There are several differences between lung cancer with GGNs and typical lung cancer. GGN is not associated with smoking, unlike smoking-related lung cancer. GGNs occur at a relatively young age and show a very indolent

course. Moreover, they develop in the peripheral portion of the lungs and many of them have a multifocal origin (15). A previous study suggested that genetic susceptibility, household air pollution attributed to solid fuel burning for heating and cooking, and cooking fumes as causative agents in China (16); however, there is no clear evidence to support this hypothesis.

Field cancerization theory could be applied to GGNs because of their multiplicity in air space. Personally, I think inhaled environmental carcinogens could be a cause of GGN-type lung cancer and am eagerly awaiting the next research that elucidates the issue. Understanding the etiology of GGNs is very important for the prevention of GGNs and development of novel management strategies.

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Footnote

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

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