Does Pulmonary Resection Promote the Progression of Unresected Ground-glass Nodules?

KAZUHIRO UEDA[1], FUMIHO SANO[1], JUNICHI MURAKAMI[1], MASATARO HAYASHI[1], TAIGA KOBAYASHI[2], YOSHIE KUNIHIRO[2] and KIMIKAZU HAMANO[1]

[1]*Department of Surgery and Clinical Science, Division of Chest Surgery, and*
[2]*Department of Radiopathology and Science, Division of Radiology,*
Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan

Abstract. *Background: The routine use of thin-section, whole-lung computed tomographic scanning helps detect persistent ground-glass nodules (GGNs) co-existing with the target lesion in the underlying lung. Patients and Methods: The cases of 10 patients with persistent co-existing GGNs detected on whole-lung computed tomography performed prior to surgery for lung cancer were retrospectively reviewed. The co-existing lesions were not resected at the initial procedure. Results: Although no masses exhibited progression during the 15.5-month preoperative follow-up period, all lesions displayed enlargement during the first year after the initial procedure, with the exception of one tumor. Three lesions arose in the ipsilateral lung, while the remaining lesions arose in the contralateral lung. The nine enlarged lesions were diagnosed as adenocarcinoma on subsequent resection. Conclusion: Lung adenocarcinoma with persistent GGNs tends to progress after lung resection for other lesions. This phenomenon should be kept in mind when selecting for surgical procedure in patients with persistent co-existing GGNs.*

With the increasing availability of whole-lung computed tomographic (CT) scanning for the purpose of screening for various respiratory diseases, lung tumors possessing ground-glass opacity (ground-glass nodule: GGN) are frequently detected. According to a statement for the management of GGNs presented by the Japanese Society of CT Screening, GGNs can simply be monitored unless the lesion increases in size or exhibits internal attenuation, regardless of the presence of features suggestive of adenocarcinoma *in situ* (1). Many investigators have reported the results of long-term observations of cases of GGNs (2-9), and several factors associated with an early increase in size or internal attenuation in GGNs have been identified, including an initial size >10 mm, history of smoking or malignant disease, and specific radiological features (2-9). Therefore, non-increasing GGNs, particularly those associated with such risk factors, should be carefully followed-up on CT, so as not to miss the appropriate timing for radical treatment. However, in cases in which a non-increasing GGN co-exists with another pulmonary nodule that must be resected, the management of the co-existing GGN remains controversial. Simultaneous resection of the GGN is occasionally feasible, especially if the GGN arises in the ipsilateral lung, although this procedure may result in additional loss of pulmonary function. In contrast, if the GGN is not simultaneously resected, it may undergo various pathogenic processes, such as by cytokine efflux (10), immunological suppression (11, 12) and tumor neovascularization *via* marrow-derived progenitor cell mobilization (13). Moreover, according to some experimental studies, the portion of the lung remaining after partial lung resection presents a tumor-friendly environment (14, 15), likely because growth factors are abundant in the remaining lung due to compensatory lung hypertrophy. In the present study, we retrospectively reviewed patients with co-existing non-increasing GGNs prior to lung cancer surgery that were not resected simultaneously during the operation in order to assess the effects of pulmonary resection on the progression of the co-existing GGN in the remaining lung.

Patients and Methods

Patients. This study was a retrospective analysis of a prospective database comprising 413 consecutive patients scheduled to undergo surgery with curative intent for diagnosed or suspected lung neoplasms between January 2006 and December 2012. Among these patients, 10 with coexisting non-increasing GGNs detected on whole-lung CT performed prior to surgery for the lung neoplasm

Correspondence to: K. Ueda, Department of Surgery and Clinical Science, Division of Chest Surgery, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan. Tel: +81 836222259, Fax: +81 836222423, e-mail: kaueda@c-able.ne.jp

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Table I. *Clinical outline of 10 patients.*

	Initial operation					Second operation for GGN							
Case	Gender	Age	Preop. f/u (months)	Affected lobe	Mode	Initial size (mm)	Final size (mm)	Time to progression (months)	Affected lobe	Mode	Histological type	Subtype	Prognosis (months*)
1	F	68	51	LU	Lobectomy	6	12	110	RU	Lobectomy	Ad	IA	Survival (88)
2	F	72	34	RM	Lobectomy	24	26	192	RU	Lobectomy	Ad	MIA	Survival (27)
3	F	82	17	RU	Lobectomy	14	16	189	LU	Segmentectomy	Ad	MIA	Survival (27)
4	M	64	3	LU	Segmentectomy	28	33	145	RL	Lobectomy	Ad	MIA	Survival (32)
5	F	63	3	RU	Lobectomy	14	20	350	LU	Segmentectomy	Ad	AIS	Survival (40)
6	F	67	21	RU	Lobectomy	12	12	-	LU	-	-	-	Survival (24)
7	F	65	10	LL	Partial resection	16	19	41	LL	Lobectomy	Ad	AIS	Survival (64)
8	M	64	2	RU	Lobectomy	14	17	210	LU	Segmentectomy	Ad	MIA	Survival (78)
9	M	76	14	RU	Lobectomy	14	20	135	LU	Segmentectomy	Ad	AIS	Survival (88)
10	F	72	67	LU	Lobectomy	10	20	150	RL	Segmentectomy	Ad	MIA	Survival (95)

GGN; Ground glass nodule, Preop. f/u ;length of preoperative follow up of GGN (months), RU; right upper, RM; right middle, LU; left upper, LL; left lower, Ad; adenocarcinoma, IA; invasive adenocarcinoma, MIA; minimally invasive adenocarcinoma, AIS; adenocarcinoma *in situ*, *months after the initial operation.

were retrospectively reviewed. In our database, we generally record the presence or absence of coexisting GGNs measuring 10 mm or more in maximum diameter. The 10 coexisting lesions were diagnosed as being non-increasing based on preoperative serial CT, and exhibited features radiologically suggestive of adenocarcinoma *in situ* or minimally invasive adenocarcinoma; the lesions predominantly consisted of ground-glass opacity with or without a small solid component measuring less than 5 mm. The lesions were evaluated for the presence or absence of characteristic internal or marginal features, such as air bronchograms, a bubble-like appearance, a well-defined, lobulated or spiculated margin, and pleural tags or indentation. This study was approved by the Institutional Review Board of the Yamaguchi University School of Medicine. The patient characteristics are shown in Table I. The radiological characteristics of the GGNs are shown in Table II.

Surgery was performed *via* three-port access using a thoracoscopic approach. We generally selected lung lobectomy for patients with adenocarcinomas larger than 2 cm in diameter and optionally selected lung segmentectomy in patients with lesions smaller than 2 cm in diameter after obtaining informed consent if the tumor was located at least 2 cm from the intersegmental plane.

Chest CT scans were obtained periodically during the follow-up period. The interval between chest CT scans for routine follow-up was three months during the first postoperative year and then extended to six months until the fifth postoperative year.

CT scanning. Helical CT scans were obtained using four-detector (Somatom plus4 or Somatom volume zoom; Siemens Medical Solutions, Erlangen, Germany) and 64-detector (Somatom Definition or Sensation 64; Siemens) row CT scanners. For all patients, the scanning settings were 140 kVp and 160-250 effective mAs. The CT procedures were diverse due to the long observation period and retrospective nature of the study design. Contiguous 10- or 7-mm CT was performed of the chest. Additional 2-mm high-resolution CT collimated images were acquired using retrospective reconstruction of the raw data. All image data were reconstructed using a high spatial frequency algorithm. The CT scans were obtained at suspended end-inspiration effort in the supine position without intravenous contrast material.

All image data were interfaced directly to our picture archiving and communication system (PACS) (Shade-Quest; Yokogawa Medical Solutions, Tokyo, Japan), which displayed all image information on monitors (1,280×1,080 matrix, 8-bit viewable grayscale). The monitors were used to view both the lung (window width: 1,500 or 1,750 HU and window level: −600 or −700 HU) and mediastinal (window width: 250-400 HU and window level: 40-50 HU) window images.

Interpretation of the CT images. All images were reviewed on the PACS monitors. Each CT scan was assessed by observing the size and marginal and internal characteristics of the nodule. With regard to size, the longest diameter of the nodule was measured using electronic calipers on the monitor image on which the largest cross-sectional area of the nodule was depicted. The lung window settings were used for the diameter measurements. The marginal characteristics were classified as either well- or ill-defined. The presence or absence of lobulated or spiculated margins and pleural tags was also recorded as marginal characteristics. The presence or absence of air bronchograms and a bubble-like appearance was assessed as internal characteristics. A bubble-like appearance was defined as an area of round or branching air attenuation in a GGN (16). The emergence or enlargement of a solid lesion in a GGN on follow-up CT was also recorded. Solid lesions were defined as lesions with a soft tissue density that obscured the contour of the vessels with which they were in contrast. The nodule characteristics were generally assessed only on the CT scan obtained immediately prior to surgery.

After assessing the nodule characteristics on high-resolution CT, we evaluated changes in the size of each nodule from the initial evaluation to the final follow-up visit. The nodules were classified as ‘increasing’ or ‘non-increasing’ based on whether the longest nodule diameter changed by more than 2 mm. A value of 2 mm was

Table II. *Radiological features of the 10 ground glass nodules*.

Case	Radiological features						
	Air bronchogram	Bubble-like appearance	Well-defined margins	Lobulated margins	Spiculated margins	Pleural tags or indentation	Solid component
1	−	−	−	−	−	−	−
2	−	−	−	−	−	−	+
3	+	−	−	−	−	−	+
4	+	−	−	−	−	+	+
5	−	−	−	−	−	−	−
6	−	−	−	−	−	−	−
7	−	+	−	−	−	−	−
8	+	−	−	−	−	−	+
9	−	−	−	−	−	−	−
10	−	−	−	−	−	−	−

used as the criterion for the change in size based on the report of Revel *et al.,* who estimated that an increase of 1.73 mm in the measurement is the appropriate threshold for differentiating between visually stable and increased nodules (17). In order to prevent overestimation of the change in size induced by compensatory inflation of the remaining lung, we also evaluated the change in diameter based on the distance between the nodules and the surrounding bronchovascular structures. In addition, the nodules were classified as either 'increasing' or 'non-increasing' when an apparent visual change in the nodular area was detected due to a change in the shortest nodule diameter.

Results

The study participants comprised of three males and seven females, with a mean age of 69 years (Table I). Four patients had a history of smoking. The patients underwent lung lobectomy (n=8), left upper-division segmentectomy (n=1) or partial resection (n=1) for lung neoplasms (primary lung cancer in nine patients and a metastatic lung tumor in one patient). All patients had GGNs in the ipsilateral (n=2) or contralateral (n=8) lung that were not resected at the time of surgery due to lack of apparent size change during the preoperative follow-up period (median=15.5 months, range=2 to 67 months). The mean diameter of the GGNs at the time of detection was 15.2 mm (median=14 mm, range=6 to 28 mm).

According to high-resolution CT, four lesions were diagnosed as minimally-invasive adenocarcinoma (with a solid component of less than 5 mm in size), while the remaining six lesions were diagnosed as adenocarcinoma *in situ* (Figure 1). Some lesions presented air bronchograms (n=3), a bubble-like appearance (n=1) or pleural tags or indentation (n=1) (Table II). During the first year after the initial operation, nine GGNs increased in size and two GGNs increased in internal attenuation. The time to the increase in the size among the GGNs is shown in Figure 2. The size of the lesion remained unchanged in the remaining one case of GGN during the 24-month follow-up period after the initial operation. The nine increasing lesions were subsequently excised *via* either lobectomy (n=4) or segmentectomy (n=5) and were diagnosed as adenocarcinoma (*in situ* in three patients, minimally-invasive in five patients and invasive in one patient).

Neither lymph node metastasis nor lymphovascular or pleural invasion were found in any of the patients. Furthermore, no episodes of postoperative recurrence were detected during the follow-up period after the second operation (median=28 months). The mean size of the GGNs before the second procedure had increased to 19.5 mm (Figure 1).

Discussion

According to a statement for the management of GGNs presented by the Japanese Society of CT Screening, small GGNs can be followed-up without a definitive diagnosis if the lesions are radiologically-suggestive of minimally-invasive adenocarcinoma (a solid component measuring less than 5 mm in size), regardless of whether they are increasing (1). However, increasing GGNs are usually considered candidates for pulmonary resection, especially in patients with an adequate life expectancy, as such lesions may convert to invasive adenocarcinomas during subsequent follow-up. Nevertheless, the management of non-increasing GGNs remains controversial in cases in which the lesions coexist with other lung lesions that must be resected. In the present study, we assessed 10 patients diagnosed with non-increasing GGNs prior to undergoing surgery for other lung lesions. Interestingly, nine out of the 10 lesions exhibited enlargement during the first postoperative year, seven of which were located in the contralateral lung. Subsequent surgery revealed

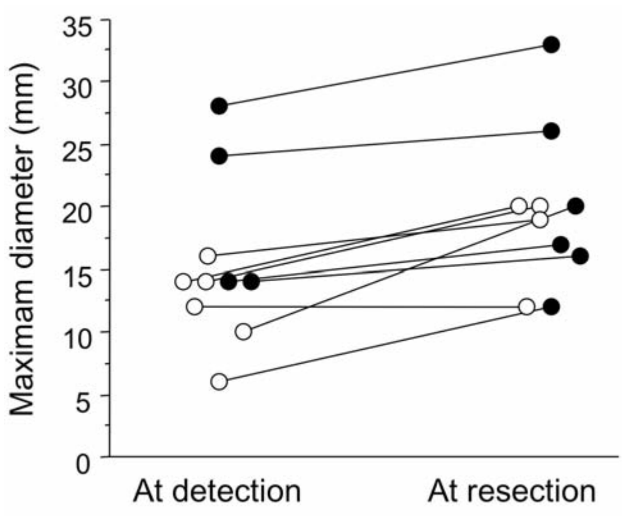

Figure 1. *Maximum diameter of the ground-glass nodules in each patient at detection and resection. Nine out of the 10 ground-glass nodules increased in size or internal attenuation after the initial lung resection procedure for cancer. Open circle: pure ground-glass nodule (suggestive of adenocarcinoma in situ), Solid circle: ground-glass nodule with a solid component (suggestive of minimally invasive adenocarcinoma).*

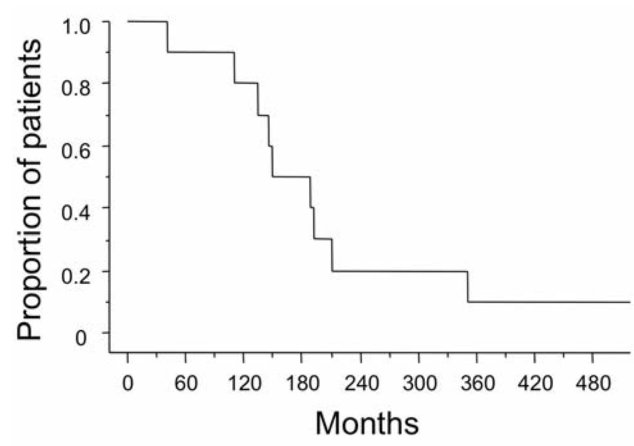

Figure 2. *Time to the increase in size or internal attenuation in the ground-glass nodules after the initial operation. Nine out of the 10 nodules increased in size during the first year after the initial operation.*

all nine lesions to be adenocarcinomas. Therefore, physicians must be aware that pulmonary resection may promote enlargement of remaining co-existing GGNs.

With respect to the natural history of GGNs, larger lesions (tumor diameter larger than 10 mm) are associated with risk of progression (4, 6, 8, 9, 18). Additionally, lesions exhibiting greater CT attenuation (2) or various specific structural features (5, 8, 10) are recognized as carrying a risk of progression. GGNs in patients with a history of cancer are also likely to progress during follow-up (2, 6, 7). Kim *et al.* reported characteristic differences between solitary and multiple GGNs (5), documenting that invasive lesions were predominantly found in cases of solitary lesions, while pre-invasive lesions were predominantly found in patients with multiple lesions. Among the present patients, eight out of the nine with enlarged GGNs had synchronous primary lung adenocarcinoma, while the remaining patient had synchronous metastatic lung cancer. In addition, 9 out of the 10 lesions exhibited a tumor diameter greater than 10 mm, 4 lesions presented mixed GGN features and 4 patients had a history of smoking. Therefore, the majority of our patients had risk factors for tumor progression. However, considering that the lesions began to enlarge during the first postoperative year, surgical lung resection can be considered an additional risk factor for GGN progression.

Many investigators, including ourselves, have demonstrated the potential contribution of surgical intervention to recurrence or metastatic progression in experimental models. For instance, we reported that surgical tumor resection results in a reduction in the level of angiostatin, an endogenous angiogenesis inhibitor, thereby promoting the progression of micrometastasis (19). We also found that surgical injury accelerates tumor growth by inducing the mobilization and recruitment of bone marrow-derived stem cells (13). Meanwhile, Goldfarb *et al.* reported that postoperative preservation of the immune status contributes to suppression of tumor growth (12). In addition, various growth factors produced during recovery from surgical injury promote the development of recurrence (10). Interestingly, Brown *et al.* reported that the progression of pulmonary micrometastases was enhanced by pulmonary resection in a mouse model (15). Although the exact mechanisms remain unclear, the residual lung that grows after lung resection may function as a tumor-friendly microenvironment.

The growth of the remaining lung after major lung resection in rodents reflects compensatory lung growth accompanied by the multiplication of alveolar units, leading to gains in the remaining lung weight and volume (20). Such compensatory responses are also found in large mammals with prominent proliferation of type II pneumocytes, although it remains controversial whether alveolar septal tissues increase (20). We reported that major lung resection results in a net increase in lung volume of normal attenuation on CT, which represents the functional lung volume (21). This gain in functional lung volume is accompanied by a proportionate gain in ventilatory capacity. Because the pulmonary function continues to improve during the first postoperative year (22), we believe that compensatory lung responses are completed by the corresponding term. Considering that the GGNs observed in our patients began to increase in size during the first postoperative year, the enlargement of such lesions may be triggered by compensatory lung responses.

Kim *et al*. reported the natural history of 139 GGNs identified after major lung resection for cancer (18). During the follow-up period (mean=44.4 months), only 23 (17%) out of 139 GGNs increased in size, which appear to be inconsistent with our results. However, the present study is unique in that we generally evaluated GGNs of more than 10 mm in size and the GGNs were identified as being persistent prior to the initial operation. In contrast, according to Kim *et al*.'s report, only 35 (25%) out of the 139 GGNs had a nodular size of more than 10 mm and the lesions were identified after lung cancer surgery. Therefore, their results do not reflect the influence of lung cancer surgery on the progression of co-existing GGNs.

One limitation of the present study is that the length of the preoperative follow-up period was not long enough for some patients, which may have complicated the ability to distinguish increasing GGNs from non-increasing GGNs. An additional limitation is that the postoperative anatomical rearrangement of the remaining lung may have compromised the capacity to obtain accurate measurements of the size of the GGNs, particularly in two patients with GGNs in the ipsilateral lung (cases 2 and 7). However, we believe that the changes in size were significant because we carefully measured the size both quantitatively and qualitatively in reference to the surrounding bronchovascular structures. In addition, it should be noted that GGNs do not expand in accordance with the expansion of the remaining lung after major lung resection.

Conclusion

Lung adenocarcinoma associated with persistent GGNs measuring more than 10 mm in maximum diameter is likely to progress after lung resection for other lesions. This phenomenon should be kept in mind when selecting the surgical procedure in patients with persistent coexisting GGNs.

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