Efficacy of thoracoscopic resection for multifocal bronchioloalveolar carcinoma showing pure ground-glass opacities of 20 mm or less in diameter

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Objective: Small bronchioloalveolar carcinoma showing pure ground-glass opacity on high-resolution computed tomographic scans is commonly multifocal. Surgical treatment for these lesions is controversial. We discuss the efficacy of video-assisted thoracic surgery for multifocal bronchioloalveolar carcinoma in patients at our institution.

Methods: Twenty-seven patients with multifocal bronchioloalveolar carcinoma lesions less than or equal to 20 mm in diameter (105 lesions) underwent video-assisted thoracic surgery pulmonary resection between 2000 and 2006. Their clinicopathologic features were investigated retrospectively.

Results: Twenty-seven patients (10 male and 17 female) with a median age of 64 years (range, 41–78 years) had 91 ground-glass opacity lesions on high-resolution computed tomography. Sixteen patients (59%) were women with no history of smoking. The distribution of bronchioloalveolar carcinoma lesions was unilateral in 14 patients and bilateral in 13 patients. Ten patients underwent wedge resection. Seventeen patients underwent single-stage segmentectomy or lobectomy (alone or with wedge resection) for technical reasons. All lesions were completely resected. One patient underwent conversion to thoracotomy for bleeding. Histologic diagnoses showed 62 bronchioloalveolar carcinoma type A lesions, 28 type B lesions, and 15 type C lesions according to Noguchi's classification, and atypical adenomatous hyperplasia in 43 lesions (13 patients). All patients had N0 disease. The median postoperative observation period was 46 months. All patients have survived to date, but new lesions have developed in 7 (26%). Patients with new lesions had a higher incidence of bronchioloalveolar carcinoma lesions of 3 mm or less in diameter ($P = .0254$) and atypical adenomatous hyperplasia ($P = .011$).

Conclusion: Video-assisted thoracic surgery management of multifocal bronchioloalveolar carcinoma yielded satisfactory results. However, the appearance of new lesions remains a problem.

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Bronchioloalveolar carcinoma (BAC) is a subtype of adenocarcinoma and has a broad spectrum of radiographic and pathologic appearances.¹⁻³ As the result of recent advances in diagnostic imaging modalities, the detection rate of multifocal BAC showing pure ground-glass opacities (GGOs) on high-resolution computed tomographic (HRCT) scanning has increased. In the recently revised histologic classification of lung and pleural tumors,⁴ nonmucinous BAC was clearly defined as a form of adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular, or pleural invasion. The present article discusses the efficacy of limited surgical resection of focal BAC.⁵⁻¹¹ The optimal management of multifocal early-stage BAC has not been clearly determined. In many cases the focal BAC of 20 mm or less in diameter showing pure GGO is not invasive. Therapeutic guidelines, such as the optimal duration of observation and

Abbreviations and Acronyms

AAH	= atypical adenomatous hyperplasia
BAC	= bronchioloalveolar carcinoma
CT	= computed tomography
GGO	= ground-glass opacity
HRCT	= high-resolution computed tomography
VATS	= video-assisted thoracic surgery

optimal treatment strategy, have not yet been established. We have been surgically treating selected patients with multifocal BAC with video-assisted thoracic surgery (VATS) in our department. In this retrospective study, we focused on resected multifocal early-stage BAC and studied the correlation between pathologic features and radiographic appearances, the prognosis, and the problems.

Materials and Methods

This study was approved by the Toranomon Hospital Institutional Review Board of Clinical Research. Informed consent from patients was waived because of the retrospective study design.

From January 2000 to December 2006, 939 patients underwent surgery for primary lung cancer in our department. Retrospective examination of their records indicated that in 27 patients, preoperative computed tomography (CT) had revealed the presence of multifocal GGO lesions. Patients with multiple lesions that were all classified as BAC type A or B because of their pure GGO appearance on HRCT were observed for at least 6 months, and VATS resection was planned if the size or density of the lesions increased or did not change. Single-stage surgical treatment was undertaken in 26 patients with performance status 0-1 and a predicted postoperative forced expiratory volume in 1 second of more than 800 mL who consented to single-stage surgery. Two-stage surgical treatment was undertaken in 1 patient at her request. The site of the cancer, preoperative respiratory complications, and estimated postoperative respiratory function were taken into consideration when determining the best surgical procedure for each individual patient. Wedge resection with VATS was selected as the primary therapy for cases with BAC type A or B according to Noguchi's classification.¹² In cases with multiple GGO lesions confined to a single lobe or a GGO lesion located deep in the hilum, VATS segmentectomy or VATS lobectomy was performed for technical reasons. In cases involving wedge resection, all resected specimens underwent intraoperative frozen-section examination. If frozen-section results indicated a positive staple line margin, reexcision was performed. If frozen-section results indicated BAC type C with active fibroblastic proliferation, conversion to VATS lobectomy was undertaken.

Lesions visualized mainly as GGOs that were less than 20 mm in diameter and deep in the lungs (>20 mm from the pulmonary surface) were marked under CT guidance the day before the operation, using VATS markers with a hook wire, because intraoperative palpation under thoracoscopic observation would be difficult.

TABLE 1. Characteristics of 27 patients with multifocal bronchioloalveolar carcinoma

Characteristics	Years	n
Age range (mean)	41–78 (64.3)	27
Male		10
Female		17
Symptoms		
Yes		0
No		27
Detection of GGO		
CT mass-screening		18
Incidental		9
Smoking history		
No. (female)		18 (16)
Current or ex-smoker		9
History of malignant disease		
No		19
Yes		8 (1)*
No. of GGOs on HRCT (total 91)		(colon 3, thyroid 3, uterus 1, kidney 1, prostate 1)
1		2
2		10
3		9
5		1
6		1
>7		4

BAC, Bronchioloalveolar carcinoma; GGO, ground-glass opacity; HRCT, high-resolution computed tomography; CT, computed tomography. *History of malignancy at 2 sites (thyroid and uterus)

VATS Procedures

All procedures were performed using 3 access ports (7, 10, and 11.5 mm in diameter) without minithoracotomy. VATS wedge resection was performed using an endo-stapler or resection and suturing techniques. In lobectomy and segmentectomy, the endo-stapler was used to staple the hilar bronchus and vessels after dissection. One of the 3 wounds was extended by 20 to 40 mm to remove the specimens. A metal chest retractor was not used in this incision; instead a 25-mm diameter silicon rubber instrument (Lap Protector Minimini, Hakko, Tokyo, Japan) was applied to maintain the wound and provide access for an extra instrument for mediastinal lymph node sampling.

Follow-up information was obtained from 6-month follow-up visits and CT scans. The cumulative survivals were calculated using the Kaplan–Meier method.

Results

Of the 939 patients with primary non-small cell lung cancer who underwent pathologically complete resection during

TABLE 2. Surgical procedures (video-assisted thoracic surgery) and operative findings in 27 cases

Surgical procedure	Unilateral	Bilateral	Total
	14	13	n = 27
Wedge resections (2-stage)	6 (0)	4 (1)	10
Segmentectomy (plus wedge resection)	3 (2)	0	3
Lobectomy	5	9	14
Simple lobectomy	3		
Plus ipsilateral wedge resection	2		
Plus contralateral wedge resection		8	
Bilobectomy		1	
Lymph node dissection			
Hilar node/mediastinal sampling			6/11
Converted to thoracotomy			1*
Reason for segmentectomy or lobectomy			17
BAC type C			9
Multifocal lesions in a lobe			6
Deep in parenchyma			2
CT-guided markers	22 (10 patients)	14 (12 patients)	36 (22 patients)

VATS, Video-assisted thoracic surgery; BAC, bronchioloalveolar carcinoma; CT, computed tomography. *VATS segmentectomy converted thoracotomy.

the study period, 104 patients (11%) were diagnosed with BAC 20 mm or less in diameter on examination of the frozen section, and 27 (26%) of those 104 had multifocal BAC. The characteristics of patients with multifocal BAC are listed in Table 1. There were 10 men and 17 women with a median age of 64 years (range, 41–78 years). Sixteen patients (59%) were women with no history of smoking. All patients were asymptomatic with multifocal GGOs detected on helical CT during screening for lung cancer or investigation of other conditions. The number of lung tumors per patient ranged from 1 to 8 (mean 3.4), including those visualized as almost pure GGOs on HRCT.

Surgical Procedures

The surgical procedures are shown in Table 2. All procedures were performed using VATS. Preoperative percutaneous CT-guided marking using a hook wire was performed for 36 GGOs in 22 patients (78%). There were no serious complications from the marking procedures. Single-stage surgical resection was performed in 26 patients, and 2-stage bilateral wedge resection was performed in 1 patient at her request. Wedge resections were performed in 10 patients (unilateral 6, bilateral 4) in whom intraoperative frozen section showed that the surgical margins were free of BAC type A or B. Three patients underwent segmentectomy (2 with wedge resection) for a deep pulmonary lesion (2 patients) or BAC type C on intraoperative frozen section (1 patient). Fourteen patients underwent lobectomy (simple lobectomy, 3 patients; with wedge resection, 10 patients; bilobectomy, 1 patient) for multiple lesions in a lobe (7 patients) or BAC type C (7 patients). One patient underwent conversion from segmentectomy using VATS to thoracotomy for bleeding. In 11 of 14 patients who underwent

lobectomy, mediastinal lymph node sampling was performed without lymph node dissection (ND1/sampling = 3/11).

Pathologic Examination

Ninety-one GGO lesions less than or equal to 20 mm in diameter were detected on preoperative HRCT. Postoperative histopathologic examination diagnosed 105 BAC lesions and 43 atypical adenomatous hyperplasia (AAH) lesions. The final histopathologic diagnoses of the 105 BAC lesions in 27 patients are presented in Table 3. The final diagnosis was BAC type A in 62 lesions, type B in 28 lesions, and type C in 15 lesions. Thirteen patients with multifocal BAC lesions had 2 primary cancers, 7 patients had 3 primary cancers, 1 patient had 4 primary cancers, 2 patients had 7 primary cancers, 1 patient had 8 primary cancers, 2 patients had 10 primary cancers, and 1 patient had 12 primary lung cancers. No lymph node metastases were detected in any patients who underwent

TABLE 3. Relationships between size and pathology (105 bronchioloalveolar carcinoma lesions and 43 atypical adenomatous hyperplasia lesions)

Pathology	Size		Total
	<10 mm	10–20 mm	
LBAC type A	58	4	62
LBAC type B	17	11	28
LBAC type C	2	13	15
AAH	43	0	43

BAC, Bronchioloalveolar carcinoma; LBAC, localized bronchioloalveolar carcinoma; AAH, atypical adenomatous hyperplasia.

TABLE 4. Mismatches between pathologic diagnosis and radiologic lesions and relationship with postoperative new lesions

No.	Operation	BAC (right/left)	BAC size (mm) (right/left)	Radiologic lesions ≤ 20 mm*	Pathologic BACs ≤ 20 mm†	*†	AAH (n)	Postoperative new lesions	DFI (mo)
1	Unilateral	A1, B1	5, 8	3	2	↓	1	None	
2	Unilateral	A1, B1	10, 17	3	2	↓	1	2	12
3	Unilateral	A3	3, 5, 6	2	3	↑	4	1	20
4	Unilateral	A4	4, 5, 6, 7	3	4	↑	2	None	
5	Unilateral	A1, B1	8, 8	1	2	↑	0	None	
6	Unilateral	A2	1, 4	1	2	↑	0	None	
7	Unilateral	A1, B1	4, 6	2	2		0	1	7
8	Bilateral	A1/C1	6/10	3	2	↓	1	None	
9	Bilateral	A2/B1	4, 5/8	7	3	↓	5	Multiple	30
10	Bilateral	A2, B3/A1, C2	4, 5, 6, 7/4, 4, 12, 20	6	8	↑	1	None	
11	Bilateral	A5, B3/A1, B1	1, 3, 4, 4, 5, 3, 4, 20/6, 6	9	10	↑	10	3	9
12	Bilateral	B1/A3, B2, C1	10/3, 4, 5, 8, 10, 18	5	7	↑	2	None	
13	Bilateral	A1/A11	12/1-16	2	12	↑	12	None	
14	Bilateral	A3, B1, C1/A2, B2, C1	1, 1, 18, 6, 9/7, 4, 5, 9, 6	8	10	↑	1	1	23
15	Bilateral	A4, B1/A1, B1	3, 3, 6, 11, 3/3, 6	7	7		0	1	6

BAC, Bronchioloalveolar carcinoma; AAH, atypical adenomatous hyperplasia, DFI, disease-free interval. *The number of preoperative ground-glass opacity lesions ≤ 20 mm on high-resolution computed tomographic scanning. †The number of BAC lesions ≤ 20 mm diagnosed histologically.

segmentectomy or lobectomy. The most advanced lesion in any of the 27 patients was classified as stage IA. Thirteen of 27 patients (48%) had 43 AAHs (range, 1–12). Six of seven patients (86%) with more than 4 BAC lesions had AAH.

Relationships Between Computed Tomographic Findings and Pathologic Diagnoses

The relationship between preoperative radiologic findings and final pathologic diagnoses is shown in Table 4. Thirteen patients had a different number of BAC lesions on pathologic examination from the number of GGO lesions seen on HRCT. Eleven of these 13 patients (85%) had AAH. Almost all pure GGOs measuring less than 10 mm in diameter were diagnosed as BAC type A or B. Two lesions less than 10 mm in diameter were diagnosed as BAC type C, but retrospectively the HRCT of these patients showed mixed GGO lesions with an 85% GGO component. The number of BAC lesions was less than the number of GGO lesions on HRCT in 4 patients with AAH and was more than the number of GGO lesions on HRCT in 9 patients.

Postoperative Course

Delayed pulmonary fistulas persisting for 5 or more days were found in 4 patients. There were no other serious complications, and all patients were able to walk without assistance on the day after the operation. The mean length of postoperative hospitalization was 7.3 days (range, 4–18 days).

Outcomes

The median postoperative follow-up period was 46 months (range, 3–81 months). At the time of writing, all patients are still alive. However, de novo lesions developed in 7 of 27 patients (26%) (disease-free interval, 6–30 months). The 5-year disease-free survivals of patients with multifocal BAC was 70.3%, with no difference in outcome between the surgical treatments (reduction surgery, wedge resection, or segmentectomy 75%, lobectomy 65.3%; $P = .611$). The new lesions that developed after resection were visualized as small pure GGOs (range, 1 to multiple) and were not invasive in any of the cases. Patients with new lesions had a higher incidence of BAC lesions of 3 mm or less in diameter ($P = .0254$) and AAH ($P = .011$). Chemotherapy was not administered to these patients, at their request. The patients are still being followed up by CT scan every 6 months. Further therapeutic planning will occur if there is any suggestion of invasion on HRCT, such as increased internal density.

Discussion

Recent advances in diagnostic radiographic techniques and the introduction of helical CT have increased the detection rate of early-stage lung cancer. The correlation between GGO on CT and pathologic findings has been studied.¹³ The replacing growth of adenocarcinoma cells along the alveolar wall is reflected as a GGO appearance with patent alveolar spaces and small airways on HRCT. A solid lesion on CT represents the collapse of the alveoli, subsequent formation of a fibrotic focus, and proliferation of tumor cells.¹⁴ Even

small tumors have the potential for mediastinal lymph node metastasis, and lobectomy with systematic lymph node dissection is considered standard therapy for many cases of non-small cell lung cancer. Noguchi and colleagues¹² classified surgically resected peripheral type adenocarcinomas of 20 mm or less in diameter into 6 groups (types A to F) according to their clinicopathologic characteristics. Type A (localized BAC) and type B (localized BAC with foci of alveolar structural collapse) showed a 100% 5-year survival after lobectomy with systematic nodal dissection and no lymph node metastases. The present article discusses the efficacy of limited surgical resection (wedge resection or segmentectomy) of early-stage BAC presenting as small pure GGO on HRCT.⁵⁻¹¹

Barsky and colleagues¹⁵ published their genetic research of BAC using a novel strategy for clonality determination. They determined that these tumors were mostly multifocal independent cancers, and that lung-sparing operations (wedge resections) should therefore be performed. In some reports, 18% to 20% of BAC were multifocal. However, the most suitable timing and method of surgical resection for multifocal BAC is still controversial. There are as yet no therapeutic guidelines. At our institution, we made decisions about the timing and method of surgical treatment according to the HRCT images and the results of intraoperative frozen-section pathologic examination. Staged resection may cause considerable physical stress and also risks cancer progression. We therefore recommend single-stage, aggressive, curative pulmonary resection using VATS in all cases with helical CT images indicating multifocal BAC. Performance status, pulmonary reserve, and patient consent for single-stage surgery should be taken into consideration. VATS gives a wide view of intrathoracic structures and is minimally invasive. However, one of the disadvantages is that tumors, especially those visualized as pure GGOs, cannot be directly manipulated, necessitating preoperative CT-guided marking. If no pneumothorax occurred, marking was performed multiple times in the same patient if needed, including for bilateral lesions.¹⁶ Each site was marked according to the location of the lesion. When wedge resection was planned, the marker was set on the opposite side of lesions near the interlobular region and at the base of lesions in other regions, so that all lesions would be included if the resection was performed up to the level of the markers. For segmental resection of a small deep lesion using VATS, the staple line placement depended on tumor location. The CT-guided marking was a reliable surgical guide for placement of the staple line for parenchymal division. The staple line could be placed beyond the anatomic border of the diseased segment, enabling VATS tumor resection with a safe surgical margin.

In 13 patients, there was a difference between the number of preoperative GGO lesions on HRCT and the number

of BAC lesions diagnosed histologically. This may be the result of limitations of CT resolution and the presence of AAH. It has been suggested that AAH is the adenoma in an adenoma-carcinoma sequence in the lung periphery. Chapman and Kerr¹⁷ reported that AAH was found in 23.4% of lungs with adenocarcinoma, and that a greater percentage of women (30%) than men (18.8%) with adenocarcinoma had AAH. In our series of 27 patients who underwent operations for multifocal pure GGO lesions, 13 (48%) had an AAH lesion on histopathologic examination. AAH was classified as a preinvasive lesion of adenocarcinoma by the World Health Organization in 1998,¹⁸ because many investigators had provided evidence of a sequence from AAH to adenocarcinoma, especially BAC.¹⁹ It seems to be difficult to discriminate AAH from noninvasive BAC preoperatively, because of the similar appearances of the focal, round GGO lesions without a solid component on HRCT. The most advanced lung cancer lesion in all our 27 patients was class IA. All of the patients are still alive, but *de novo* lesions developed in 7 of 27 patients (26%). There are no previous data regarding the development of new BAC lesions after surgical resection of multifocal BAC. In our study, patients with new lesions after resection had a higher incidence of BAC lesions of 3 mm or less in diameter ($P = .0254$) and AAH ($P = .011$). Three patients with new lesions had a short disease-free interval (<10 months), which might be because the new lesions already existed at the time of operation even though they were not seen on preoperative CT. Five of the seven patients with new lesions were diagnosed with multifocal BAC with AAH. Our results support a sequence from AAH to BAC.

The new lesions developing after resection were seen as pure GGOs less than 10 mm in diameter. These lesions were not invasive in any of the cases, and the patients are still being followed up by CT scan every 6 months. The time taken for BAC to become invasive is still unknown. Further examination of the therapeutic strategy is necessary by accumulating a larger number of cases and comparing the recurrence rates and outcomes in the course observation group, chemotherapy only group, surgery only group, and surgery plus postoperative chemotherapy group. However, in our report, aggressive VATS pulmonary resection for the patients with pure GGOs more than 10 mm in diameter who were observed for at least 6 months may be accepted because half of these pure GGOs more than 10 mm in diameter were BAC type C.

Recently, the relationship between mutation of the epidermal growth factor receptor gene and the therapeutic efficacy of the selective inhibitor of epidermal growth factor receptor gene tyrosine kinase (ZD1839 or Iressa) in patients with multifocal BAC has been reported.²⁰ We propose to investigate this further in our department.

In our study, VATS management for multifocal BAC lesions was less invasive than other procedures and was feasible even for single-stage bilateral surgical resection. If we decide to perform further resection for new lesions that appear after the initial resection, the first operation should be performed with VATS because it is less invasive, particularly in relation to the effect on postoperative respiratory function, and causes fewer adhesions between the lung and the chest wall.

Conclusions

VATS pulmonary resection of multifocal BAC may be associated with a favorable outcome, even with bilateral lesions, in selected patients in whom complete resection is feasible. However, the size of the subject population and duration of follow-up were insufficient to properly determine the effectiveness of VATS management for these patients. Postoperative patients need careful follow-up because new lesions may develop. Therapeutic guidelines should be established for these new lesions.

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