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Surgical treatment of synchronous multiple lung adenocarcinomas: experiment of 171 cases

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Background: It is unclear how to treat synchronous multiple lung adenocarcinoma (SMLA) cases, which are increasing with the development of high-resolution computed tomography (HRCT).

Methods: Retrospective review of 171 cases of SMLA who underwent curative intent surgery between 2010 and 2018. Lung volume-preserving surgery, segmentectomy or wedge resection, is preferred for ground glass opacity nodules (GGN) within 2.0 cm. Clinical observation is allowed for pure GGN within 1.0 cm.

Results: The 5-year recurrence-free survival rate after surgery was 95.2%, and the overall survival rate was 93%. Prognosis was correlated with the degree of progression of the dominant tumor. Tumor number, surgical procedure and remnant tumor after surgery were not correlated with prognosis.

Conclusions: The prognosis of SMLA was relatively good, and was dependent on the stage and malignant potential of the dominant tumor. Limited resection and clinical observation for GGN are acceptable.

Keywords: Synchronous multiple lung adenocarcinoma (SMLA); limited surgery; clinical observation

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Introduction

Synchronous multiple lung adenocarcinoma (SMLA) cases are increasing with the development of high-resolution computed tomography (HRCT). In these cases, multiple ground glass opacity nodules (GGN) are detected in the peripheral lung, and are often diagnosed as adenocarcinomas with lepidic growth or atypical adenomatous hyperplasia (AAH). The prognoses are reported to be relatively good (1,2). In these cases, surgeons tend to choose lung-preserving surgery because of the multiple lesions in the peripheral lung, which are often bilateral. Limited resection for single GGN is reported to be acceptable in some non-randomized trials (3,4), and clinical trials are ongoing in Japan (5,6). The National Comprehensive Cancer Network (NCCN) guideline recommends clinical follow-up for pure GGN less than 2 cm (7).

In this study, the prognosis of SMLA after surgery was retrospectively reviewed, and optimal treatment was examined.

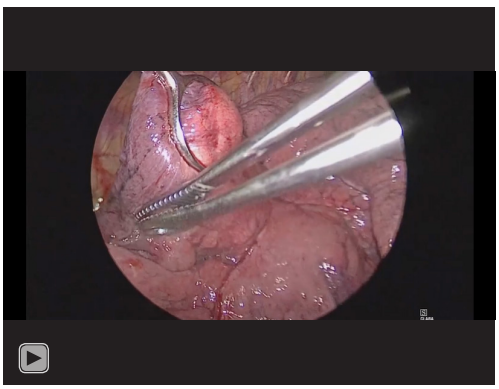
Methods

We included 171 patients with SMLA who underwent surgical resection between January 2010 and March 2018 in Kumamoto University Hospital. SMLAs were diagnosed clinically, at least two nodules were noted on HRCT, and the nodules were pathologically diagnosed as lung adenocarcinomas; pulmonary metastases were deniable based on CT images or pathological findings. Mucinous adenocarcinomas, which show a pneumonia-like shadow in the peripheral lung, were excluded from this study. Our policies of treatment for SMLA were as follows: (I) treatments for the most progressive nodules

Table 1 Most surgeries performed on SMLA cases

Variable	Surgical procedure	N
Bilateral	Lobectomy + lobectomy	5
	Bilobectomy + segmentectomy	1
	Lobectomy + segmentectomy	2
	Lobectomy + partial	8
	Segmentectomy + partial resection	3
Ipsilateral	Pneumonectomy	2
	Bilobectomy	4
	Lobectomy	100
	Segmentectomy	17
	Partial resection	29

SMLA, synchronous multiple lung adenocarcinoma.



Video 1 A representative case of surgery for SMLA (8). Rt. S3 segmentectomy for a part-solid nodule and rt. S6 wedge resection for a pure GGN were performed on a 71-year-old male patient. SMLA, synchronous multiple lung adenocarcinoma; GGN, ground glass opacity nodules.

were prioritized; (II) lung volume-preserving surgery, segmentectomy or wedge resection, was preferred for GGN (part solid nodules or pure GGN) within 2.0 cm; (III) pure GGN were resected by wedge resection, if possible. Lipiodol markings were performed for untouchable nodules; and (IV) clinical observation was allowed for pure GGN within 1.0 cm. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by ethical committee of Kumamoto University (No. 202, 402). Written informed consent was obtained from all patients.

Seventy-one patients were male, and 100 were female. Their median [range] age was 70 [39–87] years. Smoking histories were negative in 99 patients, and positive in 72. The numbers of nodules first found on HRCT were 2 in 86 patients, 3 in 32 patients, 4 in 35 patients and more than 4 in 18 patients. Pathological stages of the most progressive nodule were 0/IA1 in 101 cases (59.1%), IA2/IA3 in 49 cases (28.7%) and IB or above (IB in 11, IIA in 2, IIB in 5, IIIA in 2 and IIIB in 1) in 21 cases (12.3%). The most surgeries performed in each lung are shown in *Table 1*. Bilateral surgeries were performed in 19 patients. In 49 cases, limited resection (segmentectomy or wedge resection) was performed for the most progressive nodules. A representative case of surgery for SMLA is shown in *Video 1*. Right S3 segmentectomy for a part-solid nodule and rt. S6 wedge resection for a pure GGN nodule were performed. A pure GGN nodule in the left upper lobe was left unresected and observed clinically.

Statistical methodology

All statistical analyses were performed with the SPSS program for Windows (version 18 statistical software; Texas Instruments, IL, USA). Numerical data were compared with an independent sample *t*-test, and categorical data were compared with a Pearson chi-square test. Recurrence-free survival (RFS) and overall survival (OS) were calculated from the date of surgery and estimated using Kaplan-Meier analysis. Differences between curves were evaluated using log-rank tests. To evaluate whether a biomarker was an independent prognostic factor for survival, a multivariate, stage-stratified Cox proportional hazard model was constructed to compute a hazard ratio (HR) that was based on the clinicopathological parameters. All p values were two-sided, and differences with P values of less than 0.05 were considered significant.

Results

Kaplan-Meier curves for all patients are shown in *Figure 1*. The median follow-up period was 51.8 months. The 5-year RFS rate after surgery was 95.2%, and the OS rate was 93%.

Survival comparisons among pathological stages of the dominant tumor are shown in *Figure 2*. The 5-year RFS rate was 100% for stage 0/IA1 and 94.3% for stage IA2/IA3; these rates were significantly higher than for stage IB and above (83.0%: P<0.01). The 5-year OS rate was

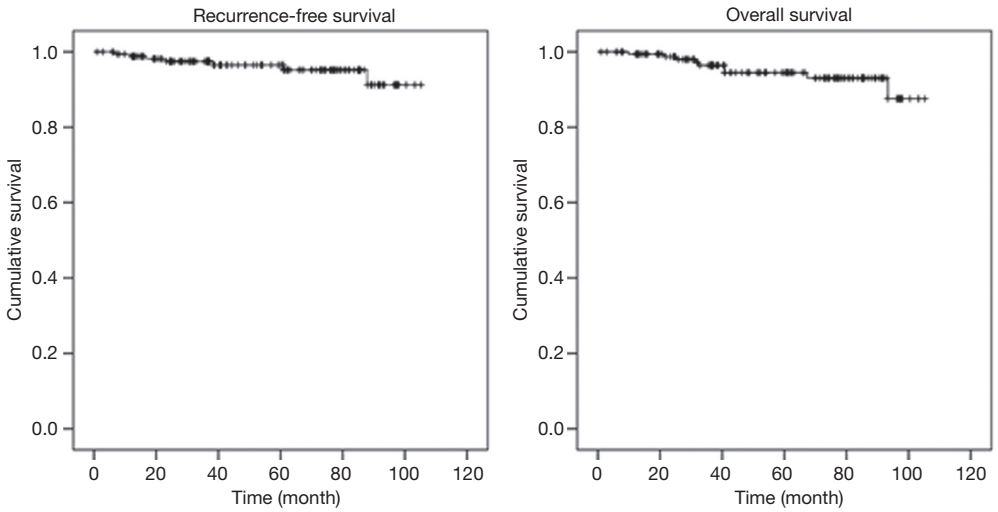


Figure 1 General survival curves of patients with SMLAs. SMLA, synchronous multiple lung adenocarcinoma.

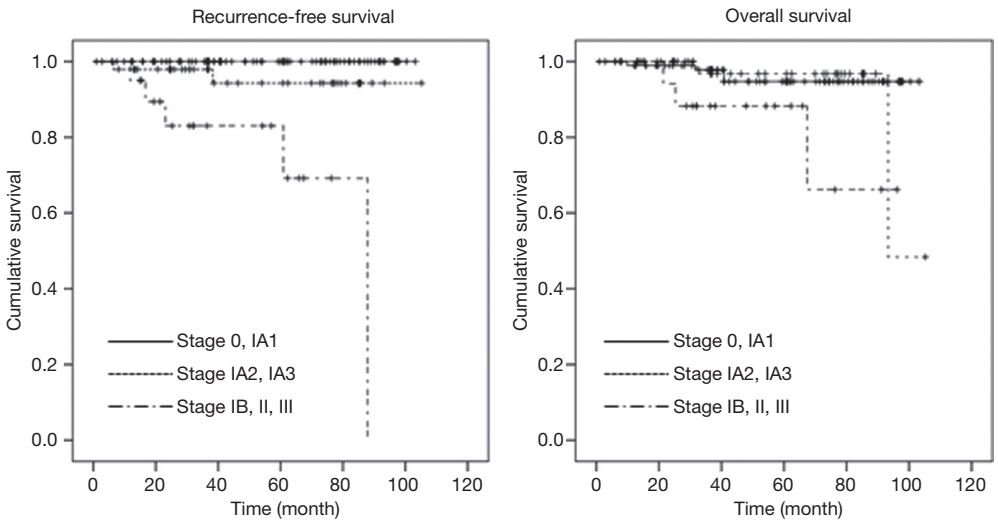


Figure 2 Survival curves of patients by pathological stage.

94.7% for stage 0/IA1 and 96.8% for stage IA2/IA3; these rates were significantly higher than for stage IB and above (88.2%: P=0.05). With regard to RFS, the survival analysis for clinicopathological factors is shown in *Table 2*. A CT finding of solid, high carcinoembryonic antigen (CEA) level (>5.0 μg/L), pleural invasion, vascular invasion, and lymph node metastasis were significantly associated with poor prognosis on univariate analysis. However, only a CT finding of solid remained significant on multivariate analysis. As for OS (*Table 3*), high age (>75 years) and high CEA (>5.0 μg/L) were significantly associated with poor prognosis. Both remained significant on multivariate analysis. Tumor number (>3), surgical procedure (limited surgery) or remnant tumors were not associated with prognosis.

Differences between the groups with and without remnant tumors are shown in *Table 4*. There was no significant difference between the groups except in tumor number (P=0.03). Existence of remnant tumors was not associated with prognosis for either RFS or OS (*Figure 3*).

Discussion

Lepidic-type adenocarcinoma is known to occur frequently in Asians and non-smokers. The prognosis is good, and

Table 2 Recurrence-free survival and patient characteristics

Variable	N	HR	95% CI	P value	P value (multivariate)
Gender				N.S.	–
Female	100	1	–		
Male	71	0.98	0.23–4.58		
Age, years				N.S.	–
≤75	122	1	–		
>75	49	0.47	0.06–3.90		
Smoking status				N.S.	–
Negative	99	1	–		
Positive	72	1.31	0.29–5.89		
CT finding				0.005	0.048
GGN	122	1	–		
Solid	49	21.40	2.52–181.06		
Tumor number				N.S.	–
≤3	118	1	–		
>3	53	1.70	0.37–7.60		
CEA, μg/L				0.046	N.S.
≤5.0	153	1	–		
>5.0	18	5.95	1.07–33.07		
Surgery				N.S.	–
S or P	49	1	–		
Lobectomy	122	2.93	0.35–34.64		
Pleural invasion				0.001	N.S.
Negative	159	1	–		
Positive	12	12.33	2.74–55.47		
Vascular invasion				0.001	N.S.
Negative	162	1	–		
Positive	9	13.94	3.11–60.45		
LN metastasis				<0.001	N.S.
Negative	164	1	–		
Positive	7	24.00	5.27–109.26		
Remnant tumor				N.S.	–
Negative	124	1	–		
Positive	47	0.45	0.05–3.76		

HR, hazard ratio; CI, confidence interval; N.S., not significant; GGN, ground glass opacity nodules; CEA, carcinoembryonic antigen; S, segmentectomy; P, partial resection; LN, lymph node.

Table 3 Overall survival and patient characteristics

Variable	N	HR	95% CI	P value	P value (multivariate)
Gender				N.S.	–
Female	100	1	–		
Male	71	2.59	0.65–10.37		
Age, years				0.001	0.008
≤75	122	1	–		
>75	49	10.33	2.10–50.91		
Smoking status				N.S.	–
Negative	99	1	–		
Positive	72	3.60	0.89–14.50		
CT finding				N.S.	–
GGN	122	1	–		
Solid	49	2.68	0.71–10.11		
Tumor number				N.S.	–
≤3	118	1	–		
>3	53	0.32	0.04–2.55		
CEA, μg/L				0.046	0.03
≤5.0	153	1	–		
>5.0	18	7.15	1.69–30.32		
Surgery				N.S.	–
S or P	49	1	–		
Lobectomy	122	1.69	0.35–8.23		
Pleural invasion				N.S.	–
Negative	159	1	–		
Positive	12	2.11	0.26–17.0		
Vascular invasion				N.S.	–
Negative	162	1	–		
Positive	9	2.33	0.19–18.91		
LN metastasis				N.S.	–
Negative	164	1	–		
Positive	7	4.81	0.59–39.39		
Remnant tumor				N.S.	–
Negative	124	1	–		
Positive	47	1.55	0.39–6.10		

HR, hazard ratio; CI, confidence interval; N.S., not significant; GGN, ground glass opacity nodules; CEA, carcinoembryonic antigen; S, segmentectomy; P, partial resection; LN, lymph node.

Table 4 Characteristics of patients with and without remnant tumors

Variables	Remnant negative	Remnant positive	P value
Gender			N.S.
Male	55	16	
Female	69	31	
Age (mean ± SD)	68.4±9.4	68.6±8.9	N.S.
Smoking history			N.S.
Positive	69	30	
Negative	55	17	
Tumor number (CT)			0.03
2	71	15	
3	23	9	
≥4	30	23	
CT findings of dominant tumor			N.S.
GGN	91	31	
Solid	33	16	
pStage of dominant tumor			N.S.
0/IA1	75	26	
IA2/IA3	32	17	
Above IB	17	4	

N.S., not significant; SD, standard deviation; GGN, ground glass opacity nodules.

the propensity of lymph node and distant metastasis is low in comparison to solid adenocarcinomas (9). Multifocal parenchymal nodules are frequently found in patients with lepidic-type adenocarcinoma (10). In this study, we retrospectively reviewed the results of surgery for SMLAs. The most progressive nodules of our cases were GGN (part solid nodules or pure GGN) in 122 cases (71.3%), and their pathological stages were stage 0/IA in 101 cases (59.1%). That is why the prognosis of our series was extremely good (5-year RFS was 95.2%, and OS was 93%).

In the treatment of SMLAs, surgeons are forced to select limited resection to preserve lung function. The standard surgical procedure for lung cancer, even for small-sized lung cancer, is lobectomy with hilar and mediastinal nodal dissection, based on the results of a randomized controlled trial (11). Based on the results of a prospective multi-institutional study on the relationship between radiologic and pathologic findings in peripheral lung cancer (12), the Japan Clinical Oncology Group (JCOG) and the West Japan Oncology Group (WJOG) conducted a randomized, phase III trial investigating lobectomy versus limited resection for small invasive peripheral lung cancers (6). In our series, limited resection for dominant tumors was performed in 28.6% of patients, and surgical procedure was not associated with prognosis. In addition, the non-dominant tumors, mostly GGN, were frequently treated with limited resection. However, the survival of our patients was extremely good.

According to several studies (13,14), solitary pure GGN should be followed up until they increase in size or develop a new solid component. Nevertheless, whether this strategy is also appropriate for SMLAs is controversial. In this study, although GGN were left in 27.5% of cases, this was not associated with prognosis. In some cases, we could not treat all of the nodules because there were multifocal nodules in the lungs bilaterally. Our strategy for SMLA cases was to focus on invasive nodules, with CT findings that were solid or sub-solid, and to leave pure GGN unresected and observe them clinically. When a GGN became enlarged or a solid component appeared, additional local treatment,

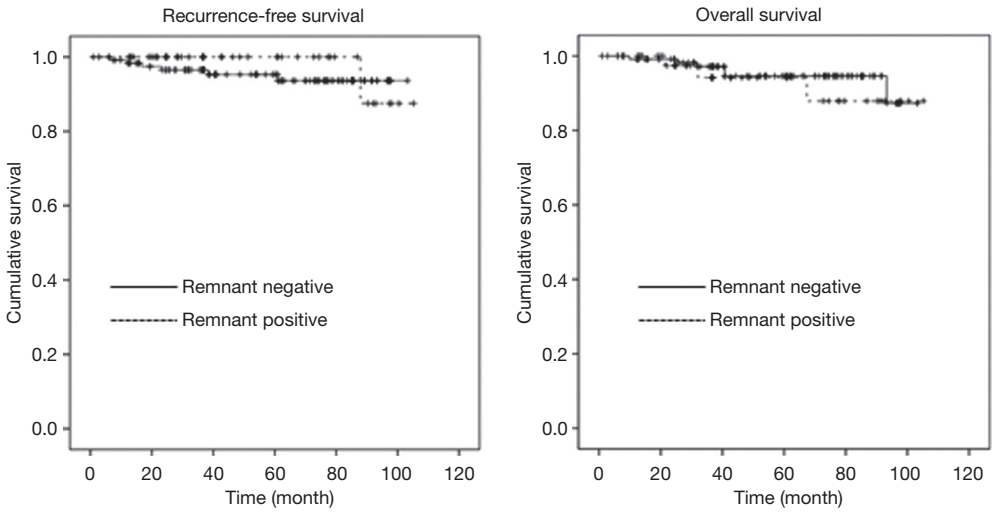


Figure 3 Survival curves of patients with and without remnant nodules.

including radiofrequency ablation or stereotactic radiation therapy, could be incorporated.

This study had some limitations. Due to its retrospective nature, a prospective study is necessary to verify the results. The observation period was relatively short, and the safety of clinical observation of remnant tumors is unclear.

In conclusion, the prognosis of SMLA in these patients was relatively good. The prognosis was dependent on the pathological stage of the dominant tumor. Non-solid tumors less than 1 cm can be clinically observed, and GGN can be treated with limited surgery.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by ethical committee of Kumamoto University (No. 202, 402). Written informed consent was obtained from all patients.

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