Tumor Size and N2 Lymph Node Metastasis Are Significant Risk Factors for Early Recurrence in Completely Resected Centrally Located Primary Lung Cancer Patients

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Abstract. *Background/Aim: In centrally-located lung cancer treatment, it is difficult to attain a sufficient resection margin. It is important to investigate recurrent styles in centrally-located lung cancer patients. Patients and Methods: Primary lung cancer located at the hilar area that requires pneumonectomy or sleeve lobectomy is defined as centrally-located lung cancer. Early recurrence was defined as that within 1 year after surgery. Results: This study included 43 centrally-located lung cancer patients. Ten patients underwent pneumonectomy and 33 underwent sleeve lobectomy. Eleven patients experienced early recurrence. Non-squamous cell carcinoma (p=0.012), tumor size>64 mm (p<0.001) and pathological N2 (p=0.012) were significant predictors for early recurrence by univariate analysis. Also, tumor size >64 mm (p=0.006) and pathological N2 (p=0.019) were independent predictors by multivariate analysis. Conclusion: Non-squamous cell carcinoma, tumor size and pathological N2 were significant predictors of early recurrence in centrally-located lung cancer. The type of surgical procedure did not affect recurrence development.*

Tumor size (1), preoperative nutritional condition (2), and serum carcinoembryonic antigen concentration (3) are reported predictors of early recurrence after complete resection in primary lung cancer patients. Clinicopathological features differ between peripherally and centrally located primary lung cancer, and are observed in both lung adenocarcinoma and squamous cell carcinoma (4, 5). Tumor extension along the bronchus and pulmonary vessels is an important prognostic factor (6).

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Although sleeve lobectomy is recommended if anatomically appropriate in centrally located lung cancer treatment, it is sometimes difficult to achieve a sufficient resection margin because of the tumor location, and complex techniques are required to achieve complete resection We speculated whether local controllability of lung-preserving surgery for centrally located lung cancer is reliable.

This study was designed to identify the recurrence form and the risk factors of postoperative early recurrence in centrally located primary lung cancer patients.

Patients and Methods

Primary lung cancer located at the hilar area that requires pneumonectomy or sleeve lobectomy for complete removal is defined as centrally located lung cancer. We retrospectively investigated the clinical courses of 43 patients with centrally located lung cancer who underwent surgical treatment at our institute between January 2010 and December 2019. Lung cancer requiring pneumonectomy or sleeve lobectomy to remove a metastatic hilar lymph node was excluded. The right lower sleeve lobectomy was selected to avoid the middle and lower bilobectomy. Thus, patients who had undergone right lower sleeve lobectomy were excluded. Before surgery, all patients provided informed consent for the use of their examination outcomes and data in clinical studies. The local institutional ethics committee approved this study (approval no. 4403; approval date, October 3, 2019).

Mediastinal lymph nodes with a short axis of >10 mm on enhanced computed tomography (CT) were diagnosed as clinically positive for metastasis. Our selection criteria for surgical resection were the absence of distant metastasis, no cancer cell-positive pleural or pericardial effusion, no N2 disease at equal to or more than two mediastinal levels, no bulky N2 disease, and no N3 disease, as well as a predicted postoperative forced expiratory volume in 1 second of more than 40%. Patients with T4 lung cancer with N0 or N1 nodal extension and tumors that could be removed completely were candidates for surgery.

Sleeve lobectomy was selected if anatomically appropriate. Bronchial stumps were usually confirmed as free of cancer cell infiltration by intraoperative pathological diagnosis. Bronchoplasty was performed using interrupted or continuous 4-0 absorbable

monofilament sutures. The anastomosis site was covered with pedunculated pericardial fat pad or thymus.

Five patients who had undergone induction treatments were excluded from this study. Pathological stage II and III lung cancer patients had adjuvant platinum-based doublet chemotherapy, and stage I lung cancer patients received oral-tegafur adjuvant chemotherapy. We did not set criteria for the avoidance of adjuvant treatment. The initiation of treatment was based on the empirical decision made by the physician in charge of each case.

After discharge, all patients had follow-up examinations every 2-4 months consisting of chest X-rays and measurement of tumor markers, and CT was performed at 6 months and every year thereafter. Early recurrence was defined as that within 1 year after surgery. Disease recurrence was commonly detected using imaging methods. The last follow-up review was conducted on December 31, 2020.

Differences in clinicopathological factors between patients with and without early recurrence were assessed using the Mann–Whitney U-test and the χ^2 test. A cutoff value of tumor size for predicting early recurrence was calculated using receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was used for univariate analysis, and multiple logistic regression was used for multivariate analysis. Hazard ratios were used to estimate the relative risk for early recurrence. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using statistical software (JMP 10; SAS Institute, Cary, NC, USA).

Results

The clinical courses of 43 patients with centrally located primary lung cancer were investigated. Ten patients underwent pneumonectomy and the other patients underwent sleeve lobectomy. Only one patient was a never smoker, while the others had a history of smoking. Table I shows the types of surgical procedures conducted in this study and the number of patients. Figure 1 shows the recurrence sites and the patient numbers. Some patients had more than two recurrence sites. Lymph node recurrence was observed outside of the usual dissection area in all patients. One patient developed lung recurrence around the cut edge of the residual lobe after lung-preserving surgery. Pathological examination revealed the tumor had spread through air spaces (STAS) in her resected specimens.

Table II shows patients' characteristics according to the presence of early recurrence. Eleven patients had early recurrence. There were significant differences in histological type ($p=0.049$), tumor size ($p=0.004$), and pathological nodal status ($p=0.012$) between the two groups. The type of surgical procedure did not affect the development of recurrence.

Table III shows univariate and multivariate analyses of risk factors for early recurrence. A cutoff value of tumor size for predicting early recurrence was calculated as 64 mm using ROC curve analysis (area under the curve was 0.80). Non-squamous cell carcinoma ($p=0.012$), tumor size larger

Table I. *Details of surgical methods.*

Rt pneumonectomy	4
Rt upper lobectomy	10
Rt middle and lower bilobectomy	2
Rt upper and middle bilobectomy	1
Lt pneumonectomy	6
Lt upper lobectomy	7
Lt lower lobectomy	5
Lt upper and segment 6 lobectomy	3
Lt lower and lingulare lobectomy	3

Rt: Right; Lt: left.

than 64 mm ($p<0.001$) and pathological N2 ($p=0.012$) were significant predictive factors for early recurrence by univariate analysis. Among these factors, tumor size larger than 64 mm ($p=0.006$) and pathological N2 ($p=0.019$) were independent predictive factors for early recurrence in multivariate analysis.

Discussion

We found that non-squamous cell carcinoma, tumor size and pathological N2 were significant predictive factors for early recurrence in centrally located primary lung cancer. Of these factors, pathological N2 and tumor size were independent predictive factors for early recurrence. Type of surgical procedure did not affect recurrence development.

Patient prognosis (7, 8) and quality of life (9) have been found to be improved following sleeve lobectomy compared with pneumonectomy. However, the incidence of locoregional recurrence is controversial (10, 11). In the current study, only one patient had lung recurrence at the cut edge of the residual lobe after lung-preserving surgery, and we speculated that the presence of STAS must have been the cause of it (12). No patient had recurrence at the hilar area around bronchus and pulmonary vessels. Kim *et al*. reported that there was no difference in the incidence of local recurrence according to the bronchial resection margin in centrally located lung cancer patients (13). Thus, lung-preserving surgery is recommended when cut ends are diagnosed as free of cancer cell infiltration by intraoperative pathological diagnosis.

This study included five lung adenocarcinoma patients, and three of them had early recurrence. Kim *et al*. reported that the histological subtype of adenocarcinoma was a risk factor of recurrence after both sleeve lobectomy and pneumo-nectomy (14). In a previous study, the surgical outcomes of 114 patients with adenocarcinoma were investigated according to their tumor locations (4). The results showed that patients with central-type adenocarcinoma had a significantly shorter disease-free survival period. However, there was no difference
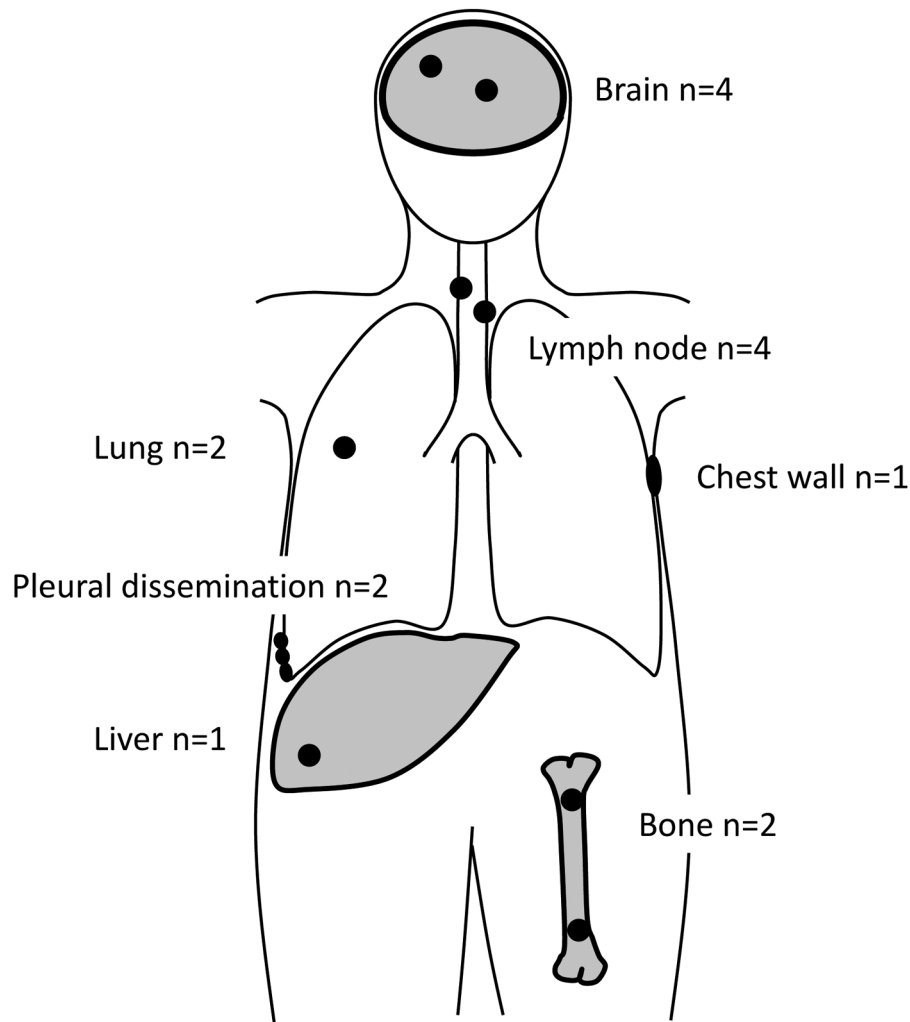
Figure 1. *Early recurrence sites observed in this study. The number of patients for each early recurrence site is shown.*

in the overall survival period according to the tumor location. In this previous study, half of patients had *EGFR* mutations, and treatment tolerability might have prevented a poor prognosis in relapsed patients.

Squamous cell carcinoma is the main histological type in centrally located lung cancer but molecular therapies for lung squamous cell carcinoma have not been established. Eighteen patients (37%) underwent conventional adjuvant chemotherapy in this study. The remaining patients could not undergo adjuvant therapy because of their poor general condition or advanced age, highlighting the requirement for more tolerable adjuvant treatments. The use of immune checkpoint inhibitors has been approved in the advanced and metastatic settings for many types of solid tumors. Nonetheless, their role in the adjuvant setting is limited to the treatment of surgically resected melanomas (15). A treatment benefit of adjuvant

immunotherapy for lung cancer patients has not yet been defined. After validation studies, adjuvant immunotherapy is considered to be an essential treatment for patients at high risk of recurrence. Predicting early recurrence may contribute to selecting appropriate patients and therapeutic methods. Induction chemoradiotherapy followed by surgery is a reliable method for treating locally-advanced lung cancer (16, 17). However, this is still a challenging method in the treatment of centrally-located lung cancer because of the high risk of bronchial complications (18).

Solid tumors are usually hypoxic, because growth is more rapid than angiogenesis. Expression of hypoxia-induced factor-1 (HIF-1), which is associated with tumor proliferation and antiapoptosis, is highly expressed in hypoxic conditions (19). HIF-1 alpha expression is also associated with T-stage and poor prognosis in non-small cell

Table II. *Patient characteristics accroding to the presence of early recurrence.*

		Early recurrence			
		All (n=43)	No (n=32)	Yes (n=11)	*p*-Value
Age		70 (33-83)	71 (48-83)	65 (33-80)	0.163
Gender	Male/Female	34/9	27/5	7/4	0.161
Performance status	0/1/2	22/20/1	18/13/1	4/7/0	
Blood examination	White blood cells (/μl)		7150 (3900-34200)	6500 (3700-20600)	0.296
	CRP (mg/dl)		1.09 (0.05-34.00)	0.90 (0.05-8.12)	0.686
	Albumin (g/dl)		3.7 (2.2-4.6)	3.8 (2.9-4.2)	0.933
Clinical stage	I/II/III	8/18/17	7/14/11	1/4/6	
Clinical nodal status	0/1/2	12/27/4	10/20/2	2/7/2	
	0-1/2	39/4	30/2	9/2	0.269
Tumor markers	CEA (ng/ml)		2.8 (0.6-11.3)	3.8 (1.6-7.6)	0.606
	CYFRA (ng/ml)		2.0 (0.7-60.5)	2.0 (1.0-16.1)	0.900
Histological type	Sq	36	29	3	0.049
	non-Sq	7	3	4	
Surgical procedure	Pneumonactomy	10	6	4	0.248
	Sleeve lobectomy	33	26	7	
Tumor size (mm)			38 (7-87)	65 (30-120)	0.004
Pathological stage	I/II/III	7/20/16	7/17/8	0/3/8	
Pathological nodal status	0/1/2	16/19/8	13/16/3	3/3/5	
	0-1/2	35/8	29/3	6/5	0.012
Adjuvant chemotherapy		16 (37%)	11 (34%)	5 (45%)	0.515

CRP: C-reactive protein; CEA: carcinoenbryonic antigen; CYFRA: cytokeratin 19 fragment; Sq: squamous cell carcinoma. Values are median (range).

Table III. *Results of univariate and multivariate analyses of risk factors of early recurrence.*

			Univariate analysis			Multivariate analysis		
		n	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Histological type	Sq	36	0.18	0.03-0.99	0.049	0.19	0.02-1.44	0.109
	non-Sq	7						
Tumor size (mm)	≤64	30	0.07	0.01-0.32	<0.001	0.08	0.01-0.49	0.006
	>64	13						
Pathological N	0-1	35	0.12	0.02-0.64	0.012	0.1	0.01-0.69	0.019
	2	8						

HR: Hazard ratio; CI: confidence interval; Sq: squamous cell carcinoma.

lung cancer patients (20). These molecular mechanisms might contribute to poor prognostic behavior in patients with large tumors.

This study had some limitations. First, it was a retrospective study that included a small number of patients. Accumulation of data from more patients and further analyses are now ongoing. Second, the initiation of treatments was based on the empirical decision made by the physician in charge of each case. The selection criteria of surgical procedures and perioperative therapy should be established in further prospective studies. Finally, preoperative examination has not yet been standardized and there were divergences between clinical and pathological findings. A standard preoperative examination schedule including positron emission tomography/computed tomography or endobronchial ultrasound-guided biopsy, as necessary, should be established. Therefore, staging accuracy must be improved.

In conclusion, histological type of non-squamous cell carcinoma, tumor size and pathological N2 were significant predictive factors for early recurrence in centrally located primary lung cancer. Of these factors, tumor size and pathological N2 were independent predictive factors for early recurrence. The type of surgical procedure did not affect recurrence development.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Takuma Tsukioka designed this study, analysed the data, prepared the figures and wrote the original draft. Nobuhiro Izumi and Noritoshi Nishiyama oversaw the study and revised the article. All Authors reviewed the article.

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