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Clinical Features of Bronchogenic Large Cell Carcinoma Confirmed by Surgical Resection

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Background : To define the final outcome of large cell carcinomas (LCC) after surgical treatment, the histopathology, clinical features and follow-up results of 28 cases were reviewed.

Methods : Twenty eight patients, with LCC that underwent a surgical resection between 1986 and 2001, at the Severance Hospital, were retrospectively reviewed. We analyzed clinical data, radiological findings, pathologic findings, treatment modalities, and survival.

Results : The prevalence of LCC was 2.9% (29 cases) among the surgically resected primary lung cancer cases (1003 cases) during the 15 year period of the study. The mean age of the patients was 59 years old, with 25 male cases. There were 23 smokers, smoking an average of 33 pack years. A cough was the most frequent symptom. There were 15 cases located in the peripheral part of the lung and 26 consisted of a lobulated mass. From a chest CT scan, 26 cases had necrotic portions, which appeared to be low density. The postoperative stages were IA, IB, IIB, IIIA and IV in 1 (3.6%), 11 (39.3%) 8 (28.5%), 7 (25%), 1 case (3.6%), respectively. The concordance rate of the pre- and postoperative stage was 43%. The median survival time and 5 year-survival rate were 54.5 months and 45%, respectively.

Conclusion : Our results suggested that a LCC in the lung was predominant in males, and equally located at the center and periphery of the lung in the surgically resected cases. To define the treatment outcome and risk factors of a LCC of the lung, further multicenter studies are needed.

Key Words : Carcinoma, Large cell, Diagnosis, Treatment outcome

INTRODUCTION

A large cell carcinoma (LCC) is one of the typical histologic types of lung cancer, but their incidence is lower than 10%, which is relatively less frequent than other types[1]. With the use of light microscopy they are defined as large malignant epithelial tumors, with large nuclei, prominent nucleoli and abundant cytoplasm, and they usually have well defined cell borders, without the characteristic features of squamous or small carcinomas or adenocarcinomas[2]. However, because they are difficult to distinguish from other undifferentiated types, other then by surgical resection, their prevalence varies between 6~31% according to reporters, and consequently studies about their definite clinical characteristics and survival rates are lacking[3, 4].

With the use of electron microscopy and immunohistochemical staining method, a LCC, with neuroendocrine features, was recently separated as a large cell neuroendocrine carcinoma, with a reported prognosis worse than that of a LCC itself, further augmenting the confusion and debate relating to the diagnosis of LCC[5, 6].

Attempts were made to find the concordance rate between

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the pre- and post-operative diagnoses, clinical characteristics and survival rates of patients diagnosed with a large cell carcinoma, between May 1986 and June 2001, at the Severance Hospital, Yonsei University College of Medicine.

MATERIALS AND METHODS

5,069 cases of primary lung cancer were diagnosed, between May 1986 and June 2001, at the Severance Hospital, Medical College, Yonsei University, with 1,003 being surgically resected (Table 1). Of the 31 confirmed LCC cases, 28 were analyzed, as 2 cases, re-diagnosed by pathological re-evaluation as adenocarcinoma and squamous cell carcinoma, and 1 where only an open lung biopsy was performed, were excluded.

For the pathological re-evaluation, the tissue was fixed in 10% formalin, embedded in paraffin, cut into 5-μm sections and stained with Hematoxylin-Eosin. When differentiation of the adenocarcinoma was, Periodic acid-Schiff (PAS) and mucicarmine stain were used, which was classified as a LCC if the results were negative.

Basaloid and large cell neuroendocrine carcinomas especially, were differentiated using neuron-specific enolase (1:100; DAKO, Santa Barbara, CA, USA), chromogranin A (1:10; Boehringer Mannheim, Indianapolis, IN), synaptophysin (1:10; DAKO, Santa Barbara, CA, USA) and CD56 (1:50; DAKO, Santa Barbara, CA, USA).

By reviewing the medical records, sex, age, smoking history, symptom, preoperative diagnosis, findings of initial chest computerized tomography, pre- and post-operative stages, pathological findings, postoperative treatment, the incidence of recurrence, follow-up, and survival rates were sought.

RESULTS

1. Clinical characteristics

Among the 5,069 primary lung cancer cases diagnosed during the 15 year period, a squamous cell carcinoma was the most common, with 2,230 cases (44%), but there were only 85 cases (1.7%) of LCC. Of the 1,003 surgically resected lung cancer cases, 29 (2.9%) were confirmed as LCC, and 1 case, where only an open lung biopsy was performed, was excluded from the study (Table 1).

The average age of the 28 patients, with LCC, was 59 years, ranging from 41 to 75, with 25 male (average age 59 years) and 3 female (average age 55 years) patients. There were 2 non-smokers and 22 smokers, and 2 cases where this was unknown. The average smoking indices of smokers were 33 pack years (Table 2). Ten patients (36%) had a history of pulmonary tuberculosis, and 3 had previously been treated for extrapulmonary malignant tumors (hepatocellular carcinoma, advanced gastric cancer, and laryngeal cancer). At the time of diagnosis they were completely cured, which had no effect on the treatment and prognosis of lung cancer. A cough was the most common symptom at the time of diagnosis (Table 3).

Table 1. Frequency of primary and surgically resected primary lung cancers, by histologic types, at the Severance Hospital during the 15 year period (1986~2001)

Histologic type	All primary lung ca	Surgically resected primary lung ca
Adenocarcinoma	1,456 (28.7%)	268 (27.0%)
Bronchioloalveolar cell carcinoma	129 (2.5%)	67 (6.7%)
Squamous cell carcinoma	2,230 (44.0%)	523 (52.0%)
Small cell carcinoma	770 (15.2%)	14 (1.4%)
Large cell carcinoma	85 (1.7%)	29 (2.9%)
Giant cell carcinoma	11 (0.2%)	3 (0.3%)
Large cell neuroendocrine carcinoma	18 (0.4%)	7 (0.7%)
Carcinoid	13 (0.3%)	9 (0.9%)
Mucoepidermoid carcinoma	10 (0.2%)	6 (0.6%)
Adenoid cystic carcinoma	8 (0.2%)	4 (0.4%)
Adenosquamous cell carcinoma	49 (1.0%)	27 (2.7%)
Others and unspecified carcinoma	279 (5.5%)	40 (4.0%)
Sarcoma	6 (0.1%)	1 (0.1%)
Mesothelioma	1 (0.0%)	1 (0.1%)
Miscellaneous	4 (0.1%)	4 (0.4%)
Total	5,069 (100.0%)	1,003 (100.0%)

2. Radiological and pathological findings

A fine needle aspiration biopsy was carried out in 14 cases (50%), and was the most common pre-operative diagnostic method. A bronchoscopic biopsy and bronchial washing were the methods of diagnosis in 10 (36%) and 9 (35%) cases, respectively (Table 4). Among the 28 cases, 23 were preoperatively diagnosed with lung cancer. The preoperative histologic cell types of lung cancer were adenocarcinomas, squamous cell carcinomas, unclassified non-small cell cancers, and LCC in 6, 9, 7 and 1 case, respectively (Table 5).

According to the preoperative computerized tomography, the tumors were observed at the center and the periphery in 13 and 15 cases, respectively. The mass was most commonly located at the right lower lobe (9 cases, 32.2%), and the margin was lobulated in 20 cases (71%). In 26 cases (93%) the internal density was low, suggestive of central necrosis.

The postoperative pathological examinations revealed central necrosis in all but one case (96%). If a lymph node

Table 2. Clinical features of large cell carcinomas, 28 cases

Case	Sex	Age	Smoking (PY)	FOB/TBLB		FNAB	Preop-pathol	Preop-staging	Postop-staging	Op name	CTx	RTx	Follow up
				Bx	Cyto								
1	M	45	20	N	N	N	N	T1N2M0 (IIIA)	T1N2M0 (IIIA)	MR	adj	adj	Alive (74 mon)
2	M	41	0	T-	-	-	-	T2N2M0 (IIIA)	T2N2M0 (IIIA)	P	adj	adj	Alive (45 mon)
3	M	67	60	F+	+	N	Squam	T2N1M0 (IIB)	T2N0M0 (IB)	P	N	N	Alive (86 mon)
4	M	57	40	F-	+	+	Squam	T2N2M0 (IIIA)	T2N0M0 (IB)	P	N	N	Alive (101 mon)
5	M	61	30	F+	+	-	NSCLC	T3N1M0 (IIIA)	T2N1M0 (IIB)	P	adj	adj	Alive (939 mon)
6	M	44	30	T-	-	N	-	T2N0M0 (IB)	T2N0M0 (IB)	L	adj	adj	Alive (42 mon)
7	M	52	45	F+	-	N	Adeno	T2N2M0 (IIIA)	T2N0M0 (IB)	BL	adj	N	Alive (114 mon)
8	M	57	40	F-	-	+	NSCLC	T1N0M0 (IA)	T1N0M0 (IA)	P	N	N	Alive (61 mon)
9	M	64	45	T-	-	+	Squam	T2N1M0 (IIB)	T2N0M0 (IB)	L	N	N	Alive (3 mon)
10	M	68	0	T+	+	N	Adeno	T2N0M0 (IB)	T2N1M0 (IIB)	L	adj	adj	Died* (66 mon)
11	M	64	0	F+	+	N	Squam	T4N2M0 (IIIB)	T3N0M0 (IIB)	P	N	adj	Died* (55 mon)
12	M	72	50	F-	-	+	Adeno	T3N2M0 (IIIA)	T2N2M0 (IIIA)	L	adj	adj	Died* (55 mon)
13	M	59	50	F-	-	+	Squam	T4N2M0 (IIIB)	T3N1M0 (IIIA)	P	adj	a+p	Died* (20 mon)
14	M	75	30	T+	-	+	Squam	T3N0M0 (IIB)	T3N0M0 (IIB)	L	N	N	Died* (7 mon)
15	M	72	50	N	N	+	Squam	T3N0M0 (IIB)	T3N0M0 (IIB)	L	N	adj	Died* (7 mon)
16	M	70	25	F-	-	+	Adeno	T2N0M0 (IB)	T2N0M0 (IB)	L	N	N	Died* (1 mon)
17	F	61	7	T-	+	+	NSCLC	T2N2M0 (IIIA)	T2N2M0 (IIIA)	P	N	N	Died* (29 mon)
18	F	42	0	T+	+	N	Adeno	T2N2M0 (IIIA)	T2N0M0 (IB)	BL	N	N	Alive (35 mon)
19	M	62	60	F-	-	N	-	T4N3M0 (IIIB)	T3N0M0 (IIB)	P	N	adj	Alive (41 mon)
20	M	43	NR	F-	-	+	NSCLC	T4N2M0 (IIIB)	T2N0M0 (IB)	L	N	pall	Died* (20 mon)
21	M	56	40	F-	-	+	Squam	T4N2M0 (IIIB)	T4N2M1 (IV)	P	adj	N	Alive (49 mon)
22	M	58	40	F-	-	+	NSCLC	T3N2M0 (IIIA)	T3N1M0 (IIIA)	P	adj	N	Died* (7 mon)
23	M	64	40	F-	-	+	Squam	T4N0M0 (IIIB)	T3N1M0 (IIIA)	P	N	adj	Died* (34 mon)
24	M	65	45	T+	+	N	NSCLC	T2N2M0 (IIIA)	T2N0M0 (IB)	P	N	N	F/U loss
25	F	63	NR	F+	-	N	Adeno	T3N2M0 (IIIA)	T3N0M0 (IIB)	BL	N	N	F/U loss
26	M	56	40	F-	-	+	NSCLC	T2N0M0 (IB)	T2N0M0 (IB)	L	N	N	F/U loss
27	M	63	30	F-	-	N	-	T4N2M0 (IIIB)	T3N0M0 (IIB)	L	N	N	F/U loss
28	M	60	40	T+	+	N	Lcca	T2N0M0 (IB)	T2N0M0 (IB)	P	N	N	Alive (143 mon)

Abbreviations: Adeno, adenocarcinoma; adj, adjuvant; a+p, adjuvant + palliative; BL, bilobectomy; Bx, biopsy; CTx, chemotherapy; Cyto, washing cytology; FNAB, fine needle aspiration biopsy; FOB (F), fiberoptic bronchoscopy; L, lobectomy; Lcca, large cell carcinoma; mon, months; MR, mass resection; N, not performed; NSCLC, non-small cell lung carcinoma; Op, operation; P, pneumonectomy; pall, palliative; PY, pack year; RTx, radiation therapy; Squam, squamous cell carcinoma; TBLB (T), transbronchial lung biopsy; -, negative; +, positive; *, died of neoplastic disease

Table 3. Clinical Symptoms

Symptoms	No. of patients
Cough	19 (68.0%)
Sputum	15 (54.0%)
Chest pain	11 (39.0%)
Hemoptysis	11 (39.0%)
Dyspnea	5 (18.0%)
Weight loss	5 (18.0%)
Asymptomatic	2 (7.0%)
Chest wall mass	1 (3.5%)

Table 4. Malignancy rate of preoperative diagnostic methods

Methods	No. of patients	Malignancy diagnosis rate
Fine needle aspiration biopsy	16	14 (88%)*
Fiberoptic bronchoscopy	26	10 (38%)
- Visible mass	10	5 (50%)
- No visible mass	7	0 (0%)
- TBLB	9	5 (55%)*
Bronchial washing	26	9 (35%)
Non-diagnostic	5	0 (0%)

*One case was diagnosed by both TBLB and FNAB.
Abbreviations: TBLB, transbronchial lung biopsy

was larger than 1cm in diameter it was considered as tumor involved, the sensitivity, specificity and accuracy for detecting mediastinal lymph node metastasis were 100, 52, and 61%, respectively (Table 7).

3. Treatment

The concordance rate of the pre- and post-operative stage was 43%, i.e. 12 out of 28 cases; with stages IA, IB, IIB

Table 5. Preoperative diagnostic methods and cell types

Cell type / Dx methods	FOB	FNAB	Total
Adenocarcinoma	4 (40%)	2 (14%)	6 (25%)
Squamous cell carcinoma	3 (30%)*	7 (50%)*	10 (42%)*
NSCLC unknown type	2 (20%)	5 (36%)	7 (29%)
Large cell carcinoma	1 (10%)	0 (0%)	1 (4%)
Total	10 (100%)*	14 (100%)*	24 (100%)*

*One case was diagnosed by both TBLB and FNAB, with 23 real cases of preoperative diagnosis of lung cancer.
Abbreviations: FNAB, fine needle aspiration biopsy; FOB, fiberoptic bronchoscopy; NSCLC, non-small cell lung carcinoma

Table 7. Comparison between preoperative chest CT scan and postoperative pathology for hilar and mediastinal lymph node infiltration

Pathology	Chest CT findings			
	N1 nodes		N2 nodes	
	(+)	(-)	(+)	(-)
(+)	1	4	5	0
(-)	3	20	11	12

N1 nodes sensitivity 20%, specificity 87%, accuracy 75%,
N2 nodes sensitivity 100%, specificity 52%, accuracy 61%,
N1 & N2 nodes sensitivity 60%, specificity 70%, accuracy 68%

and IIIA in 1, 4, 2 and 5 cases, respectively (Table 8). The complete resection rate was 93% (26 cases). In 2 cases, where the resection margin was involved with the tumor, the tumors recurred at the margin, and the patients expired 55 and 7 months following the operation. A pneumonectomy was the most commonly performed extension of the resection (14 cases, 48%).

Ten patients received chemotherapy as a postoperative adjuvant therapy, but in the recurred cases, chemotherapy was not undertaken due to the poor general condition or refusal of the patients.

Of the 13 cases where postoperative radiotherapy was undertaken, the therapy was adjuvant in 11, and conservative,

Table 6. Chest CT scan and pathologic findings in 28 cases of a large cell carcinoma

Case	CT finding					Pathologic finding		
No.	Centrality	Mass locationz	Mass size (cm)	Mass margin	Internal low density	Lymph-adenopathy	Necrosis	Lymph-adenopathy
1	central	RUL	8 * 8	lobulated	Yes	PT	Yes	PT
2	peripheral	RLL	6 * 5	smooth	Yes	SC, PT	Yes	SC, PT
3	peripheral	RLL	3.5 * 3.5	smooth	Yes	H	Yes	N0
4	central	LLL	6 * 6	lobulated	Yes	PA	Yes	N0
5	central	LLL	7 * 7	lobulated	Yes	H	Yes	IP
6	peripheral	LUL	4 * 3	lobulated	Yes	No	Yes	N0
7	central	RLL	4 * 4	lobulated	Yes	SC, PT	Yes	N0
8	peripheral	RML	1.5 * 2	smooth	No	No	Yes	N0
9	peripheral	RLL	5 * 5.5	lobulated	Yes	H	Yes	N0
10	peripheral	RUL	3 * 3	lobulated	Yes	No	Yes	IP
11	central	RLL	6.5 * 4	lobulated	Yes	PT, SC	Yes	N0
12	peripheral	RML	4.5 * 5	lobulated	Yes	SC, PT	Yes	PT
13	central	LUL	4 * 3.5	lobulated	Yes	PA	Yes	H
14	peripheral	RUL	4 * 4	spiculated	Yes	No	Yes	N0
15	central	RUL	5 * 5	spiculated	Yes	No	Yes	N0
16	peripheral	LLL	4 * 4	lobulated	Yes	No	Yes	N0
17	peripheral	LLL	5.5 * 3.5	lobulated	Yes	PA,PT	Yes	PA
18	central	RLL	6.5 * 6	spiculated	Yes	H, SC	Yes	N0
19	central	RUL	8 * 6	lobulated	Yes	PT, SCLN	Yes	N0
20	central	RUL	9 * 5	lobulated	Yes	PA, SC	Yes	N0
21	peripheral	RLL	6 * 5	lobulated	Yes	PT	Yes	PT
22	central	LUL	15 * 11	lobulated	Yes	PA	Yes	H
23	peripheral	LLL	12 * 10	lobulated	Yes	No	Yes	IP
24	peripheral	LLL	3 * 3	lobulated	Yes	PA	Yes	N0
25	central	RLL	3 * 2	lobulated	No	SC	No	N0
26	peripheral	RUL	7 * 6	lobulated	Yes	No	Yes	N0
27	central	LUL	5 * 4	spiculated	Yes	PA	Yes	N0
28	peripheral	RLL	4 * 3	spiculated	Yes	No	Yes	N0

Abbreviations: H, hilar; PA, preaortic; PT, paratracheal; SC, subcarina; SCLN, supraclavicular lymph node

Table 8. Comparision of preoperative and postoperative stages

Preop. stage	Postoperative stage							
	IA	IB	IIA	IIB	IIIA	IIIB	IV	Total
IA	1	0	0	0	0	0	0	1
IB	0	4	0	1	0	0	0	5
IIA	0	0	0	0	0	0	0	0
IIB	0	2	0	2	0	0	0	4
IIIA	0	4	0	2	5	0	0	11
IIIB	0	1	0	3	2	0	1	7
Total	1	11	0	8	7	0	1	28

Stage concordance 12/28 (43%)
Up staged 2 cases, down staged 14 cases

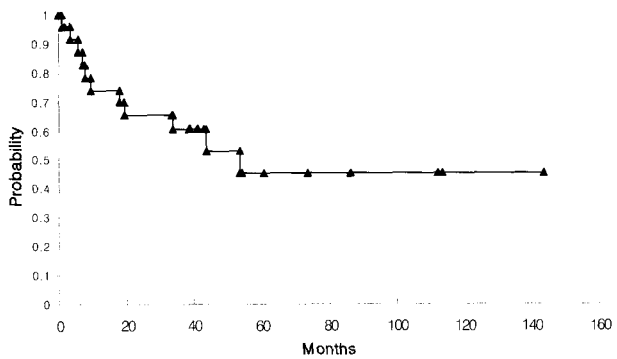

Figure 1. Survival of surgically resected a large cell carcinoma in 28 cases

for brain and bone metastasis, in 2.

At the follow-up to August, 2001 13 patients still survived, with stages IA, IB, IIB, IIIAand IV in 7, 2, 2 and 1 cases, respectively, and there were no recurrences following a complete resection In IA, IB, and IIB (10 cases).

The median follow-up was 41.5 months, ranginge from 3 to 143 months. An extrapulmonary recurrence occurred in 6 cases, with a lymph node recurrence being the most common (4 cases), followed by bone (3 cases), liver (1 case), brain (1 case), maxillary sinus (1 case) and pericardium (1 case). The median survival time and 5-year survival rate of the 28 cases were 54.5 months and 45% (Figure 1). Due to the small number of cases, the prognostic factors could not be analyzed.

DISCUSSION

According to the 1967 WHO criteria, amended in 1982, a LCC is defined as "a malignant epithelial tumor, with large nuclei, prominent nucleoli and abundant cytoplasm, usually with well defined cell borders, but without the characteristics features of squamous or small cell carcinomas or adenocarcinomas". Undifferentiated tumors, with intracytoplsmic mucin, which had previously been categorized as LCC, have been re-categorized as adenocarcinomas[2]. Even though immunohistochemical staining and electron microscopy can be used to detect features of differentiation (squamous, glandular, neuroendocrine), the diagnosis of a LCC is mainly based on routine histochemical staining methods and the light microscopic findly[2]. Even with these diagnostic criteria, it is not easy to distinguish a poorly differentiated LCC from a poorly differentiated squamous cell carcinoma or adenocarcinoma.

Recently, Travis et al[5] suggested that a non-small cell carcinoma of the lung, viewed as a neuroendocrine differentiation by light microscopy, and confirmed by immunohistochemical stain and electron microscopy, but not categorized as another neuroendocrine tumor, such as carcinoid, atypical carcinoid, and small cell carcinoma, should be named a large cell neuroendocrine carcinoma, on the basis of the reports suggesting such tumors have a poor prognosis. The WHO/IASLC lung cancer classification of 1999 defined a large cell neuroendocrine carcinoma as a variant of a LCC[7].

Our relative prevalence of a LCC was 1.7%, 85 out of 5,069 lung cancers, which was lower than the reports of other Countries, including one by Travis et al. that reported a prevalence of about 10%[1, 3, 4], which was also lower than the 6.3% prevalence reported by Kim et al[8]. Even if only the surgically resected primary lung cancers were considered, the 2.9% prevalence was still lower than the 3.5 and 7.6% reported by Ham et al[9] and Han et al[10]. Our suggestions for this lower prevalence, compared to previous reports, are as followed; firstly, since 1982 some LCC were reclassified as mucinous adenocarcinoma. Secondly, if not surgically resected, a LCC could have been misdiagnosed as another type due to central necrosis and hemorrhage. A report by Kim et al.[8] analyzed the primary lung cancers that occurred between 1957 and 1977, and at that time the prevalence of an adenocarcinoma was 11.9%. Our report dealt with the lung cancers that occurred between 1986 and 2001, and while the prevalence of adenocarcinomas have increased to 27% since the mid-1980s, undifferentiated cancers, including LCC, decreased, possibly due to the wider application of immunohistochemical staining methods.

Table 2 summarizes the clinical characteristics of our patients. The gender ratio was 8.3:1, with a male predominance, which was similar to the 10.5:1 ratio reported by Han et al[10], but different from the 3.9:1 reported by Kim et al[8], which was based on all lung cancers. Travis et al reported a 2.2:1 ratio[5].

The average smoke index of the 22 smokers was 33 pack

years. Of the 25 male patients, 3 were non-smokers, 21 (88%) had a positive history of smoking and 1 had an unknown history. Compared to the study of Barbone et al[11], where 95% of the male patients with a LCC were reportedly smokers, ours showed a slightly lower rate. It is unknown whether smoking was associated with the predominance of LCC prevalence in male patients, and to find other involved factors involved more studies will be required.

Our study revealed that malignant cells were found in only 1 out of 25 cases using the sputum cytology method; with a diagnostic rate was 4%. According to Gledhill et al.[12] the low diagnostic rate of the sputum cytology method was due to a too smaller amount of sputum and number of diagnostic trials. To overcome this short fall, he suggested that an adequate amount of sputum should be acquired, in the morning, by coughing after a deep breath, and the tests should be repeated more than 4 times. In our study, the low diagnostic rates, even with 13 cases of central tumor and 11 cases of hemorrhage, were thought be due to the acquisition of sputum from just one test and the inaccuracy of the collection method. This emphasizes the need for repeated and accurate sputum cytology tests.

Only 10 out of 26 cases (38%) were diagnosed as lung cancer using fiberoptic bronchoscopy, with a diagnostic rate of 38%. The low diagnostic rate was because in 7 cases, where the lesion was not visible, all the biopsy samples were negative, with only 5 out of 10 cases having visible lesions, and in 5 out of 9 cases where a transbronchial biopsy was performed, was lung cancer diagnosed. Even the diagnostic rate of the visible lesion was low, as severe necrosis and hemorrhage hindered the diagnosis. Including the 2 cases where the bronchial washing cytology test was positive for malignancy, the diagnostic rate by bronchoscopy was 46.2%, i.e. 12 out of 26 cases. According to Ham et al.[9] in 189 cases where bronchoscopy was performed, the diagnostic rate was 71.4%, and according to Kamholz et al.[13] this value was 73%. Mak et al.[14] also reported on 125 cases where the tumor was visible with bronchoscopy, where the positive rate offor a biopsy was 76%, of the bronchial washing method was 49.6%, and of the bronchial brushing method was 52%. In 63 cases where the tumor was not visible, the corresponding figures were 36.5, 38.1, and 28.6%, respectively. From this it was recommended combining the washing and brushing methods with a biopsy during bronchoscopy. In our study, the malignancy detection rate of the bronchial washing method was 36%, 9 out of 26 cases, which was slightly lower than the reports by Mak et al[14]. Even when the tumor was visible, a biopsy through bronchoscopy might be unable to diagnose, due to too few, or no, cancer cells in the tumor, or from tissue damage that could cause difficulty in the interpretation. Especially in LCC, central necrosis, hemorrhage and obstructive pneumonia might be anticipated in the low diagnostic rate.

The diagnostic rate of a fine needle aspiration biopsy was 88%, i.e. 14 out of 16 cases. According to Allison et al[15], the diagnostic rate was 90%, with almost no false positive results, and a false negative rate of 5~10%, which were compatible to our results.

Among 28 surgically resected cases, only 1 was pre-operatively diagnosed as a LCC. Confusion in the diagnostic guide could be the reason for the low preoperative diagnostic rate, with central necrosis, hemorrhage and obstructive pneumonia also making diagnosis potentially difficult by methods other than surgery. For precise confirmation, an analysis of the concordance rate between preoperative diagnosis of a LCC and the postoperative confirmation of the same histologic type is required. In our literature review no such study could be found.

The tumor was sited at the periphery in 15 cases (54%), with a similar number being found centrally. Taking into account all the LCC, the peripheral type might be more abundant our study only considered the patients having undergone surgery. The tumors were located in the right lung in 18 cases (68%), which was twice as often as in the left lung. According to the report by Kim et al[8], the prevalence in the right lung was also twice that in the left lung, but reasons for this was unknown. Radiologically, our study showed that surgically confirmed LCC were distributed evenly at the periphery and center, with lobulated rather than smooth margins, with the presence of central necrosis.

Computerized tomography is most useful for diagnosing the extension of a primary tumor, its relationship to adjacent organs, mediastinal lymph node enlargement and also helps to determine the resectability. However, according to Heidenberg et al[16], the size of lymph node alone could not differentiate metastasis from inflammation, as not all the enlarged lymph nodes were involved with the cancer, where 87% of the involved lymph nodes were larger than 1.4 cm. With the criterion of 1.5 cm, Modini et al[17] achieved sensitivity, specificity and accuracy of 55, 91 and 75%, and in the report by Ham et al[9], were 78.9, 72.7 and 75%, respectively. With the criterion of 1 cm, according to Webb et al[18], the sensitivity and specificity were 52 and 69%, respectively, and a large scaled multivariable analysis by Dales et al.[19] revealed a sensitivity, specificity and accuracy each of 79%.

Our study showed that if the enlargement of the mediastinal lymph nodes were defined as larger than a diameter of 1 cm, the sensitivity was 100%, but the specificity was 52%. For the parenchymal and the hilar lymph node, the sensitivity was 20%, but the specificity and accuracy were 87

and 75%, respectively, but compared to other studies, the accuracy was still low. Pulmonary tuberculosis, which is highly prevalent in Korea, and obstructive pneumonia and central necrosis by cancer, could induce reactive lymph node hypertrophy. The concordance rate of the pre- and post-operative stage was as low as 43% due to the difference between the pathologic findings and the computerized tomography with regard to the lymph node enlargements and major organ involvements.

Generally, surgical resection is the primary treatment for a non-small cell carcinoma, including a LCC, where after radiotherapy or chemotherapy is undertaken according to the stage. Mitchell et al.[20] analyzed the prognosis of 208 patients with a LCC, and reported that the median survival time and 5-year survival rate of 55 patients that received surgical treatment were 13 months and 21.2%, and for 4 patients that received postoperative radiotherapy were 6.2 months and 0%. Downey et al.[21] reported that even with precise surgical staging and clear diagnostic criteria, the prognosis of LCC was poor, regardless of the treatment. At the time of diagnosis, 90% of cases were already at an advanced stage (stage III, IV), with only 10% at stage I. He reported that most patients expired within 9 months' with an average survival time for the stage I patients of 15.9 months and therefore the prognosis was very poor.

According to Downey et al[22], the 5-year survival rate of 61 patients with LCC having undergone surgery was 37%, suggesting an improvementd in the results due to aggressive surgery. The 28 patients in our study had a median survival time and 5-year survival time of 54.5 months and 45%, respectively, which were higher than reports from other Countries. Compared to the report of Mitchell et al[20], the distribution of stages were similar, but those of the postoperative chemotherapy and radiotherapy were not, and compared to the reports of Downey et al[21, 22], more low stages, such as stages I and II, were included in our study (Table 9). According to a Korean report by Lee et al[23], in 1987, the 3-year survival rate of 8 patients with LCC out of

Table 9. Comparison of clinical features and surgical treatment outcomes of large cell carcinomas

Author (published year)	Mitchel et al[20] (1980)	Downey et al[21] (1989)	Downey[22] (1999)	This study
Study durations (year)	1968 - 1978	1973 - 1983	1982 - 1986	1986 - 2001
Subjects	All LCC	All LCC	Surgically resected LCC	Surgically resected LCC
Total No. of LCC (% of all lung cancer)	208 (9.0)	96 (6.7)	NR	85 (1.7)
Surgically resected cases (% of all LCC)	59 (28.4)	13 (13.3)	61 (NR)	28 (32.9)
Centrality of mass (%)	Peripheral (43)	NR	NR	Peripheral (54)
Smoker (%)	95	96	98	85
Most common Symptom (%)	Cough (61.5)	Cough (22.0)	Cough (38.0)	Cough (68.0)
FOB biopsy Dx rate (%)	87/208 (42)	35/96 (37)	23/42 (55)	10/28 (36)
Sputum cytology Dx rate (%)	29/208 (14)	NR	4/31 (13)	1/25 (4)
Postoperative stage (%)	I, II 46 (78.0) III 13 (22.0)	I 6 (46.1) III 5 (38.5) IV 2 (15.4)	I, II 37 (61.0) III 22 (36.0) IV 2 (3.0)	I, II 20 (71.4) III 7 (25.0) IV 1 (3.6)
Surgery and other treatment modality (%)	Sur 55 (93.2) Sur+RTx 4 (6.8)	Sur 9 (69.2) Sur+RTx 4 (30.8)	NR	Sur 13 (46.4) Sur+RTx 5 (17.9) Sur+CTx 3 (10.7) Sur+CTx+RTx 7 (25.0)
Median survival of surgically resected patients (months)	13.0	Overall 15.9	NR	54.5
5-year survival of surgically resected patients (%)	21.2	Unable	NR	45.0

Abbreviations: CTx, chemotherapy; Dx, diagnosis; FOB, fiberoptic bronchoscopy; LCC, large cell carcinoma; NR, not reported; RTx, radiotherapy; Sur, surgery

147 patients with primary lung cancer that underwent a surgical resection was 44.5%, and in the report of Han et al[10], in 1996, the 2-year survival rate of 29 out of 382 such patients was 59%.

There have been few trials of postoperative chemotherapy and radiotherapy for LCC, suggesting multi-centered clinical studies, based on a larger population of patients, are needed.

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