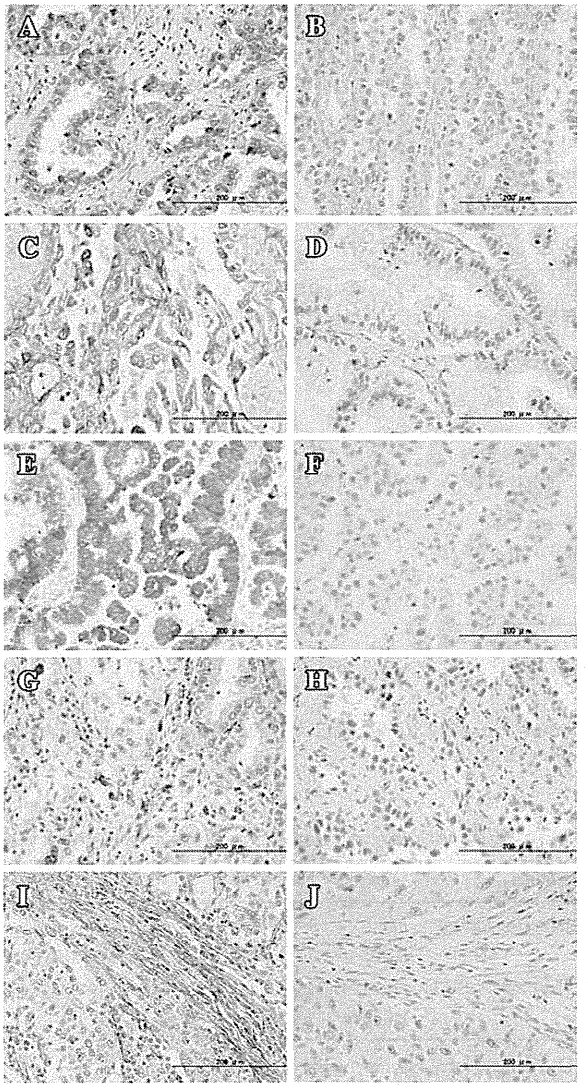

Fig. 1 Immunohistochemical staining of tumor tissue. a Case with BCRP-positive cancer cells, b case with BCRP-negative cancer cells, c case with ezrin-positive cancer cells, d case with ezrin-negative cancer cells, e case with ALDH1-positive cancer cells, f case with ALDH1-negative cancer cells, g case with a high number of CD204-positive TAMs, h case with a low number of CD204-positive TAMs, i case with podoplanin-positive CAFs, and j case with podoplanin-negative CAFs

Multivariate analysis

A multivariate analysis was performed using the Cox proportional hazards model (Table 4). A tendency for podoplanin-positive CAFs to be correlated with the PFS was observed (hazard ratio [95 % CI] = 1.583 [0.935–2.681], P = 0.087).

Discussion

Not only cancer-cell-intrinsic factors but also stromal-cell-extrinsic factors have been reported as predictors of chemotherapy (Kawai et al. 2008; Chung et al. 2012; Farmer et al. 2009; Rong et al. 2013). The relationship between TAMs in NSCLC and the resistance to epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKI) has been previously reported: Patients with high number of CD68-positive TAMs had a shorter PFS (Chung et al. 2012). Farmer et al. (2009) reported that increased stromal gene expression predicts resistance to preoperative chemotherapy with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) in breast cancer patients, suggesting that the activation of stromal cells could be involved in chemotherapy resistance. Actually, CAFs are composed of heterogeneous cell populations, but these results have not focus on subpopulations of stromal cells. This is the first study to indicate that the presence of a special subtype of CAFs, podoplanin-positive CAFs, could be a predictor of PFS in patients with recurrent lung adenocarcinoma who have been treated with platinum-based chemotherapy.

In the present study, the presence of podoplanin-positive CAFs in the primary tumor was significantly related to a shorter PFS in patients with recurrent tumors. These data suggest that the presence of podoplanin-positive CAFs in the primary tumor may predict the resistance of recurrent tumors to chemotherapy. There are several possibilities that could explain this phenomenon. Firstly, podoplanin-positive CAFs in the primary tumor might merely act as surrogate markers for metastasized cancer cells with natural drug resistance. Secondary, cancer cells within a primary tumor composed of podoplanin-positive CAFs might obtain a higher malignant potential through cancer–stroma interactions, leading to the development of resistance to chemotherapy in metastatic lesions. Lastly, podoplanin-positive CAFs are also recruited in recurrent lesions and might play roles in the resistance of metastatic cancer cells to chemotherapy. A recent study by our group showed that podoplanin-positive CAFs were recruited in metastatic lymph node tumors when the primary tumors contained these CAFs (Neri et al. 2012). In addition, our previous study demonstrated that podoplanin-positive CAFs in metastatic lymph nodes were significantly associated with overall survival, but not with recurrence-free survival in N2 lung adenocarcinoma cases (unpublished data). Considering these results, the recruitment of podoplanin-positive CAFs in recurrent tumors might indicate cancer cell resistance to chemotherapy.

While the presence of podoplanin-positive CAFs was associated with the PFS, a significant association with overall survival was not shown. This discrepancy may have

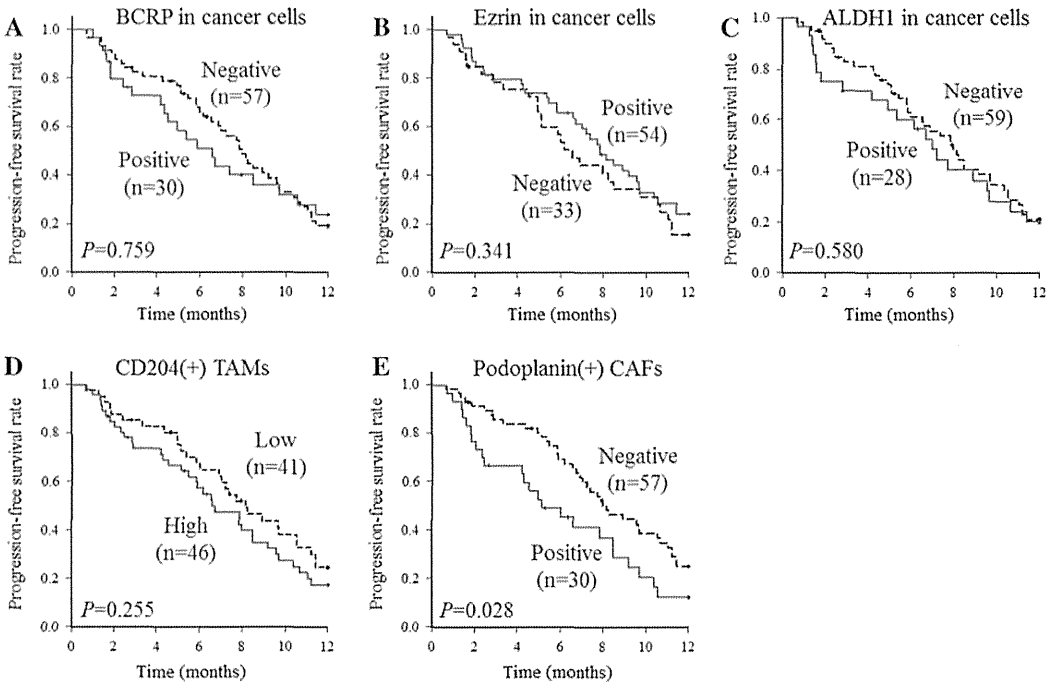

Fig. 2 Kaplan–Meier analyses of progression-free survival according to the expressions of BCRP (a), ezrin (b), and ALDH1 (c) in cancer cells, the number of CD204-positive TAMs (d), and the presence of podoplanin-positive CAFs (e)

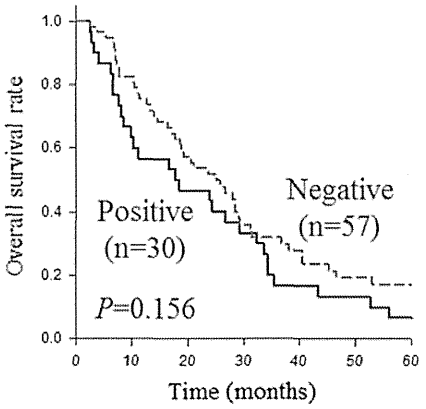

Fig. 3 Kaplan–Meier analysis of overall survival according to the presence of podoplanin-positive CAFs

resulted from the relatively small number of patients. We cannot rule out the possibility that cancer cells with podoplanin-positive CAFs might intrinsically have a higher malignancy and might be associated with a shorter survival period independent of chemotherapy.

Several microenvironmental factors are reported to affect drug resistance, such as survival signals to cancer cells secreted by stromal cells, limitations of drug delivery,

Table 4 Multivariate analysis to predict progression-free survival

Variables	Category	Hazard ratio	95 % CI[a]	P value[†]
Pathological stage	I/II	1		
	III/IV	1.545	0.920–2.595	0.100
Podoplanin + CAFs	Negative	1		
	Positive	1.583	0.935–2.681	0.087

[†] Cox proportional hazards model

[a] Confidence interval

and the participation of immunosuppressive microenvironments (Olson and Joyce 2013; Shree et al. 2011; McMillin et al. 2010; Olive et al. 2009; DeNardo et al. 2011). Nevertheless, how podoplanin-positive CAFs induce resistance to chemotherapy remains unclear. Whether podoplanin-positive CAFs act as functional proteins or surrogate markers remains to be determined.

In lung cancer cells, the enzymatic inactivation of platinum agents has been known to explain resistance (Chang 2011). The expressions of DNA-repair-related proteins, excision repair cross-complementation group 1 (ERCC1), and breast cancer type 1 susceptibility protein (BRCA1) in cancer cells have been shown to be useful for predicting the response to platinum-based chemotherapy (Lord et al. 2002; Olaussen et al. 2006; Rosell et al. 2007). We

previously showed a significant relationship between the high expression of BCRP, an ABC transporter protein, in cancer cells and resistance to cisplatin-based chemotherapy (Yoh et al. 2004; Ota et al. 2009). While the current study evaluated the expression of BCRP in operable primary cancer, previous studies have evaluated the expression of BCRP in advanced inoperable cancer. The controversial results may have arisen because of the different cancer statuses.

Expression levels of ezrin and ALDH are reportedly associated with response to chemotherapy in other various cancers such as breast cancer and esophageal cancer (Ma and Jiang 2013; Ginestier et al. 2007; Ajani et al. 2014), but this study showed no association. It may be caused by the difference in cancer type, or the difference in cancer status as well as BCRP in operable primary cancer showed no association with chemotherapy resistance. Although the association of CD204-positive TAMs to poor prognosis or tumor progression has also been reported in lung carcinoma (Ohtaki et al. 2010; Ito et al. 2012; Maeda et al. 2014), no relationship between its number and clinical outcome of platinum-based chemotherapy was observed. The presence of CD204-positive TAMs may be poor prognostic factor, but not related with outcome of platinum-based chemotherapy.

Shree et al. (2011) showed that combining paclitaxel with an inhibitor of cathepsin, a survival signal secreted by TAMs, slowed the growth of breast cancer containing abundant cathepsin-positive TAMs, compared with paclitaxel treatment alone. This result shows the importance of the integrated targeting of tumor and stromal cells. Podoplanin-positive CAFs may become new target of therapy if their role in the development of resistance to chemotherapy can be clarified.

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Conflict of interest The authors have no conflict of interest to disclose.

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Surgical Treatment for Synchronous Primary Lung Adenocarcinomas

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Background. Surgical treatment has become the mainstay of treatment for multiple primary lung cancers. In particular, the prevalence of synchronous primary lung adenocarcinomas (SPLA) has recently increased, but few studies have evaluated surgical outcomes of patients with SPLA. We reviewed the clinicopathologic features and surgical outcomes of SPLA to identify factors related to survival.

Methods. Data on 2,041 consecutive patients with primary non-small cell carcinoma who underwent surgical resection in our hospital from 1995 through 2009 were retrospectively analyzed.

Results. The SPLA was pathologically diagnosed in 93 patients, including 26 with bilateral tumors. The rates of overall survival and recurrence-free survival at 5 years were 87.0% and 81.8%, respectively. There was no surgical mortality at 30 days. On univariate analysis, lymph node metastasis ($p = 0.0000$), nonlepidic predominant histologic subtype ($p = 0.0018$), and a solid appearance of the largest tumor on computed tomography ($p = 0.0088$) were significantly related to poor overall survival. On multivariate analysis, bilateral distribution of tumors ($p = 0.031$), lymph node metastasis ($p = 0.004$), and sublobar resection ($p = 0.042$) were independent predictors of poor survival.

Conclusions. Surgery has good outcomes and should be aggressively performed for patients with SPLA. The evaluation of lymph node status has an important role in deciding whether surgery is indicated. Bilateral tumors are a predictor of poor outcomes, requiring that caution be exercised. Lobectomy has a high cure rate and should be performed whenever possible. However, sublobar resection should be considered for patients likely to have poor residual lung function postoperatively.

(Ann Thorac Surg 2014;98:1983–8)

Owing to recent progress in diagnostic imaging techniques and the increased use of computed tomography (CT), patients with a confirmed or suspected diagnosis of multiple lung cancers are occasionally encountered. Recent studies have reported that 2.6% to 7.9% of patients who undergo resection of non-small cell lung cancer (NSCLC) have synchronous lung cancers [1–6], and this trend is increasing [6]. Surgical resection has become the mainstay of treatment for synchronous lung cancers, but the 3-year survival rate broadly ranges from 40% to 92% [1–3, 7–10]. The wide variability in outcomes is attributed not only to differences in treatment timing and demographic characteristics of patients, but also to the lack of standard criteria for differential diagnosis from intrapulmonary metastasis and for the selection of surgical procedures.

The seventh edition of the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system defined the presence of additional tumor nodules in the same lobe as T3 M0 and the presence of additional tumor nodules in other ipsilateral lobes as T4 M0, whereas nodules in the contralateral lung were defined as M1a disease [11]. Such nodules are generally regarded to be intrapulmonary metastases from the primary tumor, but may include separately staged synchronous primary lung cancers that require surgical resection. If multiple lung cancers are of different histologic types, differential diagnosis is relatively straightforward. However, if the histologic type is the same, the differential diagnosis of synchronous primary lung cancers and intrapulmonary metastasis remains challenging.

Recent studies have reported that multiple adenocarcinomas account for 40.3% to 91.3% of synchronous primary lung cancers [3–5, 8–10], making the differential diagnosis of multiple adenocarcinomas particularly important. To date, however, few studies have specifically focused on the diagnosis and surgical outcomes of synchronous primary lung adenocarcinomas (SPLA). Given progress in diagnostic imaging techniques and adenocarcinoma classification systems, we analyzed surgical outcomes in a recent series of patients with SPLA. Our main objective was to define appropriate methods and criteria for diagnosis and selection of surgical procedures on the basis of the outcomes of surgical therapy for patients with SPLA.

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Patients and Methods

This retrospective study was approved by the Ethics Committee of Kanagawa Cancer Center. Among 2,041 consecutive patients with primary lung cancer who underwent surgical resection in our hospital from April 1995 through December 2009, we studied patients with a pathologically confirmed diagnosis of SPLA who underwent complete surgical resection. Patients who had adenocarcinoma admixed with other histologic types were excluded from the study.

Preoperative evaluation included chest radiography, thin-section CT (TSCT) of the chest and upper abdomen, and positron emission tomography-CT. An expert consensus meeting attended by specialists from the fields of respiratory medicine, surgery, and diagnostic radiology was convened to evaluate preoperative findings. Patients with clinical (c) N2 disease were excluded from surgery. If patients had a mediastinal lymph node 1 cm or greater on the short axis on TSCT and a positive finding was identified on positron emission tomography-CT, mediastinoscopy or endobronchial ultrasonography was performed for histologic confirmation. Actually, because all patients in this study were cN0 or N1, no patients were offered endobronchial ultrasonography or mediastinoscopy.

Imaging features of the tumors, the presence or absence of ground-glass opacity (GGO), and tumor disappearance rates (TDR) were evaluated on TSCT. To calculate TDR, the maximum tumor diameter was measured on the lung window image (A) and the mediastinal window image (B), and TDR was calculated by the following formula: $(A - B) / A \times 100$ [12]. In our study, the CT features of tumors were classified into the following three subgroups according to the imaging features of the tumors and the TDR: pure GGO, entire nodules show GGO with a TDR of 100%; mixed GGO, nodules show some consolidation in GGO with a TDR of more than 25%; and solid, nodules consist mainly of consolidation with a TDR of 25% or less.

The same team of surgeons performed all resections. Surgical procedures were selected based on the size, location, and TSCT features of tumors, as well as performance status and pulmonary function. Solid and mixed GGO tumors were usually resected by lobectomy and pure GGO tumors by segmentectomy or wedge resection. For patients with poor pulmonary reserve or performance status, segmentectomy or wedge resection was selected instead of lobectomy.

The pathologic criteria for diagnosis of SPLA in our hospital are based on the Martini-Melamed criteria [13] and incorporate elements of the new international multidisciplinary lung adenocarcinoma classification [14] (Table 1). Patients with adenocarcinoma in situ and those with minimally invasive adenocarcinoma were included in analysis, but those with atypical adenomatous hyperplasia were excluded. For the analysis of survival rates according to the histologic type, adenocarcinoma in situ, minimally invasive adenocarcinoma, and the lepidic predominant subtype of invasive adenocarcinoma were included in the "lepidic predominant" subtype.

The disease stage was reclassified according to the seventh edition of the TNM classification [15]. Each tumor was staged, and the most advanced disease stage of all tumors was used as the disease stage of the patient. Tumor size on pathologic examination and CT features of the largest tumor and second tumor were included in the analysis. Postoperative adjuvant chemotherapy was mainly indicated for patients with pathologic (p) stage II or more advanced disease, and data on these patients were included in analysis.

Table 1. Pathologic Criteria for Diagnosis of Synchronous Primary Lung Adenocarcinomas

1. Major histologic subtypes of tumors are significantly different.
2. Major histologic subtypes are similar, but all tumors have lepidic growth component to a certain proportion, or immunohistologic features or genetic profiles of tumors are different.

Overall survival (OS) and recurrence-free survival were defined, respectively, as the time from initial surgery to the date of death and the date of recurrence or the final follow-up visit. Survival curves were calculated by the Kaplan-Meier method, and log rank tests were used for univariate analysis. Multivariate analysis was performed using a Cox proportional hazards model. Clinicopathologic features were compared according to tumor distribution with the use of Pearson's c^2 test. All p values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS 11.0.1 software (SPSS, Chicago, IL).

Results

During the study period, synchronous primary lung cancers were diagnosed in 111 patients. Of these patients, 93 (4.6% of 2,041 patients undergoing resection of NSCLC) with SPLA were included in the study. The other 18 patients had other histologic types of tumors—adenocarcinoma plus squamous cell carcinoma in 8, squamous cell carcinoma plus squamous cell carcinoma in 3, adenocarcinoma plus other histologic types of cancer (large cell neuroendocrine carcinoma, pleomorphic carcinoma, and so forth) in 3, squamous cell carcinoma plus other types of cancer in 3, and a mixture of other histologic types in 1—and were excluded.

Patient Demographics

Demographic characteristics of the patients are shown in Table 2. Median age at the time of initial surgery was 68 years. There were 36 men (39%) and 33 smokers (36%). We confirmed that SPLA is more common among women and nonsmokers than lung cancer in general. The preoperative serum carcinoembryonic antigen level was elevated ($\geq$ 5.0 ng/mL) in 13 patients (14%).

Tumor Characteristics

Tumor characteristics are shown in Table 2. The number of tumors was 2 in 71 patients (76%), 3 in 18 patients (19%), and 4 or 5 in 4 patients (4%). The size of the largest tumor ranged from 10 mm to 57 mm (median 23). The tumor distribution was ipsilateral in 67 patients (same lobe, 31; different lobes of the ipsilateral lung, 36) and bilateral in 26.

Table 2. Patient Characteristics and Clinicopathologic Features

Characteristics	n (%) or Median (range)
Age	68 (49–84)
Sex	
Male	36 (39)
Female	57 (61)
Smoking status	
Current and former	33 (36)
Never	60 (65)
Preoperative CEA elevation, ≥ 5.0 ng/mL	13 (14)
Number of tumors	
2	71 (76)
3	18 (19)
4 or 5	4 (4)
Size of the largest tumor, mm	23 (10–57)
Distribution of tumors	
Ipsilateral same lobe	31 (33)
Ipsilateral different lobe	36 (39)
Bilateral	26 (28)
CT features of tumors, largest + second	
Solid + solid	11 (12)
Solid + mixed GGO	11 (12)
Solid + pure GGO	8 (9)
Mixed GGO + solid	8 (9)
Mixed GGO + mixed GGO	24 (26)
Mixed GGO + pure GGO	26 (28)
Pure GGO + mixed GGO	2 (2)
Pure GGO + pure GGO	3 (3)
Clinical stage	
I	87 (94)
II	5 (5)
IIIA[a]	1 (1)
Pathologic stage	
I	75 (81)
II	9 (10)
IIIA[b]	9 (10)
Histologic subtypes of the largest tumor	
Lepidic predominant[c]	63 (68)
Acinar predominant	10 (11)
Papillary predominant	10 (11)
Micropapillary predominant	3 (3)
Solid predominant	7 (8)

[a] One patient was cT3N1. [b] Eight patients were pT1-2N2 and 1 patient was pT3N1. [c] Adenocarcinoma in situ (n = 24) and minimally invasive adenocarcinoma (n = 11) were included.

CEA = carcinoembryonic antigen; CT = computed tomography; GGO = ground-glass opacity.

The CT features of the largest tumor were mixed GGO in 58 patients, solid pattern in 30, and pure GGO in 5. One or more solid lesions were present in 38 patients (41%).

Pathologic Findings

Pathologic findings are also shown in Table 2. The histologic subtype of the largest tumor was lepidic predominant in 63 patients (68%). The 1 patient with c-stage IIIA disease had T3 N1 cancer. Lymph node metastasis was found in 18 patients (19%); 10 had pN1 disease, and 8 had pN2 disease.

Surgical Procedures

Among the 26 patients with bilateral tumors, one-stage bilateral operations were performed in 6 patients, and two-stage bilateral operations in 20 (Table 3). One patient (1%) underwent pneumonectomy. Sublobar resection (wedge resection and segmentectomy) was included in treatment procedures for 54 patients (58%).

Surgical Outcomes

The follow-up period ranged from 8.1 to 198.1 months (median 56.0). At final follow-up, 12 patients (13%) had died, and 81 (87%) were alive. There was no perioperative death. Twelve patients died in the late phase; the cause of death was lung cancer in 9 patients, postoperative chronic empyema in 1, flare-up of tuberculosis in 1, and unknown in 1. The 3-year and 5-year OS rates were 93.6% and 87.0%, respectively (Fig 1). Recurrence developed in 17 patients (18%). The initial site of recurrence was intrapulmonary metastasis in 7 patients, lymph node metastasis in 5, distant metastasis in 3, pleural dissemination in 1, and recurrence at the resection stump in 1. All patients with pN2 disease had recurrence. The 3-year and 5-year recurrence-free survival rates were 89.2% and 81.8%, respectively (Fig 1).

Table 4 shows the results of univariate analysis of factors related to OS. The presence of lymph node metastasis ($p = 0.0000$), a nonlepidic predominant subtype of the largest tumor ($p = 0.0018$), and solid CT features of the largest tumor ($p = 0.0088$) were significantly related to poor outcomes. Bilateral tumors ($p = 0.0950$) and pathologic T2 to T3 disease ($p = 0.0885$) were slightly, but not significantly, related to poor outcomes. On multivariate analysis including the surgical procedure and tumor distribution in addition to the three significant factors identified on univariate analysis, the presence of lymph node metastasis

Table 3. Operative Details (n = 93)

Distribution and Type of Resection	n
Ipsilateral	
Pneumonectomy	1
Bilobectomy	5
Lobectomy	28
Lobectomy + segmentectomy	3
Lobectomy + wedge	14
Segmentectomy + segmentectomy	1
Segmentectomy + wedge	4
Multiple wedges	11
Bilateral	
Lobectomy + lobectomy	5
Lobectomy + segmentectomy	5
Lobectomy + wedge	5
Segmentectomy + wedge	5
Multiple wedges	6

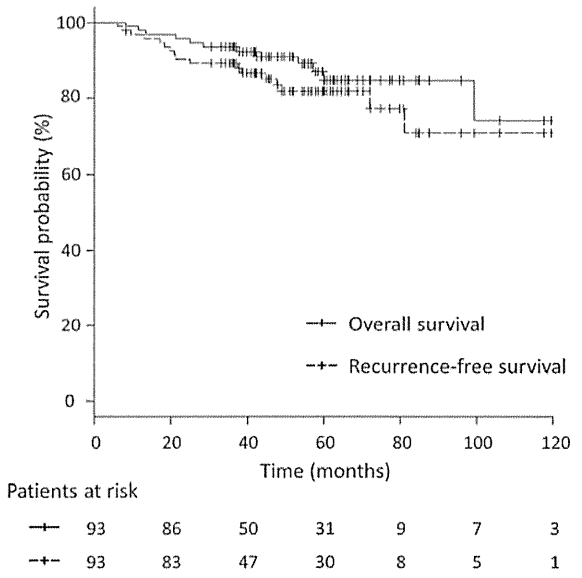

Fig 1. Overall survival (solid line) and recurrence-free survival (dashed line) of 93 patients with synchronous primary lung adenocarcinomas who underwent surgical resection. Five-year rates were 87.0% and 81.8% for overall and recurrence-free survival, respectively.

($p = 0.004$), bilateral distribution of tumors ($p = 0.031$), and the use of sublobar resection ($p = 0.042$) were independent predictors of poor survival (Table 5).

Comment

When we encounter patients with multiple tumors in the lung in clinical practice, it is extremely difficult to distinguish SPLA from intrapulmonary metastasis. The Martini-Melamed criteria [13] have been widely used for differential diagnosis in previous studies. Tumors of the same histologic type that arise in the same segment of the lung are diagnosed as intrapulmonary metastasis. Even if different segments are involved, tumors of the same histologic subtype are diagnosed as intrapulmonary metastasis if metastasis is found at shared lymphatic pathways. However, in the current era of genetic analysis of factors such as epidermal growth factor receptor, SPLA involving multiple lobes of the same lung and accompanied by mediastinal lymph node metastasis have been reported [16]. In addition to the Martini-Melamed criteria, it is therefore necessary to evaluate other factors for diagnosis of this type of cancer. In patients with multiple adenocarcinomas, the histologic subtypes of the tumors must be considered. The recently proposed comprehensive histologic assessment has facilitated the differential diagnosis of multiple primary NSCLC and metastases [17]. However, the problem remains that lepidic predominant primary tumors are likely to be diagnosed as intrapulmonary metastasis if the histologic subtype ratio is similar. Recently, there has been an increasing trend in multiple tumors showing GGO, particularly among nonsmoking women in Asia. Such lesions are likely to be

Table 4. Univariate Analysis of Predictors of Survival

Predictors	n	Overall 5-Year Survival	p Value
Age, years			
< 70	53	83.8%	0.9152
≥ 70	40	92.0%	
Sex			
Male	36	77.4%	0.1265
Female	57	93.1%	
Smoker			
Current and former	33	81.8%	0.6533
Never	60	90.0%	
Preoperative serum CEA, ng/mL			
< 5.0	80	90.0%	0.2167
≥ 5.0	13	68.4%	
Size of the largest tumor, mm			
≤ 30	72	84.5%	0.2365
> 30	21	95.2%	
CT features of the largest tumor			
Solid	30	75.6%	0.0088
Mixed and pure GGO	63	92.5%	
Distribution of tumors			
Ipsilateral	67	90.9%	0.0950
Bilateral	26	76.9%	
Number of tumors			
2	71	90.7%	0.3327
≥ 3	22	71.1%	
Highest pT			
T1	66	90.7%	0.0885
T2–3	27	78.6%	
Highest pN			
N0	75	93.4%	0.0000
N1	10	75.0%	
N2	8	41.7%	
Surgical procedures			
Lobectomy	39	92.5%	0.5086
Sublobar included			
Segmentectomy[a]	18	82.1%	
Wedge resection	36	80.4%	
Mediastinal LN management			
Systematic dissection	36	83.3%	0.9118
Sampling	20	80.0%	
Not dissected	37	88.5%	
Histologic subtype of the largest tumor			
Lepidic predominant	63	98.4%	0.0018
Nonlepidic predominant	30	66.9%	
Adjuvant chemotherapy[b]			
Yes	6	83.3%	0.7050
No	12	50.0%	

[a] Nine patients who underwent segmentectomy and wedge resection were included. [b] Eighteen patients with p-stage II or greater disease were included.

CEA = carcinoembryonic antigen; CT = computed tomography; GGO = ground-glass opacity; LN = lymph node.

Table 5. Multivariate Analysis of Predictors of Survival

Variables	n	p Value	Hazard Ratio (95% CI)
CT features of the largest tumor			
Solid/mixed and pure GGO	30/63	0.200	0.421 (0.112–1.582)
Distribution of tumors			
Bilateral/ipsilateral	26/67	0.031	4.630 (1.148–18.666)
Lymph node involvement			
Yes/no	18/75	0.004	10.560 (2.142–52.076)
Use of sublobar resection			
Yes/no	54/39	0.042	4.425 (1.054–18.580)
Predominant histology			
Lepidic/nonlepidic	63/30	0.261	2.395 (0.552–10.982)

CI = confidence interval; CT = computed tomography; GGO = ground-glass opacity.

classified as intrapulmonary metastasis. However, tumors with a high GGO ratio are most likely not intrapulmonary metastasis [18]. The diagnostic criteria for multiple lung adenocarcinomas in our hospital have taken this point into account. The good treatment outcomes in our study might have been attributed to the exclusion of patients with intrapulmonary metastasis, which is associated with a poor prognosis.

To our knowledge, this is the second largest, relatively long-term follow-up study of surgical outcomes in patients with SPLA [8]. The 5-year OS rate in our study was 87.0%, which is considered extremely good. Several factors were related to outcomes, and lymph node metastasis had the greatest impact. Previous studies have similarly reported that the presence or absence of lymph node metastasis is a significant prognostic factor [2, 3, 8, 10, 19, 20]. In our study, however, 5-year survival rates were 75.0% for patients with pN1 disease and 41.7% for patients with pN2 disease, better rates than those reported by the International Association for the Study of Lung Cancer lung cancer staging project (38% for pN1 disease, 22% for pN2 disease) [21]. The specialized design of our study in patients with adenocarcinoma might have contributed to better outcomes.

The Martini-Melamed criteria classify cases with N2 nodal involvement as intrapulmonary metastasis, but not multiple cancers. Some studies have excluded patients with N2 disease from the analysis of surgical outcomes [5, 9, 22]. In contrast, because we performed detailed histologic subtyping synchronous primary lung cancers could be diagnosed even in the presence of N2 disease. We, therefore, could obtain a better overall picture of the outcomes of surgical treatment for synchronous primary lung cancers.

Curative chemoradiotherapy is basically indicated for patients with cN2 disease. In our study, 8 cases of pN2 disease (ipsilateral, 4; bilateral, 4) were detected by chance on postoperative pathologic examination. Unexpected pN2 disease was thus detected in approximately 10% of patients, a finding that is generally consistent with the findings of previous studies. Of these patients with bilateral disease, pN2 disease was diagnosed on the second of two-stage bilateral resections in 2 patients and on one-stage bilateral surgery in 1 patient. For patients who underwent two-stage surgery, the side with more advanced lesions or with lesions likely to negatively affect outcomes is usually initially resected. In fact, however, half of all more advanced lesions were not resected at the first operation.

Synchronous surgery for bilateral tumors is considered an effective strategy for preventing disease progression and delays in adjuvant therapy in patients with clinical N0 to pathologic N2 disease. However, synchronous bilateral lobectomy with lymph node dissection is associated with increased risk and therefore should only be performed in carefully selected patients. Given the treatment outcomes in patients with pN2 disease, if N2 disease is detected at the first stage of two-stage resection, treatment options such as chemotherapy and stereotactic body radiotherapy should be also considered instead of performing lobectomy at the second stage.

The relations between surgical procedures and outcomes have been extensively studied. A number of studies have reported no difference in survival according to whether sublobar resection was performed [3, 5, 6, 10, 22]. In our study, sublobar resection was a significant independent predictor of poor outcomes on multivariate analysis. This result is attributed to a negative impact of sublobar resection on curability. In our study, 59% of the patients had tumors with a high GGO ratio, which are associated with relatively good outcomes. The latest American College of Chest Physicians evidence-based clinical practice guidelines recommend that these lesions should be handled separately as multifocal lung cancer and patients should undergo sublobar resection because single tumors with a high GGO ratio have good outcomes [18]. However, clear-cut criteria defining lesions that should be treated by sublobar resection are currently unavailable. Imaging findings of tumors may be useful for determining the range of resection. As shown in our study and previous reports [12, 23, 24], mixed or pure GGO lesions had a high TDR and good outcomes, whereas solid lesions were associated with poor outcomes. Therefore, solid lesions should be treated by radical lobectomy if permitted by lung function.

Interestingly, bilateral tumors were an independent predictor of poor outcomes in our study. Previous studies have reported that OS does not differ significantly according to tumor distribution [3, 8–10]. In contrast to our results, some studies reported that bilateral tumors were associated with significantly better outcomes [2, 20]. To investigate reasons for the poorer outcomes in patients with bilateral tumors, we studied differences in clinicopathologic factors related to tumor distribution. Bilateral tumors were found to be associated with a higher preoperative carcinoembryonic antigen level, a greater number of tumors, a larger size of the second tumor, and a higher proportion of patients who underwent sublobar resection (Table 6). These findings indicate that many of our subjects with bilateral tumors had aggressive disease, and this factor might have led to the difference in outcomes. Moreover, because patients with bilateral tumors had many lesions, it was difficult to perform lobectomy for all lesions. This factor may have also contributed to poorer outcomes.

Table 6. Correlation Between Tumor Distribution and Other Clinicopathologic Features

Variables	Ipsilateral	Bilateral	p Value
CT features of the largest tumor			
Solid	22	8	1.000
Mixed and pure GGO	45	18	
Preoperative serum CEA, ng/mL			
< 5.0	61	19	0.032
≥ 5.0	6	7	
Tumor size of the largest tumor, mm			
≤ 30	47	21	0.221
> 30	20	5	
Tumor size of the second tumor, mm			
≤ 20	62	18	0.007
> 20	5	8	
Number of tumors			
2	56	15	0.011
≥ 3	11	11	
Pathologic stage			
Stage I	53	22	0.388
Stage II–III	14	4	
Highest pN			
N0–1	63	22	0.213
N2	4	4	
Surgical procedures			
Lobectomy	34	5	0.009
Sublobar included	33	21	

CEA = carcinoembryonic antigen; CT = computed tomography; GGO = ground-glass opacity.

Finally, our study had several limitations. First, patient selection was biased because this was a single-center, retrospective study. Second, molecular phenotype such as epidermal growth factor receptor mutation was not assessed in all patients at the diagnosis of multiple lung adenocarcinomas. Finally, we did not compare patients with SPLA who underwent surgery with patients who did not undergo surgery or with patients who underwent only incomplete resection. However, because our study was a single-center trial, treatment policy, surgical procedures, postoperative care, and histopathologic evaluations were standardized. We believe that these conditions led to high-quality data.

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Prognosis of Lung Cancer Patients with a Past History of Colorectal Cancer

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Objectives: The prognosis in lung cancer patients with a prior history of extrapulmonary cancer is controversial. In the current multicenter joint research in Japan, we focused on the relationship between a history of colorectal cancer and its prognostic impact in patients with subsequent lung cancer.

Methods: Between 2000 and 2013, we designed a retrospective multicenter study at three institutes in Japan to evaluate the prognostic factors in lung cancer patients with a previous surgery for colorectal cancer.

Results: The cohorts consisted of 123/4431 lung cancer patients with/without a previous history of surgery for colorectal cancer. The median follow-up period was 6.1 years after lung cancer surgery. The 5-year overall survival in lung cancer patients with/without colorectal cancer was not significantly different, regardless of the stage of lung cancer (overall: 71.3 versus 74.7%, $P = 0.1426$; Stage I lung cancer: 83.3 versus 84.8%, $P = 0.3779$; Stage II or more lung cancer: 47.7 versus 54.4%, $P = 0.1445$). Based on multivariate Cox regression analysis in 4554 lung cancer patients, a past history of colorectal cancer was not a significant prognostic factor ($P = 0.5335$). Among the 123 lung cancer patients with colorectal cancer, age and absence of adjuvant chemotherapy for colorectal cancer were significant prognostic factors based on multivariate analysis ($P = 0.0001$ and 0.0236). Furthermore, there was no difference in the overall survival of lung cancer patients according to the stage of colorectal cancer (Stage I: 74.7%; Stage II/III: 66.5%, $P = 0.7239$).

Conclusions: A history of antecedent colorectal cancer did not contribute to the prognosis in patients with subsequent lung cancers.

Key words: lung cancer – colorectal cancer – multiple primary cancers – prognosis

INTRODUCTION

Lung cancer is the most frequent cause of major cancer and the leading cause of death worldwide (1,2). Due to recent developments in imaging technology and the widespread use of thin-section computed tomography (CT) for the screening of lung cancer, it is expected that the incidence of lung cancer will increase as a direct result of screening examinations (3). Furthermore, this will lead to an increase in the identification of early-stage lung cancers and a consequent later decrease in mortality.

The risk of developing a new malignancy in patients with an unrelated previous cancer has been reported to be 5–15

times higher than that in the general population (4). As a result of the increasing incidence of any cancers due to improved treatment modalities and long-term survival worldwide (5), we often encounter newly detected lung cancer patients with a prior history of extrapulmonary cancers, especially gastrointestinal lesions (6–10). Among these, colorectal cancer accounts for a high percentage of both incidence and death worldwide and is associated with lung cancer as a multiple primary malignancy (11–13). Many studies have reported several clinical, radiological, pathological and molecular factors that predict the prognosis in lung cancer patients (2,14,15). However, despite remarkable advances in our understanding of lung cancer over the past decade, it is not yet clear whether a history of previous treatment for any other cancers, especially colorectal cancers, affects the prognosis of surgery for lung cancer. In this study, we highlighted colorectal cancer, because it is a common malignancy and fatality rates are high (13). The incidence of multiple primary cancers in patients with colorectal cancer is ~15–20%, and the incidence of lung cancer is the second next to stomach cancer of these patients in the past literature (12). On the other hand, a few studies have addressed the clinical behavior and survival of small cohorts of patients with non-small cell lung cancer who had previously been treated for colorectal cancer. Thus, we evaluated the survival and prognostic factors of lung cancer patients with the past history of colorectal cancer.

At any single institution, the number of patients with a previous history of colorectal cancer is relatively small. Therefore, the purpose of this study was to investigate the clinicopathological impact of preceding surgery for colorectal cancer in patients with lung cancer by multi-institutional joint research in Japan.

PATIENTS AND METHODS

Approval

This was a multi-institutional joint research study (Juntendo University School of Medicine, IRB No. 13–133; National Cancer Center Hospital East, IRB No. 2013-106; Hiroshima University Hospital, IRB No. eki-862). The study protocol was approved by the institutional review boards of the three participating institutes. Due to a retrospective study, the need to obtain written informed consent from each patient was waived.

Patients

Based on their cancer history, patients were categorized as either lung cancer patients with previous surgery for colorectal cancer, or those without a history of colorectal cancer. A history of colorectal cancer was confirmed when they were diagnosed or treated for lung cancer at our institutes, otherwise documentation was obtained from other hospitals or clinics. Between January 2000 and June 2013, there were 123 lung cancer patients with a history of preceding surgery for colorectal cancer at our three institutes. The sufficient information regarding their history of colorectal cancer was included in the primary analysis as lung cancer patients with a history of preceding surgery for colorectal cancer. In contrast, we enrolled 4431 lung cancer patients without a history of colorectal cancer as a control group. All patients underwent surgical operation for lung cancer at each institute.

Demographic Data

In all cases, the medical record of each patient was reviewed with regard to age, gender, serum carcinoembryonic antigen level (ng/ml, CEA) and several clinicopathological characteristics to evaluate the prognostic factors and elucidate whether the treatment history for colorectal cancer influences the prognosis of subsequent lung cancer surgery. The clinical and pathological stages of each disease were determined based on the International Union Against Cancer, 7th edition (16).

Operation Policy

Regarding the operative modes for lung cancer, each institute had a consensus that major lung dissection with systemic lymph node dissection is the standard procedure for resectable non-small cell lung cancer despite a previous history of colorectal cancer. Segmentectomy is indicated in part for lung cancers 2 cm or less in size with ground-glass opacity dominant lesion. Nonanatomic wedge resection is also performed for a few elderly patients or for patients with high cardiopulmonary risk.

Statistics

In the statistical analysis, the Chi-square test or unpaired *t*-test were used to compare two factors. Cumulative survival rates for each group, i.e. lung cancer patients with or without a history of colorectal cancer, were calculated by the Kaplan–Meier method, where the date of surgical resection for lung cancer was used as the starting point and the date of death due to any cause or the date of the last follow-up was used as the end point. The interoperative interval was calculated from the date of surgical resection for colorectal cancer to that for lung cancer. Univariate and multivariate analyses were used to identify clinicopathological factors that significantly predicted the prognosis in patients with or without preceding surgery for colorectal cancer. A univariate analysis was performed by the log-rank test. A multivariate analysis was performed by the Cox proportional hazard model using SPSS Statistics 21 (SPSS Inc.). Forward and backward stepwise procedures were used to determine the combination of factors that were essential for predicting the prognosis. Continuous data are shown as the mean and standard deviation for normality. The results of the statistical analysis were considered to be significant when the probability value was <0.05.

RESULTS

The clinicopathological characteristics of the entire population are shown in Table 1. The average age was 70 years (range, 46–89) in patients with colorectal cancer, and 66 years (range, 20–93) in those without colorectal cancer ($P < 0.0001$). Among the 123 lung cancer patients with colorectal cancer, 91 (74.0%) were men and 32 (26.0%) were women, whereas among the 4431 patients without colorectal cancer, 2713 (61.2%) were men and 1718 (38.8%) were women, and this was a significant difference between the groups ($P = 0.0041$). With regard to the clinical stage of lung cancer, the patients with the past history of colorectal cancers showed significantly early-stage disease of lung cancer ($P = 0.0039$). A previous history of any organ cancer, including colorectal cancer, was observed in 473 (10.4%) of the total patients. The median follow-up period among the overall patients was 6.1 years after lung cancer surgery (range, 0–11.8 years). In lung cancer patients with a past history of colorectal cancer, the median time interval from the date of operation for colorectal cancer to that for lung cancer was 2.4 years (range, 0–25.1 years). The frequencies of adjuvant chemotherapy for lung cancer and the absence of malignancies other than lung and colorectal cancer were significantly higher in lung cancer patients without a history of colorectal cancer ($P = 0.0014$ and 0.0022, respectively).

Based on univariate and multivariate analyses in 4554 patients with surgically resected lung cancers, gender, age at lung cancer surgery, the presence of any cancers other than those of the lung and colorectum, the pathological stage of lung cancer and the administration of adjuvant chemotherapy for lung cancer were significant prognostic factors in this population, whereas a history of surgery for colorectal cancer was not a predictor in multivariate analysis ($P = 0.7793$) (Table 2).

The overall survival (OS) curves of the populations with and without colorectal cancer are presented in Fig. 1. As shown in Table 2, significant differences were not observed between these two groups; however, the 5-year OS in lung cancer patients with colorectal cancer (71.3%) was slightly inferior to that in patients without colorectal cancer (74.7%) ($P = 0.1426$). Moreover, we evaluated the OS of lung cancer patients with and without colorectal cancer based on the lung cancer staging. According to the results, the OS was not significantly different regardless of the presence of colorectal cancer in patients with both pathological Stage I and Stage II or more lung cancer [Stage I lung cancer (Fig. 2, $n = 3092$): with colorectal cancer = 83.3%, without colorectal cancer = 84.8%, $P = 0.3779$; Stage II or more lung cancer (Fig. 3, $n = 1462$): with colorectal cancer = 47.7%, without colorectal cancer = 54.4%, $P = 0.1445$].

The clinicopathological characteristics of lung cancer patients with a previous surgery for colorectal cancer are shown in Table 3. Of the 123 patients, 66 (53.7%) showed colorectal cancer of pathological Stage I. The mean interoperative interval from colorectal cancer to lung cancer was 3.9 ± 4.4 years (range, 0–25.1 years). Adjuvant chemotherapy for colorectal cancer was administrated to 33 (26.8%) patients. With regard to the cause of death, death due to lung

Table 1. Clinicopathological characteristics of all lung cancer patients

Factors	Overall lung cancer patients		*P* value*
	With colorectal cancer (%)	Without colorectal cancer (%)	
Total	123	4431	
Average age (year)	70	66	<0.0001
Gender			
Male	91 (74.0)	2713 (61.2)	0.0041
Female	32 (26.0)	1718 (38.8)	
CEA (ng/ml)	6.8 ± 9.3	8.9 ± 65.4	0.7253
Clinical stage of lung cancer			
IA	74 (60.2)	2463 (55.6)	0.0039
IB	31 (25.2)	1006 (22.7)	
IIA	9 (7.4)	319 (7.2)	
IIB	3 (2.4)	263 (5.9)	
IIIA	3 (2.4)	334 (7.5)	
IIIB	0 (0)	21 (0.5)	
IV	3 (2.4)	25 (0.6)	
Pathological stage of lung cancer			
IA	65 (52.8)	2162 (48.8)	0.5283
IB	23 (18.7)	842 (19.0)	
IIA	7 (5.7)	379 (8.5)	
IIB	12 (9.8)	292 (6.6)	
IIIA	14 (11.4)	603 (13.6)	
IIIB	0	106 (2.4)	
IV	2 (1.6)	47 (1.1)	
Surgical procedures for lung cancer			
Wedge	13 (10.6)	329 (7.4)	0.3306
Segmentectomy	13 (10.6)	315 (7.1)	
Lobectomy	95 (77.2)	3635 (82.0)	
Pneumonectomy	3 (2.4)	152 (3.4)	
Histology of lung cancer			
Adenocarcinoma	90 (73.2)	3173 (71.6)	0.9093
Squamous cell carcinoma	23 (18.7)	899 (20.3)	
Others	10 (8.1)	359 (8.1)	
Adjuvant chemotherapy for lung cancer			
Yes	15 (12.2)	1098 (24.8)	0.0014
No	108 (87.8)	3333 (75.2)	
Cancers other than those of lung and colorectum			
Presence	23 (18.7)	450 (10.2)	0.0022
Absence	100 (81.3)	3981 (89.8)	

CEA, carcinoembryonic antigen.
*P value in the Chi-square test or unpaired t-test.

Table 2. Univariate and multivariate analysis of overall survival in 4554 patients with lung cancer

Covariate	Univariate	Multivariate		
	P value*	HR	95% CI	*P* value*
Gender (female)	<0.0001	0.615	0.527–0.717	<0.0001
Age at lung cancer surgery (year)	<0.0001	1.032	1.025–1.040	<0.0001
CEA (ng/ml)	0.1896	1.000	1.000–1.001	0.2862
Cancers other than those of the lung and colorectum (absence)	<0.0001	0.625	0.515–0.758	<0.0001
Pathological stage of lung cancer (pathological Stage I)	<0.0001	0.234	0.204–0.272	<0.0001
Adjuvant chemotherapy for lung cancer (absence)	<0.0001	0.726	0.617–0.855	0.0001
Surgery for colorectal cancer (absence)	0.1439	0.949	0.730–1.520	0.7793

CI, confidence interval; HR, hazard ratio.
**P* value in the Cox proportional hazard model.

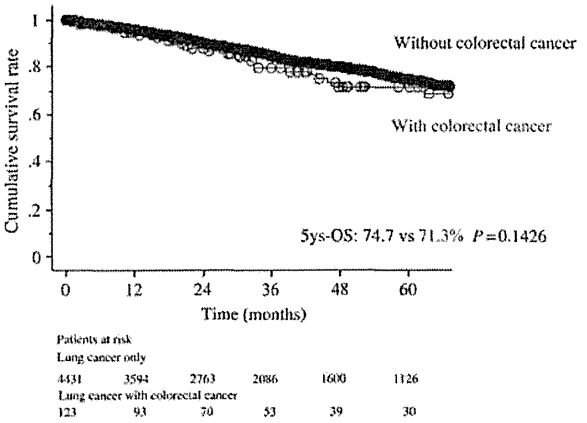

Figure 1. Overall survival curve for all lung cancer patients with and without a previous history of colorectal cancer. A statistically significant difference was not observed between the outcomes of the two groups (log-rank test, $P = 0.1426$). OS, overall survival.

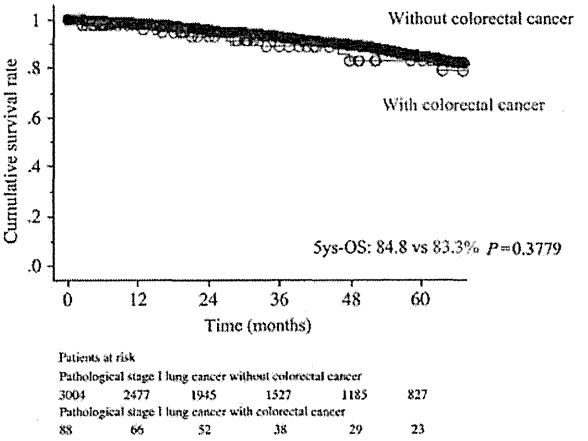

Figure 2. OS curve for pathological Stage I lung cancer patients with and without a previous history of colorectal cancer. A statistically significant difference was not observed between the outcomes of the two groups (log-rank test, $P = 0.3779$).

cancer was observed in 18 patients, whereas only 1 patient died because of the recurrence of colorectal cancer.

Based on multivariate analysis for lung cancer patients with previous surgery for colorectal cancer, age at the operation for lung cancer and the absence of adjuvant chemotherapy for colorectal cancer were significant prognostic factors ($P = 0.0001$ and 0.0236, respectively) (Table 4). We excluded these two prognostic factors from the cohort of patients with colorectal cancer and re-evaluated the OS. Based on the results, the 5-year OS for all lung cancer patients with colorectal cancers, excluding those >76 years old (the 5-year OS = 77.0%, $P = 0.8499$), and excluding those who were given adjuvant chemotherapy for colorectal cancer (the 5-year OS = 76.0%, $P = 0.4434$) compared with those in patients without colorectal cancer (the 5-year OS = 74.7%) were almost equivalent.

With regard to the OS of lung cancer patients with colorectal cancer based on their pathological status, the 5-year OS of lung cancer patients with pathological Stage I colorectal cancer (74.7%) was better than that of lung cancer patients with pathological Stage II or III colorectal cancer (66.5%), although a significant difference was not observed with regard to the stage of colorectal cancer (Fig. 4; $P = 0.7239$). Furthermore, we evaluated the prognostic factors for OS in lung cancer patients with a previous surgery for pathological Stage I colorectal cancer ($n = 66$). Based on multivariate analysis, age at the operation for lung cancer and the recurrence of colorectal cancer were significant prognostic factors in these populations ($P = 0.0298$ and 0.0285, respectively) (Table 5).

DISCUSSION

Colorectal carcinoma is one of the most frequent major cancers that are seen with lung cancer (8,11,12,17), but the

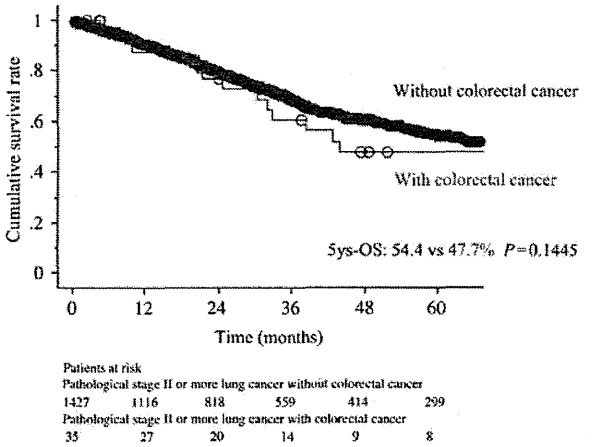

Figure 3. OS curve for pathological Stage II or more lung cancer patients with and without a previous history of colorectal cancer. A statistically significant difference was not observed between the outcomes of the two groups (log-rank test, $P = 0.1445$).

Table 3. Clinicopathological characteristics of lung cancer patients with a previous surgery for colorectal cancer

	Number of patients (%)
Pathological stage of colorectal cancer	
Stage I	66 (53.7)
Stage II or more	57 (46.3)
Interoperative interval from colorectal cancer to lung cancer	
Within 5 years	87 (70.7)
>5 years	36 (29.3)
Treatment methods for colorectal cancer	
Endoscopic resection	30 (24.4)
Surgery	93 (75.6)
Adjuvant chemotherapy for colorectal cancer	
Presence	33 (26.8)
Absence	90 (73.2)
Recurrence of colorectal cancer	
Presence	4 (3.3)
Absence	119 (96.7)
Cause of death	
Lung cancer	18 (62.1)
Colorectal cancer	1 (3.4)
Other diseases	10 (34.5)

clinicopathological features and the impact of past cancer history on the prognosis of lung cancer have been barely validated. Because the number of lung cancer patients complicated with a previous history of colorectal cancers is increasing, there is an urgent need for a study on this topic. In the current retrospective multicenter study, we focused on the relationship between a history of antecedent colorectal cancer and its prognostic impact in patients with subsequent lung cancer.

With regard to the presence of a past history of any cancers within the previous 5 years in patients with lung cancer, one of the most important points is that this is considered to be an indispensable exclusion criterion in many prospective trials in lung cancer, which could result in a reduction in enrolling the possible candidates. Some reports have indicated that lung cancer patients with preceding cancers in other organs have a poor prognosis (8–10). However, the clinicopathological features of and prognosis in lung cancer patients with a prior history of cancer are not fully resolved yet. Furthermore, recent developments in imaging technology and the widespread use of thin-section CT for screening have made it possible to detect early-stage lung cancers (2,18). Amid a paradigm shift regarding the stage of lung cancer patients, little information is available regarding the prognostic factors in lung cancer patients combined with a previous surgery for some other malignancy, especially for major cancers like cancers of the colon and rectum.

Based on our study, a history of previous surgery for colorectal cancer did not contribute to the prognosis in the overall lung cancer patients. Furthermore, multivariate analysis revealed that age at lung cancer surgery and the absence of adjuvant chemotherapy for colorectal cancer were significant prognostic factors in 123 lung cancer patients with a previous surgery for colorectal cancer. In this study, the frequencies of lung cancer death, colorectal cancer death and cancer non-related death are almost equivalent in lung cancer patients with a past history on colorectal cancer, despite the presence or absence of adjuvant chemotherapy for colorectal cancer. However, the patients administrated adjuvant chemotherapy for colorectal cancer belonged to more advanced stage of colorectal cancer, and the general conditions might be inferior to the patients without adjuvant chemotherapy for colorectal cancer, which influenced to the survival of lung cancer patients. These findings might reflect the poor general status of some colorectal cancer patients performed adjuvant chemotherapy. Interestingly, when these prognostic factors were excluded, the OS rates in lung cancer patients with and without colorectal cancer were almost equivalent by the Kaplan–Meier method. These results obtained from the overall cohort were almost the same as those in lung cancer patients with pathological Stage I colorectal cancer based on the multivariate analysis. Some of the results given above are particularly noteworthy. In particular, a history of colorectal cancer may not contribute to the prognosis in patients with subsequent lung cancers if the lung cancer patients are of a suitable age or if their preoperative status could be well managed by surgery for their previous colorectal cancer.

In a recent study, the pathological stage of colorectal cancer was not a significant predictor in patients with subsequent lung cancer. This is partly due to the retrospective nature of this study, and selection of the candidates for a lung cancer

Table 4. Univariate and multivariate analyses of overall survival in lung cancer patients with the preceding surgery for colorectal cancer

Covariate	Univariate	Multivariate		
	P value*	HR	95% CI	*P* value*
Gender (female)	0.2302	0.744	0.283–1.957	0.5940
Age (year)	0.0376	1.138	1.066–1.215	0.0001
CEA (ng/ml)	0.0067	1.021	0.991–1.053	0.1780
Clinical stage of lung cancer (clinical Stage I)	0.0094	0.411	0.152–1.110	0.0793
Cancers other than those of the lung and colorectum (absence)	0.8868	0.470	0.164–1.343	0.1586
Pathological stage of colorectal cancer (pathological Stage I)	0.7241	0.953	0.288–3.151	0.9375
Surgical procedures for colorectal cancer (surgical resection)	0.7969	0.544	0.193–1.531	0.2487
Adjuvant chemotherapy for colorectal cancer (absence)	0.4086	0.224	0.061–0.818	0.0236
Recurrence of colorectal cancer (absence)	0.1615	0.421	0.084–2.118	0.2942
Intraoperative interval from colorectal cancer to lung cancer (within 5 years)	0.6487	0.827	0.332–2.062	0.6840

*P value in the Cox proportional hazard model.

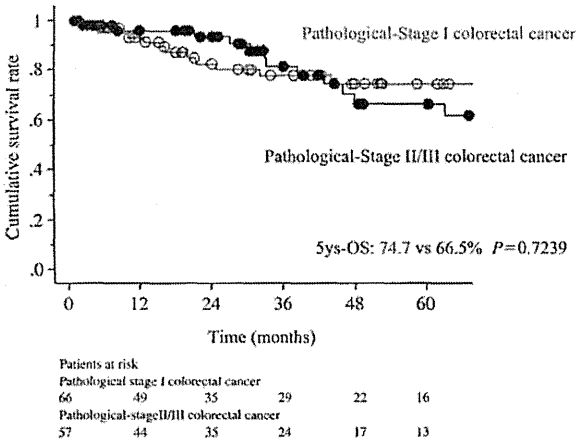

Figure 4. OS curve for lung cancer patients with pathological Stage I or pathological Stage II/III colorectal cancer. A statistically significant difference was not observed between the outcomes of the two groups (log-rank test, $P = 0.7239$).

surgery may be very strict in patients with the history of colorectal cancer. Generally, patients with pathological Stage I or II colorectal cancer have a good prognosis with the 5-year survival rate of ~90% (19). Even pathological Stage IIIA colorectal cancer showed the 5-year survival rate over 70% (19). It is easy to understand that this study population of patients with pathological Stage III colorectal cancers was a relatively minor and may have included many otherwise healthy patients. Furthermore, with the advances in diagnostic modalities such as thin-section CT scan or positron emission tomography, early detection of lung cancer may be possible and also contribute to favorable outcomes by decreasing the risk of uncontrolled colorectal cancer. Therefore, the presence of a past history of colorectal cancer treatment had relatively little effect on lung cancer prognosis if the patients were appropriately selected.

Moreover, with regard to the relationship between a preceding malignancy and subsequent lung cancer, several previous reports described a significant correlation between a history of preceding extrapulmonary malignancy and the early stage of lung cancer (20–22). On the other hand, there seemed to be no close relationship between the pathological stage of colorectal and lung cancer in the current study. If anything, the frequency of pathological Stage I lung cancer in patients with a previous history of pathological Stage II or more colorectal cancers (42/57; 73.7%) was somewhat greater than that in patients with pathological Stage I disease (46/66; 69.7%). These results suggest that more intensive follow-up and examinations are needed for more advanced colorectal lesions compared with early-stage disease.

In this study, the interoperative interval from colorectal cancer to lung cancer did not influence the prognosis of lung cancer patients. We selected 5 years as a cutoff value for the interoperative interval, since this value has often been used as an exclusion criterion in prospective studies worldwide. This lack of a relationship was also supported by multivariate analysis, even when we treated the interoperative interval as a continuous value. These results support our opinion that surgery for lung cancer patients with a previous history of colorectal cancer is feasible in adequately selected cohorts.

A major limitation of this study is its retrospective nature. Patient selection for the surgery of lung cancer may be strict among the presence of a previous history of colorectal cancer in each institute. In addition, although we have standard treatment strategies for lung cancer surgery, the indications for each surgical mode may be somewhat different in each institute in accordance with the patient characteristics. Thus, further prospective studies will be necessary in a larger number of patients. Despite these limitations, however, we

Table 5. Univariate and multivariate analyses of overall survival in lung cancer patients with a previous surgery for pathological Stage I colorectal cancer

Covariate	Univariate	Multivariate		
	P value*	HR	95% CI	*P* value*
Gender (female)	0.6945	1.082	0.243–4.826	0.9176
Age (years)	0.0154	1.105	1.010–1.210	0.0298
CEA (ng/ml)	0.0567	1.018	0.982–1.056	0.3210
Clinical stage of lung cancer (clianical Stage I)	0.0233	0.323	0.075–1.389	0.1286
Malignancies other than colorectal and lung cancer (absence)	0.5198	0.571	0.122–2.667	0.4763
Surgical procedures for colorectal cancer (surgical resection)	0.9631	0.564	0.190–1.672	0.3019
Recurrence of colorectal cancer (absence)	0.0197	0.061	0.005–0.746	0.0285
Intraoperative interval from colorectal cancer to lung cancer (within 5 years)	0.6731	0.988	0.218–3.469	0.9846

*P value in the Cox proportional hazard model.

believe that this study can be helpful in daily clinical practice and in the decision-making process of thoracic surgeons when we encounter lung cancer patients with a history of surgery for colorectal cancer. We believe that our findings address an important issue regarding the clinical trials of lung cancers. In the future, further study is warranted regarding lung cancer patients with any extrapulmonary malignancies to evaluate the clinical behavior and survival of these patients in a prospective setting.

In conclusion, as a result of long-term survival and sufficient follow-up, the incidence of lung cancer in patients with a history of colorectal cancer has changed dramatically over time. Thus, a history of antecedent colorectal cancer did not contribute to the prognosis in patients with subsequent lung cancers. In the future, a multidisciplinary team management approach may be essential for developing customized treatment strategies in patients with lung cancer associated with antecedent colorectal cancer.

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Conflict of interest statement

None declared.

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RESEARCH ARTICLE Open Access

Clinicopathological features and EGFR gene mutation status in elderly patients with resected non-small-cell lung cancer

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Abstract

Background: The rapid aging of the population in Japan has been accompanied by an increased rate of surgery for lung cancer among elderly patients. It is thus an urgent priority to map out a treatment strategy for elderly patients with primary lung cancer. Although surgical resection remains standard treatment for early stage non–small-cell lung cancer (NSCLC), it is now essential to confirm the status of epidermal growth factor receptor (EGFR) gene mutations when planning treatment strategies. Furthermore, several studies have reported that EGFR mutations are an independent prognostic marker in NSCLC. However, the relations between age group and the molecular and pathological characteristics of NSCLC remain unclear. We studied the status of EGFR mutations in elderly patients with NSCLC and examined the relations of EGFR mutations to clinicopathological factors and outcomes according to age group.

Methods: A total of 388 consecutive patients with NSCLC who underwent complete tumor resection in our hospital from 2006 through 2008 were studied retrospectively. Formalin-fixed, paraffin-embedded tissue sections were used to isolate DNA from carcinoma lesions. Mutational analyses of EGFR gene exons 19, 20, and 21 and KRAS gene exons 12 and 13 were performed by loop-hybrid mobility shift assay, a highly sensitive polymerase chain reaction-based method.

Results: EGFR mutations were detected in 185 (47.7%) and KRAS mutations were detected in 33 (8.5%) of the 388 patients. EGFR mutations were found in a significantly higher proportion of patients younger than 80 years (younger group; 178/359, 49.6%) than in patients 80 years or older (older group; 7/29, 24.1%) (P = 0.008). In contrast, KRAS mutations were more common in the older group (6/29, 20.7%) than in the younger group (27/359, 7.5%) (P = 0.014). The older group showed a trend toward a higher rate of 5-year overall survival among elderly patients with EGFR mutations (100%) than among those with wild-type EGFR (66.2%), but the difference was not significant.

Conclusions: Our results suggest that the EGFR status of patients with NSCLC differs between patients 80 years or older and those younger than 80 years. EGFR mutation status might be a prognostic marker in elderly patients with completely resected NSCLC.

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Background

Primary lung cancer remains the leading cause of the death from malignant tumors worldwide [1]. Non–small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer [2]. Although surgical resection remains the standard treatment for early NSCLC, several molecular pathways have been shown to have prognostic significance in NSCLC. The epidermal growth factor receptor (EGFR) pathway is considered particularly important. EGFR is a membrane glycoprotein with an extracellular ligand-binding domain, a transmembrane lipophilic segment, and an intracellular domain that has tyrosine kinase activity. When a growth factor binds to EGFR, EGFR is self-phosphorylated by tyrosine kinase, and phosphorylated EGFR activates cell-signaling pathway involved in the regulation of cell cycle, apoptosis, angiogenesis, and cellular proliferation. Specific mutations of EGFR induce constant phosphorylation of EGFR, and increased levels of phosphorylated EGFR activate downstream signals that induce carcinogenesis [3,4]. EGFR mutations predict the effect of EGFR tyrosine kinase inhibitors (EGFR-TKI) [5,6]. It is now essential to confirm EGFR mutation status when planning treatment strategies for advanced or recurrent NSCLC.

The population of Japan is aging rapidly. In 2011 the average life-span in Japan was 83 years (males 79 years, females 86 years) [7]. Aging of the population is accompanied by a rapid increase in the incidence of primary lung cancer as well as the number of operations for lung cancer among elderly patients. Since 2009 persons 80 years or older have accounted for more than 10% of all patients in Japan. In 2011, patients 80 years old or older accounted for 11.5% of all patients [8-12]. Aging will become a global problem in the future, and knowledge acquired in Japan may contribute to solving related problems. Previous studies have suggested a relation between EGFR mutations and several clinicopathological factors, but whether EGFR status differs according to age group remains unclear. The present study assessed the status of EGFR mutations in elderly patients with NSCLC and examined the relations of EGFR mutations and clinicopathological factors to outcomes.

Methods

Patients

We retrospectively studied 388 consecutive patients with NSCLC who underwent complete tumor resection at Kanagawa Cancer Center Hospital (Yokohama, Japan) from 2006 through 2008. This study was approved by the ethics committee of the Kanagawa Cancer Center, and informed consent was obtained from all patients. The pathological diagnoses were independently made by 2 pathologists (T.N., T.Y.). Discrepancies in diagnoses were resolved by mutual agreement. The median follow-up time was 1981 days.

Assessments

Formalin-fixed, paraffin-embedded tissue sections of the resected tumors were used for DNA extraction. Mutational analyses of EGFR gene exons 19, 20, and 21 and KRAS gene exons 12 and 13 were performed by loop-hybrid mobility shift assay (LH-MSA), a highly sensitive polymerase chain reaction–based method, as described previously (Additional file 1: Table S1) [13].

Statistical analysis

Relations between EGFR status and categorical data were evaluated with the chi-square test. Continuous variables were compared by Student's t-test. Survival curves were plotted using the Kaplan-Meier method, and differences in survival rates were assessed using the log-rank test. $P < 0.05$ was considered to indicate statistical significance. Statistical manipulations were performed using the IBM SPSS Statistics 20 for Windows software system (IBM Corp, Armonk, NY, USA).

Results

Relations between EGFR, KRAS status and clinicopathological features

The patients' characteristics are summarized in Table 1. Of the 388 patients, 228 (58.8%) were men, and 160 (41.2%) were women. The mean age was 66.6 years (range, 35–90). EGFR mutations were detected in 185 patients (185/388, 47.7%) and KRAS mutations were detected in 33 (33/388, 8.5%). EGFR mutations were found more frequently in women (110/185, 59.5%), adenocarcinoma (183/185, 98.9%), and non-smokers (106/185, 57.3%) ($P < 0.001$). Patients with EGFR mutation had fewer pre-existing cardiopulmonary comorbidities than patients with wild-type ($P = 0.028$). The mean tumor diameter was smaller in patients with EGFR mutations (2.68 ± 0.92 cm) than in those with wild-type EGFR (3.35 ± 1.71 cm; $P < 0.001$). The rate of pathological T1 disease was significantly higher among patients with EGFR mutations (114/185, 61.6%) than among those with wild-type EGFR (83/203, 40.9%; $P < 0.001$). In contrast, KRAS mutations were not significantly related to gender, histopathological type, or smoking status. Although KRAS status did not correlate with pathological T factors, mean tumor diameter was larger in patients with KRAS mutations (3.46 ± 1.99 cm) than in those with wild-type KRAS (2.99 ± 1.36 cm; $P = 0.001$).

Relations between age group and clinicopathological features

We divided the patients into two groups according to whether they were 80 years or older (older group) or