long-term survivors.

Kaira R, Kaira K, Shukuya T, Kenmotsu H, Ono A, Murakami H, Tsuya A, Nakamura Y, Naito T, Endo M, Yamamoto N, Takahashi T. Long-term survival of more than 3 years among patients with advanced non-small cell lung cancer treated with chemotherapy. *World J Respirol* 2013; 3(3): 110-115 Available from: URL: http://www.wjgnet.com/2218-6255/full/v3/i3/110.htm DOI: http://dx.doi.org/10.5320/wjr.v3.i3.110

INTRODUCTION

Non-small cell lung cancer (NSCLC) remains a major cause of cancer-related death worldwide. Surgery is the most common curative treatment, but for most patients with NSCLC, the tumor is often inoperable at the time of diagnosis. Platinum-based chemotherapy has resulted in a statistically significant improvement in survival compared to best supportive care[1,2]; however, the prognosis of patients with advanced NSCLC is still poor. Recent phase Ⅲ trials have reported a median survival time (MST) of 8 to 10 mo and a 1 year survival rate of 30%-35%[3].

In 2004, mutations in the epidermal growth factor receptor (*EGFR*) gene, conferring increased sensitivity to the chemotherapy drug gefitinib, were reported[4,5]. Recently, two phase Ⅲ studies of gefitinib as first-line therapy compared with platinum-based chemotherapy showed favorable outcomes in patients with advanced NSCLC harboring *EGFR* mutations[6,7]. The patients treated with gefitinib had a MST of 30.5 mo and a 2-year survival rate of 61.4%, indicating that some NSCLC patients may survive for more than 2 or 3 years.

Previous studies on the long-term survival of patients with advanced NSCLC treated with chemotherapy reported a 2-year survival rate of only 4%-6%[8-10]. However, these studies did not include NSCLC patients who received gefitinib and therefore, these data may no longer be accurate. Recently, we showed that a good performance status (PS), adenocarcinoma histology and EGFR-tyrosine kinase inhibitor (TKI) therapy are important factors associated with long-term survival of more than 5 years[11]. However, our previous study had a small sample size and was preliminary; therefore, further investigations on larger sample sizes were warranted. Moreover, there is no consensus on the definition of long-term survival for patients with advanced NSCLC (whether this should be more than 2, 3, 4 or 5 years). Previous reports have defined long-term survival in patients with advanced NSCLC as more than 2 years[8-10]. However, considering that advanced NSCLC patients responsive to gefitinib have a MST of more than 2 years, the clinical characteristics of patients with long-term survival of more than 3 years should be investigated. Against this background, we conducted a retrospective study to evaluate the prognostic factors associated with long-term survival of more than 3 years among advanced NSCLC patients who received chemotherapy as initial treatment.

MATERIALS AND METHODS

We analyzed the records of 474 patients with advanced ⅢB/Ⅳ NSCLC who received chemotherapy as initial treatment at the Department of Thoracic Oncology of Shizuoka Cancer Center between September 2002 and March 2007. NSCLC patients with recurrence after curative surgery were excluded from this study. The demographic characteristics of the 474 patients are listed in Table 1. The median patient age was 64 years (range, 23-85 years); 323 patients were male and 151 were female; 323 were smokers and 154 had never smoked; 333 had adenocarcinoma histology and 141 had non-adenocarcinoma histology; and 109 patients had clinical stage ⅢB disease and 365 had stage Ⅳ disease. The Eastern Cooperative Oncology Group (ECOG) PS was 0 in 148 patients, 1 in 240 patients, 2 in 65 patients, 3 in 20 patients, and 4 in 1 patient.

Of these 474 patients, 380 (80.2%) were treated with platinum-doublet regimens, 64 (13.5%) with single-agent regimens, and 30 (6.3%) with EGFR-TKI therapy (gefitinib or erlotinib) as first-line treatment. Two-hundred and thirty-eight patients (50.2%) received EGFR-TKI therapy as any line treatment. Staging was performed for all patients according to the Union for International Cancer Control TNM classification[12]. For TNM staging, all patients underwent computed tomography (CT) of the thorax and upper abdomen, bone scintigraphy or positron emission tomography, and brain CT or magnetic resonance imaging. Histological analysis of the tumors was based on the World Health Organization (WHO) classification of cell types[13].

Survival was recorded from the first day of treatment to the date of death or last follow-up, and the survival curves were calculated using the Kaplan-Meier method[14]. The median follow-up period was 323 d (range, 13-2069 d). Survival time was calculated at more than 3 years after the final registration. Fisher's exact test was used to examine the association between two categorical variables and probability values of < 0.05 indicated a statistically significant difference. We evaluated the efficacy of chemotherapy using the Response Evaluation Criteria in Solid Tumors, version 1.1. Survival difference was analyzed using the log-rank test. Multivariate analyses were performed using a stepwise Cox proportional hazards model to identify independent prognostic factors. Statistical analysis was performed using JMP 8 (SAS, Institute Inc., Cary, NC, United States) for Windows.

RESULTS

Survival analysis of all 474 patients

Figure 1 shows the survival curves for all 474 patients. The MST was 12.5 mo and the 1 year, 2 years, 3 years, 4 years and 5 years survival rates were 50.8%, 26.3%, 14.6%, 8.2% and 5.3%, respectively. Long-term sur-

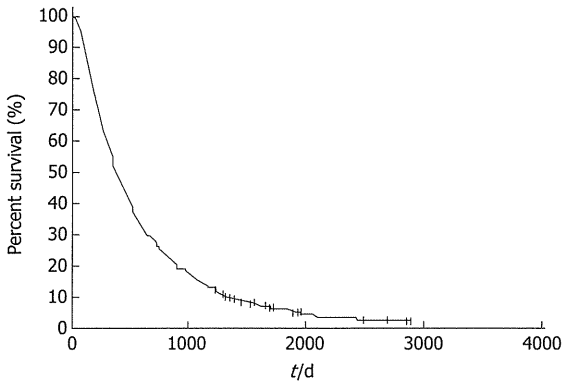

Figure 1 For the entire cohort (n = 474), the median survival time was 12.5 mo and the 1 year, 2 years, 3 years, 4 years and 5 years survival rates were 50.8%, 26.3%, 14.6%, 8.2% and 5.3%, respectively.

Table 1 Patient's characteristics (all patients) n (%)

Variables		No. of patients (n = 474)
Age (yr)		
(median 64)	< 65	264 (55.7)
(range 23-85)	≥ 65	210 (44.3)
Gender		
	Male	323 (68.1)
	Female	151 (31.9)
Performance status		
(ECOG)	0	148 (31.2)
	1	240 (50.6)
	2	65 (13.7)
	3	20 (0.04)
	4	1 (0.002)
Smoking		
	Yes	320 (67.5)
	No	154 (32.5)
Histology		
	Adenocarcinoma	333 (70.3)
	Non-adenocarcinoma	141 (29.7)
Clinical stage		
	ⅢB	109 (23.0)
	Ⅳ	365 (77.0)

ECOG: Eastern Cooperative Oncology Group.

vival of more than 3 years was observed in 65 patients and long-term survival of more than 5 years was observed in 16 patients. Univariate analysis showed that a good PS, female sex, non-smoking status and adenocarcinoma histology were significantly associated with a favorable outcome. Multivariate analysis demonstrated that a good PS and adenocarcinoma histology were independent prognostic factors for predicting a favorable prognosis (Table 2).

Demographic characteristics of patients who achieved long-term survival of more than 3 years

Of the 474 patients, 65 (33 men and 32 women) with a median age of 65 years (range, 35-78 years) survived for more than 3 years, with a MST of 61.5 mo (range, 60.1-81.0 mo). The PS, clinical stage and histology of the patients were as follows: 35 patients had a PS of 0, 25 had a PS of 1, and 5 had a PS of 2-3; 18 patients had stage ⅢB disease and 47 had stage Ⅳ disease; 65 patients had adenocarcinoma histology. With regard to metastatic sites, 23 patients had bone metastases, 18 had brain metastases, and 9 had synchronous brain and bone metastases. With regard to the efficacy of first-line treatment, a partial response was noted in 29% of cases (19/65). The median treatment-free interval between first and second-line therapy was 518 d (range, 26-1901 d) and the median total number of therapeutic lines was 4 (range, 1-13 lines).

Table 2 Univariate and multivariate analysis in overall survival in all patients

Variables		Univariate analysis (log-rank test) P value	Multivariate analysis (Cox's proportional hazard models) P value
Age (yr)	< 65/≥ 65	0.4158	0.5172
Gender	Male/Female	< 0.0001	0.0982
PS	0-1/2-4	< 0.0001	< 0.0001
Smoking	Yes/No	< 0.0001	0.1363
Histology	AC/Non-AC	< 0.0001	< 0.0001
Clinical stage	ⅢB/Ⅳ	0.2151	0.5216

PS: Performance status; AC: Adenocarcinoma.

We then compared the demographic characteristics of patients who did (n = 65) and did not (n = 409) achieve survival of more than 3 years (Table 3). Female sex, a good PS, non-smoking status and adenocarcinoma histology were significantly correlated with long-term survival of more than 3 years. The treatment regimens of patients who did and did not achieve long-term survival were also compared. Among patients who did not achieve long-term survival, 325 (79.4%) received platinum-doublet regimens, 59 (14.4%) received single-agent therapy, and 25 (6.1%) received EGFR-TKI therapy as first-line treatment. In contrast, among long-term survivors, 55 (84.6%) received platinum-doublet regimens, 5 (7.7%) received single-agent therapy, and 5 (7.7%) received gefitinib as first-line treatment. Demographic characteristics did not differ significantly between patients who did and did not achieve long-term survival, according to the first-line regimen. As any line treatment, 180 patients (44.0%) who did not achieve long-term survival and 58 patients (89.2%) who did achieve long-term survival received EFGR-TKI; this difference was statistically significant (P < 0.0001).

With regard to response to first-line chemotherapy among the 65 patients who achieved long-term survival, 17 patients were responders and 48 patients were non-responders, resulting in a response rate of 26%.

Survival analysis in patients who achieved long-term survival of more than 3 years

Univariate analysis did not identify any statistically significantly prognostic factors (Table 4). We excluded 5 patients with a PS of 2-3 from these 65 patients, thus evaluating 60 patients with a PS of 0-1 by univariate and multivariate analyses (Table 5). A PS of 0 was found to

Table 3 Comparison of patient's demographics between survivors (n = 65) of more than 3 yr and those (n = 409) of less than 3 yr

Variables		< 3 yr (n = 409)	≥ 3 yr (n = 65)	*P* value
Age	< 65/≥ 65	231/178	21/34	0.2267
Gender	Male/Female	290/119	33/32	0.0024
PS	0-1/2-4	329/80	60/5	0.0225
Smoking	Yes/No	291/118	35/30	0.0090
Histology	AC/Non-AC	268/141	65/0	< 0.0001
Clinical stage	ⅢB/Ⅳ	91/318	18/47	0.3428

PS: Performance status; AC: Adenocarcinoma.

Table 4 Univariate analysis in overall survival in 65 long-term survivors

Variables		No. of patients	Univariate analysis (log-rank test) *P* value
Age	< 65/≥ 65	31/34	0.9448
Gender	Male/Female	33/32	0.3467
PS	0-1/2-3	60/5	0.7468
Smoking	Yes/No	35/30	0.9835
Clinical stage	ⅢB/Ⅳ	18/47	0.7627

PS: Performance status.

Table 5 Univariate and multivariate analysis in overall survival in 60 long-term survivors

Variables		No. of patients	Univariate analysis (log-rank test) *P* value	Multivariate analysis (Cox's proportional hazard models) *P* value
Age	< 65/≥ 65	29/31	0.8099	0.9421
Gender	Male/Female	31/29	0.4133	0.3676
PS	0/1	35/25	0.0158	0.0244
Smoking	Yes/No	33/27	0.9062	0.5170
Clinical stage	ⅢB/Ⅳ	18/42	0.8139	0.6781

PS: Performance status.

be an independent prognostic factor for predicting a favorable outcome.

DISCUSSION

The present study showed that advanced NSCLC patients who survived for more than 3 years had a good PS and adenocarcinoma histology. Most patients who survived for more than 3 years received platinum-containing chemotherapy as initial treatment and EGFR-TKI as any line chemotherapy. Multivariate analysis of long-term survivors showed that a PS of 0 was an independent prognostic factor for predicting a favorable outcome.

A previous study reported that the best prognostic factors for long-term survivors were non-metastatic disease status and response to chemotherapy[14]. In this previous study, 1052 patients treated with platinum-based chemotherapy were analyzed and the 2 years and 5 years survival rates were 7.4% and 1.8%, respectively. All patients who survived for more than 5 years had limited disease and were treated by complementary thoracic radiation and/or surgery. Other recent studies also reported that a good PS, adenocarcinoma histology and EGFR-TKI therapy contributed to long-term survival of more than 2 years[9,11]. As EGFR-TKI therapy contributes to prolonged survival, previous reports on long-term survivors who did not receive this treatment may not be useful. Therefore, retrospective studies that include a treatment history of EGFR-TKI therapy are needed to identify the prognostic factors for a favorable outcome.

Our study suggested that a PS of 0, but not 1, was an important factor for predicting long-term survival of more than 3 years. In the ECOG experience, the rate of survival for more than 2 years in patients with metastatic NSCLC was 4.0% and pretreatment characteristics associated with long-term survival were an initial PS of 0, no bone metastases, female sex, no subcutaneous metastases, no larger cell histology, a prior weight loss of less than 5%, and no liver metastases[15]. The experience of the South West Oncology Group also documented that a good PS, female sex and an age of more than 70 years were significant independent survival predictors[16]. A good PS is known to be closely associated with a favorable outcome after chemotherapy in patients with advanced NSCLC. Although adenocarcinoma histology, use of EGFR-TKI, and an initial good PS are essential in order to achieve survival for more than 3 years in cases of advanced NSCLC, the outcome of patients with a PS of 0 may be different from that of patients with a PS of 1.

In July 2002, gefitinib was approved for pretreated NSCLC patients in Japan in clinical practice. Recently, Satouchi *et al*[17] reported on the predictive factors associated with the prognostic benefits of gefitinib, showing that survival was significantly better for female sex, adenocarcinoma histology, never-smoked status, a favorable PS and *EGFR* mutation positivity. Recent clinical studies demonstrated that the use of gefitinib or erlotinib resulted in significantly longer survival than platinum-based chemotherapy in patients with advanced NSCLC harboring *EGFR* mutation[18,19] and the MST of patients treated with gefitinib was approximately 3 years (27.7 mo)[18]. In multivariate analysis, *EGFR* mutation positivity and a PS of 0-1 have been described as independent predictors of a favorable prognosis.

It is currently unclear whether *EGFR* mutation is a prognostic factor in NSCLC patients not treated with EGFR-TKI. Therefore, Kosaka *et al*[20] examined the prognostic significance of *EGFR* mutation in a large cohort of patients with surgically treated lung adenocarcinoma. In their study, univariate analysis demonstrated that patients with *EGFR* mutations have favorable survival compared to those without *EGFR* mutations (P = 0.0046). However, *EGFR* mutation positivity was not

independently associated with poor outcome in cases of resectable lung adenocarcinoma not treated with EGFR-TKI and was a predictive factor for cases treated with gefitinib, but not for pulmonary adenocarcinoma not treated with gefitinib. In the present study, one of the limitations was that the *EGFR* mutation status had not been analyzed in all patients. Therefore, whether a PS of 0 is a useful factor for predicting favorable prognosis compared with *EGFR* mutation positivity remains unknown. Accordingly, further study is warranted for the confirmation of our results.

While PS is an important factor in determining outcomes in cases of NSCLC, there is limited available data on the distribution of PS among NSCLC patients. Recently, Kawaguchi *et al*[21] showed that PS is an independent favorable prognostic factor in a large-scale retrospective study of 26957 patients with NSCLC. In their study, most patients with a PS of 0 presented with stage I disease and were never-smokers and overall survival differed significantly between patients with a PS of 0 and those with a PS of 1. Moreover, outcomes differed significantly in patients with advanced NSCLC between those with a PS of 0 and those with a PS of 1. Qi *et al*[22] also reported that pretreatment quality of life was an independent prognostic factor for overall survival in patients with advanced NSCLC. These reports suggest that PS before treatment may be closely associated with long-term survival in patients with advanced NSCLC. Furthermore, outcomes are thought to differ between treated NSCLC patients with a PS of 0 and those with a PS of 1, but no data are available in the literature on the long-term survival of chemotherapy-treated patients with advanced NSCLC. At present, three major scales are used to measure PS in oncology, Karnofsky PS, ECOG PS and WHO PS, although the ECOG PS scale has been shown to be more effective than the Karnofsky PS scale in discriminating between patients with different prognoses[23]. Our results indicate a strong relationship between a PS of 0 and long-term survival in advanced NSCLC patients treated with chemotherapy, indicating that the ECOG PS scale may be an appropriate measure for predicting long-term survival.

In conclusion, our results suggest that a good PS and adenocarcinoma histology play an important role in long-term survival of more than 3 years. A PS of 0 was an independent prognostic factor for predicting favorable outcomes in patients with advanced NSCLC who survived for more than 3 years. In the future, a large-scale study including *EGFR* mutation analysis might be considered for determining the prognostic factors of patients with advanced NSCLC who are treated with chemotherapy and achieve long-term survival of more than 3 years.

COMMENTS

Background

Surgery is the most common curative treatment but for most patients with non-small cell lung cancer (NSCLC), the tumor is often inoperable at the time of diagnosis. Recent phase III trials have reported a median survival time of 8 to 10 mo and a 1 year survival rate of 30%-35%.

Innovations and breakthroughs

The authors' results suggest that a good performance status (PS) and adenocarcinoma histology play an important role in long-term survival of more than 3 years. A PS of 0 was an independent prognostic factor for predicting favorable outcomes in patients with advanced NSCLC who survived for more than 3 years.

Applications

PS of 0, adenocarcinoma and epidermal growth factor receptor-tyrosine kinase inhibitors therapy play an important role in the long-term survivors.

Peer review

This is a flawless manuscript, very well written, which can be useful for the readers and investigators in lung cancer.

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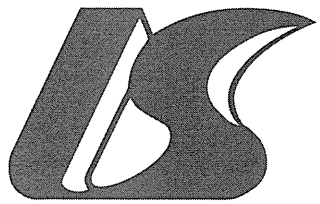

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CASE REPORT

Cystic brain metastasis of non-small-cell lung cancer successfully controlled with Ommaya reservoir placement

Gouji Toyokawa · Ryo Toyozawa · Eiko Inamasu · Miyako Kojo · Yosuke Morodomi · Yoshimasa Shiraishi · Tomoyoshi Takenaka · Fumihiko Hirai · Masafumi Yamaguchi · Takashi Seto · Mitsuhiro Takenoyama · Yukito Ichinose

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Abstract A 68-year-old male presented with hoarseness and anarthria. Computed tomography showed an irregular nodular shadow in the upper lobe of the left lung with swollen multiple lymph nodes. Magnetic resonance imaging revealed a large cystic mass in the left hemisphere of the brain and multiple brain metastases in the bilateral hemispheres. A direct biopsy with bronchoscopy of the pulmonary nodule revealed the tumor to be an adenocarcinoma clinically diagnosed as stage IV. Since the largest brain metastasis continued to grow despite the administration of whole brain irradiation, insertion of an Ommaya reservoir in the cystic lesion was performed. This resulted in a reduction of the size of the brain tumor, and the patient's neurological symptoms improved. After the Ommaya reservoir was placed, stereotactic radiosurgery was performed on the largest lesion. The patient is doing well at 6 months after the Ommaya reservoir was inserted and is currently undergoing chemotherapy. In conclusion, the placement of an Ommaya reservoir may therefore be a potentially useful therapeutic procedure to improve the neurological symptoms and performance status in non-small-cell lung cancer patients with cystic brain metastasis, thereby allowing further neurosurgical therapy and chemotherapy.

Keywords Non-small-cell lung cancer · Cystic brain metastasis · Ommaya reservoir

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Introduction

An Ommaya reservoir is a device placed under the skin of the head with the tip of the catheter positioned into the ventricles or within cystic lesions in the brain [1]. This device helps to drain the cerebrospinal fluid and contents of cystic lesions. Additionally, intraventricular administration of some drugs, such as amphotericin B, primethamine and methotrexate, can be conducted through this device [1, 2]. Although the usefulness of this device for treating cystic lesions in the brain has been previously reported, few reports of cystic brain metastases from lung cancer being controlled by the insertion of an Ommaya reservoir have been published in the English literature [3, 4]. In this report, we present a case of non-small-cell lung cancer (NSCLC) with a large cystic brain metastasis that was successfully controlled with the insertion of an Ommaya reservoir.

Case report

A 68-year-old male ex-smoker was referred to our hospital due to hoarseness and anarthria. Computed tomography (CT) revealed an irregular nodular shadow in the left upper lobe of the lung with enlargement of the left hilar, para-aortic and left subclavicular lymph nodes, which showed abnormal uptake of F-18 fluorodeoxyglucose on positron emission tomography/computed tomography (Fig. 1a). Magnetic resonance imaging (MRI) revealed a large mass in the left hemisphere (Fig. 1b, c) and multiple small nodules in the bilateral hemispheres (Fig. 1b, arrow). T1-weighted images showed very low signal intensity and T2-weighted images showed very high signal intensity in the largest mass consistent with the findings of a cystic lesion.

Bronchoscopy was then performed and a direct biopsy revealed the tumor to be an adenocarcinoma. Based on these findings, the clinical stage was considered to be stage IV (cT1bN3M1b).

Due to the presence of multiple brain metastases with the one larger than 3 cm, 30 Gray (Gy) of whole brain irradiation (WBI) was administered. Despite the administration of WBI, the largest cystic tumor continued to grow, and the surrounding edema expanded and the midline shifted (Fig. 1d). This resulted in worsened anarthria and the emergence of Gerstmann's syndrome. Various neurosurgical procedures were considered, and insertion of an Ommaya reservoir was chosen to minimize invasiveness. A dome-shaped plastic device was placed under the skin of the left head with a catheter positioned into the cavity of the cystic lesion without any complications (Fig. 2a). MRI and CT performed about 1 month after MRI as shown in Fig. 1c, revealed a reduction in the size of the tumor and the amount of surrounding edema (Fig. 2b, c). Crucially, the neurological symptoms improved. Since the cystic tumor was reduced from 4.7 to 2.9 cm, 20 Gy of stereotactic radiosurgery (SRS) was administered. Although the cystic tumor remained the same size after the SRS was completed, no punctures were needed to drain the fluid. The patient is doing well at 6 months after the insertion of the Ommaya reservoir and is currently undergoing chemotherapy with carboplatin and pemetrexed due to the improvement of performance status (PS) from 3 to 1.

Discussion

Ommaya reservoirs were originally developed to achieve aseptic access to ventricular cerebrospinal fluid. The device consists of an indwelling subcutaneous capsule made of silicone rubber that fits into a cranial burr-hole and is connected to a ventricular catheter. Percutaneous needle punctures can be repeatedly made through the dome of the capsule. This device is used for the administration of chemotherapy for neoplasia, cystic tumor drainage, ventricular drainage, special diagnostic studies and sampling of cerebrospinal fluid [1, 2]. In addition, diverse types of diseases, such as primary brain tumors, fungal meningitis, toxoplasmosis and head injury, can be indications for the placement of the device [1]. However, few reports of cystic brain metastasis from lung cancer being controlled with the

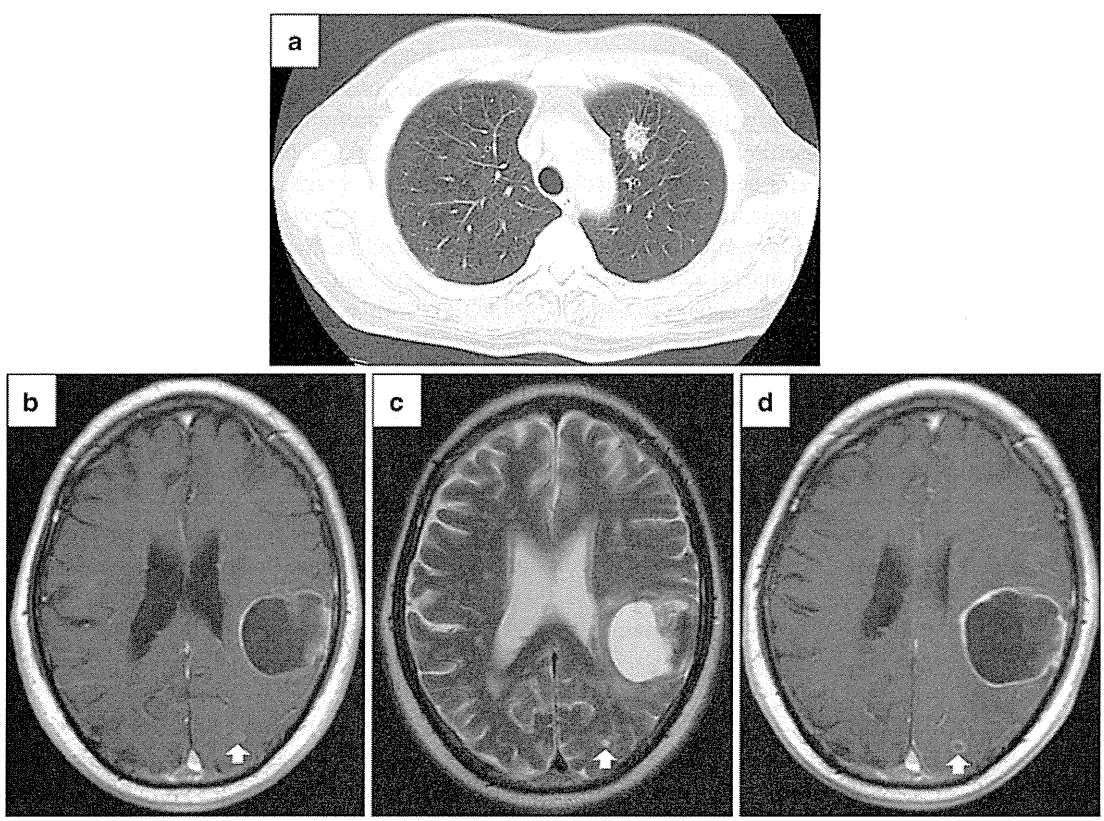

Fig. 1 CT and MRI findings. CT shows an irregular nodule in the left upper lobe of the lung (**a**). T1- and T2-weighted images indicate a large cystic brain tumor and multiple small cystic nodules (*arrow*) before the administration of WBI (**b**, **c**). T1-weighted images show the tumor after WBI (**d**)

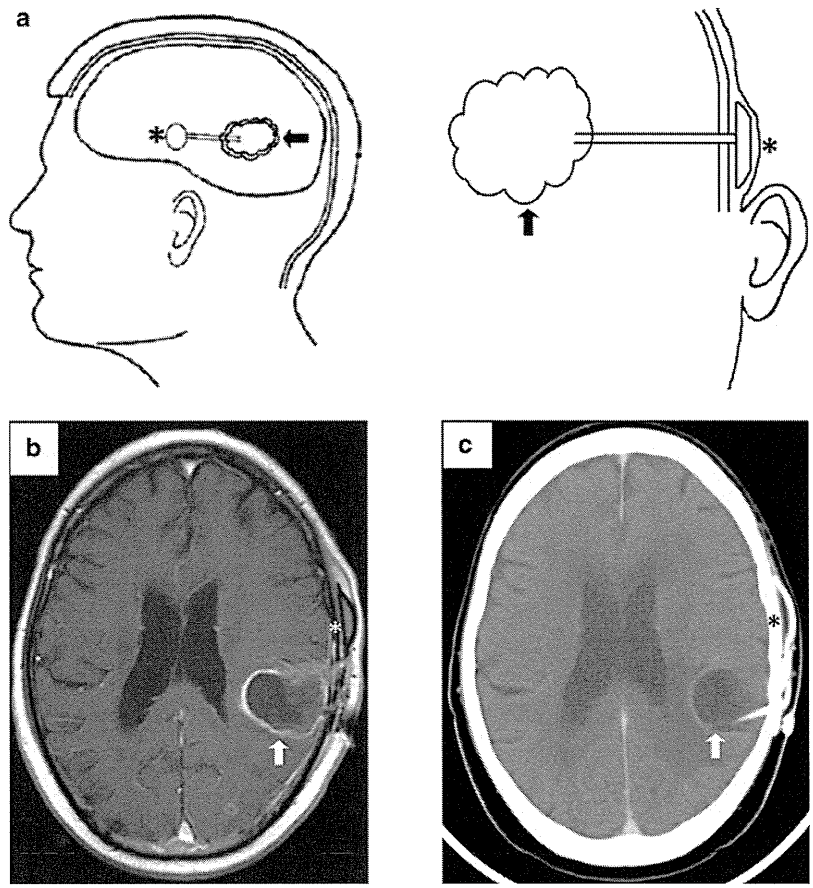

Fig. 2 Ommaya reservoir placement. Left lateral and frontal views of the head show the Ommaya reservoir (*asterisk*) placed under the skin of the left head with a catheter positioned into the cavity of the cystic lesion (*arrow*) (**a**). MRI and CT images show the inserted Ommaya reservoir (**b**, *asterisk*, **c**)

insertion of an Ommaya reservoir have been published in the English literature [3, 4]. Takeda and colleagues reported the case of a SCLC patient with solitary cystic brain metastasis who was successfully treated with a stereotactically inserted Ommaya reservoir followed by neurosurgical resection of the tumor, and the survival time of the patient after the insertion of the device was 4 months [3]. In addition, the usefulness of SRS following Ommaya reservoir placement has been reported in patients with large cystic metastatic brain tumors, including lung and breast cancer, with a median survival time of 7 months after the insertion of the device [4]. However, these papers did not mention chemotherapy after an Ommaya reservoir was placed. In the present case, a metastasized cystic lesion of the brain was controlled with the insertion of an Ommaya reservoir followed by the administration of stereotactic radiosurgery and chemotherapy, and the patient is currently doing well at 6 months, in comparison to the findings reported by others [3, 4], after the insertion of the device. Chemotherapy, as well as the insertion of the device, was also thought to have contributed the survival time of the patient, because the primary lesions and the metastasized lymph nodes were reduced after the administration of four cycles of carboplatin and pemetrexed.

Brain metastases are common in lung cancer patients, with an incidence of approximately 40 %. The majority of brain metastases of NSCLC are solid, whereas cystic brain metastases are exceedingly rare. While solid brain metastases are treated with optimal treatment modalities such as WBI, SRS or neurological surgery depending on the size and number of the metastases and the general conditions of the patient, cystic counterparts are generally resistant to radiation therapy, and neurosurgery of cystic lesions has been reported to be preferable to SRS or stereotactic aspiration when possible [5]. However, in the present case, due to the presence of multiple metastatic lesions, WBI was first chosen followed by insertion of an Ommaya reservoir for less invasiveness and to achieve ventricular drainage and drainage of the primary brain cystic tumors [1]. It is of note that no punctures were needed to drain the cystic tumors, as several punctures are generally required since the effusion typically fills the mass [3]. This may have been due to the reduction of viable cancer cells in the cystic wall by the multimodal treatments. Additionally,

although few complications are associated with the placement of the device, attention should be paid to potential adverse events caused by chemotherapy, including leucopenia, neutropenia and thrombocytopenia by chemotherapy, which can lead to critical complications such as intracranial hemorrhage or infection.

In conclusion, the insertion of an Ommaya reservoir is therefore considered to be a useful treatment modality to improve the neurological symptoms and PS in NSCLC patients with cystic brain metastasis with minimal invasiveness, thus allowing for the administration of further neurosurgical therapy and chemotherapy which are crucial for the successful treatment of advanced NSCLC.

Conflict of interest No authors have any conflict of interest to disclose.

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ORIGINAL ARTICLE

The mutations of the EGFR and K-ras genes in resected stage I lung adenocarcinoma and their clinical significance

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Abstract
Purpose This study retrospectively assessed the mutations of the epidermal growth factor receptor (EGFR) and K-ras genes and their clinical significance in patients with resected stage I adenocarcinomas.
Methods A total of 354 patients with resected lung adenocarcinomas were included, and 256 patients with stage I disease were analyzed for the prognostic and predictive value of these mutations.
Results Mutations of EGFR and K-ras genes were detected in 149 (41.1 %) and 23 (6.4 %) of all tumors, and in 122 (47.6 %) and 14 (5.5 %) of stage I tumors, respectively. There were no significant differences in the disease-free survival (DFS) and overall survival (OS) between the EGFR-mutant and wild-type groups. However, the DFS and OS were significantly shorter in patients with K-ras mutations than in those without (5-year DFS: 50.8 vs. 76.9 %, 5-year OS: 70.0 vs. 86.6 %, $p < 0.01$). A multivariate analysis showed that K-ras mutations were an independent poor prognostic factor. Twenty-four of the 41 patients with recurrent disease after surgery were treated with an EGFR–TKI. Fifteen EGFR-mutant patients treated with an EGFR–TKI had a better prognosis than did the nine EGFR-wild-type patients.
Conclusion The presence of an EGFR gene mutation was a predictive factor for the response to EGFR–TKI treatment in patients with resected stage I adenocarcinoma, but was not a prognostic factor. The presence of a K-ras gene mutation was a poor prognostic factor.

Keywords NSCLC · Adenocarcinoma · EGFR · K-ras · EGFR–TKI

Abbreviations

EGFR	Epidermal growth factor receptor
TKI	Tyrosine kinase inhibitor
DFS	Disease-free survival
OS	Overall survival
PFS	Progression-free survival
NSCLC	Non-small cell lung cancer

Introduction

Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related death worldwide, accounting for more than one million deaths annually [1]. Surgery is the only method that can provide a cure for NSCLC. Patients with early stage NSCLC are treated surgically with curative intent; however, 30–65 % develop recurrence and eventually die of their disease [2]. Several therapies can be administered after recurrence, such as chemotherapy based on platinum drugs, and radiotherapy. Efforts to improve the survival of these patients is currently focused on the development of innovative treatment options, particularly new target-based therapies directed against key signaling pathways involved in lung

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cancer growth and malignant progression. Targeting the epidermal growth factor receptor (EGFR) using tyrosine kinase inhibitors (TKIs) is a successful type of target-based therapy.

Somatically acquired mutations, such as an exon 19 deletions and exon 21 point mutations of the EGFR gene in NSCLC are associated with a significant clinical response to EGFR–TKIs, such as gefitinib and erlotinib [3–11]. A recent subset phase III trial that compared carboplatin and paclitaxel with gefitinib in patients with adenocarcinoma demonstrated that the progression-free survival (PFS) of patients with an EGFR mutation in the gefitinib arm was significantly longer than that in the chemotherapy arm [12]. Two Japanese phase III (WJTOG3405 and NEJ002) trials comparing first-line EGFR–TKI therapy with platinum-based chemotherapy among patients with an EGFR mutation revealed a significantly superior response rate and PFS with EGFR–TKI therapy [9, 13]. Furthermore, several prospective studies showed that patients with EGFR mutations treated with EGFR–TKIs have significantly longer survival times than those without such mutations after recurrence [6]. These findings indicate that the mutations of the EGFR are an important factor predicting the response to EGFR–TKIs, and they also affect the survival of adenocarcinoma patients after recurrence. On the other hand, the prognostic role of EGFR mutations in patients with resectable NSCLC has not been established.

In addition, there is also a common point mutation of K-ras gene downstream of the EGFR signal pathway [14]. K-ras mutations are frequently detected in pancreatic cancer, colon cancer and lung adenocarcinoma [15, 16], and occur primarily at codon 12 or 13 [17]. K-ras mutations have been detected in 10–15 % of Japanese patients with lung adenocarcinoma [16], but in 30 % of Europeans [15]. Several reports have shown that K-ras mutations were a poor prognostic factor in NSCLC [16, 18, 19]. Although there is an association between the presence of a K-ras mutation and a lack of response to EGFR–TKIs in patients with lung adenocarcinoma, it is unclear whether there is an association between K-ras mutations and the EGFR–TKI response [20].

This study retrospectively assessed patients who had undergone pulmonary resection. The study examined mutations of the EGFR and K-ras genes at the time of surgery and analyzed the clinical significance of these mutations in terms of their prognostic and predictive value in Stage I adenocarcinoma patients.

Patients and methods

Patients

This study included 354 patients with lung adenocarcinoma who had undergone pulmonary resection at our institution from 2002 to 2006. The profiles of the 354 patients are shown in Table 1. The subjects included 194 males and 160 females. Their age ranged from 33 to 86 years, with a mean of 64 years. One hundred eighty patients were never-smokers. Two hundred fifty-six patients had pathological stage I disease, 33 had stage II, 34 had stage IIIA, 22 had stage IIIB, and nine had stage IV disease.

Mutation analysis of the EGFR and K-ras genes

Genomic DNA was extracted and purified from fresh frozen tumors, and from tumors embedded in paraffin blocks using the TaKaRa DEXPAT reagents (TaKaRa Bio. Inc.). The quantification of extracted nucleic acids and measurement of the A260/A280 ratio were performed using a UV spectrophotometer (Beckman coulter DU800).

A common fragment analysis was used for screening to detect the deletion in exon 19 of the EGFR gene. Sample DNA was amplified with an FAM-labeled primer set: 5′-TGGCACCATCTCACAATTGC-3′ (forward) and 5′-AGGATGTGGAGATGAGCAGG-3′ (reverse). PCR products were separated by electrophoresis on an ABI PRISM 310. When a deletion mutation was present, PCR amplified the shorter segment of DNA, thereby creating a new peak in the electropherogram.

The deletion in exon19 was confirmed using primers constructed to produce a 147-bp product when the allele was wild-type. The primer sequences were 5′-TGGCACCATCTCACAATTGC-3′ (forward) and 5′-GAAAAGGTGGGCCTGAGGTTC-3′ (reverse). PCR was carried out in 25 ml reaction mixtures containing 1 ml of genomic DNA using Taq DNA polymerase (TaKaRa Taq, TaKaRa, Shiga, Japan) for 35 cycles, and samples were heated at 64 °C for annealing. For detection of the L858R mutation in exon21, PCR was performed for 35 cycles, with the annealing temperature set at 60 °C, using TaKaRa Ex-Taq (TaKaRa Bio. Inc). The sequencing primers were: 5′-CATGAACTACTTGGAGGACC-3′ (forward) and 5′-CAGGAAAATGCTGGCTGACC-3′ (reverse).

A PCR-based designed RFLP analysis was performed to detect the K-ras mutation in codon 12 and 13, as reported previously [21]. All direct sequencing was done according to the manufacturer's protocol for the Bigdye v1.1 kit (Applied Biosystems). Sequencing was performed on a 310 Genetic Analyzer (Applied Biosystems).

Statistical analysis

The overall survival (OS) was defined as the time from the initial surgery until death from any cause. Disease-free survival (DFS) was defined as the time from the initial surgery until recurrence. The Kaplan–Meier method was used to estimate the survival probabilities. The curves of

the two groups were compared statistically using the log-rank test. The rates of the two groups were compared statistically using the Chi square test. Prognostic factors for survival were determined by the Cox regression model. The differences were considered to be significant for values of $p < 0.05$.

Results

The analysis of all patients who underwent surgical resection

Two hundred fifty-six of the 354 patients examined in this study had pathological stage I (pStage I) disease and 98 patients had stage II, III or IV (pStage II-IV) disease. The pStage I group included 131 males and 125 females, whose ages ranged from 30 to 86 years, with a mean of 64 years, and 180 patients were never-smokers (Table 1). On the other hand, the pStage II–IV group included 63 males and 35 females, whose ages ranged from 30 to 86 years, with a mean of 65 years, and 40 patients were never-smokers.

EGFR and K-ras mutations were detected in 149 (41.1 %) and 23 (6.4 %) of all 354 tumors, respectively, in all stages (Table 1). Seventy-three patients with mutations of the EGFR gene showed exon19 deletion, and 76 patients showed an exon21 point mutation.

Table 1 Clinical characteristics and mutation status of the patients

Factor	All stages	pStageI	pStage II–IV
Gender			
Male	194	131	63
Female	160	125	35
Age (range/median)	30–86/64	34–81/63	30–86/65
<70 years	237	198	69
≥70 years	117	88	29
Smoking status			
Never-smoker	180	140	40
Smoker	174	116	58
Mutation status			
EGFR	149 (41.1 %)	122 (47.6 %)	27 (27.6 %)
Exon 19	73	65	8
Exon 21	76	57	19
K-ras	23 (6.4 %)	14 (5.5 %)	9 (9.2 %)
Codon 12	20	11	9
Codon 13	3	3	0
Both wild-type	182 (51.4 %)	120 (46.8 %)	62 (63.3 %)
Total	354	256	98

EGFR epidermal growth factor receptor

Twenty patients with mutations of the K-ras gene showed a codon 12 mutation and three patients showed a codon 13 point mutation. EGFR mutations were detected more frequently in the pStage I group than in the pStage II–IV group (47.6 vs. 27.6 %; $p < 0.05$). K-ras mutations were detected in 14 (5.5 %) of the patients in the pStage I group, and in nine (9.2 %) of those in the pStageII–IV group, and there was no significant difference between the two groups in terms of the mutation frequency. The mutations of the EGFR gene and K-ras gene were mutually exclusive.

The correlation between the mutations and the clinical variables was analyzed in these two groups (Table 2). The incidence of EGFR mutations in patients with pStage I disease was significantly higher in females than in males (54.4 vs. 41.2 %, $p = 0.045$). Otherwise, there was no significant relationship between the various clinicopathological factors and the K-ras gene status, although the smokers showed a higher K-ras mutation rate than never-smokers, with borderline significance. The incidence of EGFR mutations in the patients with pStage II–IV disease was also significantly higher in females than males (45.7 vs. 17.5 %, $p = 0.004$), and in never-smokers than smokers (42.5 vs. 17.2 %, $p = 0.010$). The incidence of K-ras mutations was higher in older patients (>70 years) than in the younger patients (≤70 years; 20.7 vs. 4.8 %, $p = 0.018$).

The survival analysis of all patients with pStage I after surgical resection

The survival of the patients with pStage I disease after surgical resection was analyzed. The 5-year DFS and the OS of the 256 patients were 75.4 and 85.6 %, respectively.

A univariate analysis of the DFS showed that female sex and pT1 disease were significantly favorable prognostic factors ($p < 0.05$; Table 3a). Regarding the OS, pT1 disease was a favorable prognostic factor ($p < 0.05$; Table 3a). The presence of a K-ras mutation was a significant poor prognostic factor for both the OS ($p = 0.0082$) and PFS ($p = 0.0086$; Table 3a). The 5-year DFS rates were 76.9 vs. 50.0 vs. 76.9 % for patients with an EGFR mutation, K-ras mutation and both wild-type genes (Fig. 1), and the 5-year OS rates were 89.5 vs. 70.7 vs. 83.4 % for patients with an EGFR mutation, K-ras mutation and both wild-type genes (Fig. 2).

In a multivariate forward stepwise Cox proportional hazards regression analysis, which was adjusted for the clinically significant univariate factors, a K-ras mutation remained an independent prognostic factor for the PFS (HR, 2.584; 95 % confidence interval (CI), 1.157–5.774; $p = 0.0206$) and OS (HR, 3.704; 95 %CI, 1.426–9.626; $p = 0.0072$; Table 3b).

Table 2 The associations between the mutations and clinicopathological factors

Factor	(*n*)	EGFR		*p* value	K-ras		*p* value
		Mutation (%)	Wild		Mutation (%)	Wild	
pStage I							
Gender	Male (131)	54 (41.2)	77	0.0450	10 (7.6)	121	0.1692
	Female (125)	68 (54.4)	57		4 (3.2)	121	
Age	<70 years (168)	85 (50.6)	83	0.2358	8 (4.8)	160	0.5657
	≥70 years (88)	37 (42.0)	51		6 (6.8)	82	
Smoking status	Never-smoker (140)	73 (52.1)	67	0.1319	4 (2.9)	136	0.0543
	Smoker (116)	49 (42.2)	67		10 (8.6)	106	
pT	T1 (183)	89 (48.6)	94	0.6783	10 (5.5)	173	0.9999
	T2 (73)	33 (45.2)	40		4 (5.5)	69	
pStage II–IV							
Gender	Male (63)	11 (17.5)	52	0.0043	8 (12.7)	55	0.1515
	Female (35)	16 (45.7)	19		1 (2.9)	34	
Age	<70 years (69)	19 (27.5)	50	0.9999	3 (4.8)	63	0.0183
	≥70 years (29)	8 (27.6)	21		6 (20.7)	23	
Smoking status	Never-smoker (40)	17 (42.5)	23	0.0106	3 (7.5)	37	0.7339
	Smoker (58)	10 (17.2)	48		6 (10.3)	52	

EGFR epidermal growth factor receptor

Table 3 The results of the analysis of the relationships between the survival rates and the clinicopathological factors in patients with pStage I disease

Factor	(*n*)	5-year DFS (%)	*p* value	5-year OS (%)	*p* value
A. Univariate analysis					
Gender	Male (131)	67.5	0.0163	80.2	0.1445
	Female (125)	83.3		91.0	
Age	<70 years (168)	77.2	0.2995	87.8	0.1218
	≥70 years (88)	71.5		81.2	
Smoking status	Never-smoker (140)	77.5	0.3168	85.1	0.6293
	Smoker (116)	72.8		86.4	
pT	T1 (183)	81.1	0.0012	88.9	0.0102
	T2 (73)	61.1		77.2	
EGFR	Mutant (122)	76.9	0.3586	89.5	0.1269
	Wild-type (134)	73.9		81.9	
K-ras	Mutant (14)	50.0	0.0086	70.7	0.0082
	Wild-type (242)	76.9		86.6	

Factor	HR (95 % CI) of DFS	*p* value	HR (95 % CI) of OS	*p* value
B. Multivariate analysis				
Gender (female/male)	0.589 (0.348–0.998)	0.0491	–	–
pT (T1/T2)	0.441 (0.266–0.731)	0.0015	0.216 (0.142–0.328)	0.0082
K-ras (mutation/wild)	2.584 (1.157–5.774)	0.0206	3.704 (1.426–9.626)	0.0072

EGFR epidermal growth factor receptor

The analysis of the pStage I patients who had recurrence after pulmonary resection

Forty-one of the 256 patients developed recurrent disease, and the 5-year survival rate after recurrence was 23.6 %. The 41 patients with recurrent disease after surgery included 24 patients treated with EGFR–TKIs, such as gefitinib or erlotinib, and 17 patients treated with other anticancer drugs.

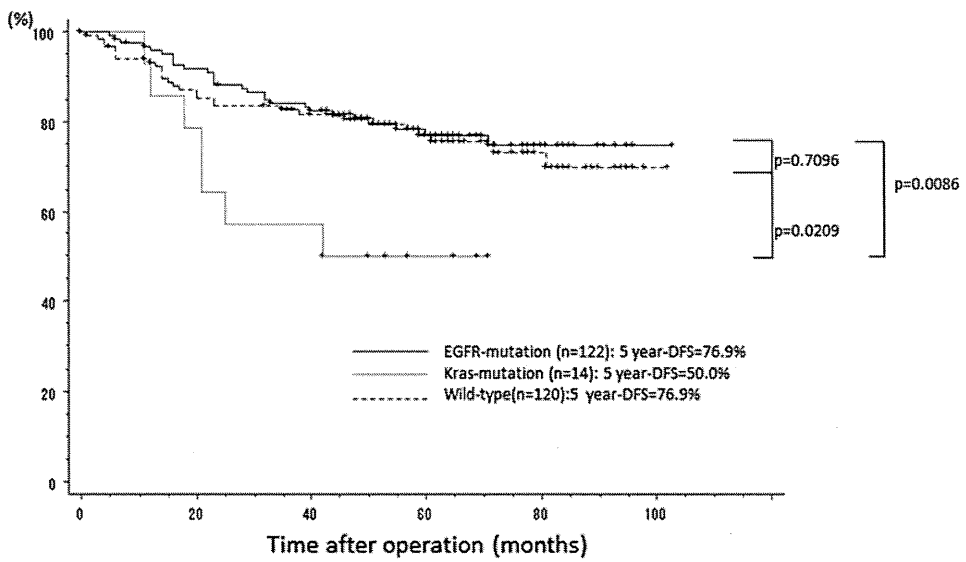
A univariate analysis showed the clinical factors that correlated with the prognosis after recurrence (Table 4). The median survival time (MST) after recurrence in patients with an EGFR mutation was 54.3 months, while it was 43.0 months in patients without an EGFR mutation. The median survival time after recurrence in patients with K-ras mutations was 38.3 months, and it was 51.4 months for patients without K-ras mutations.

We next analyzed the survival of the patients treated with EGFR–TKIs. A significant survival benefit was detected in the patients with EGFR mutations ($n = 15$) in comparison to those without EGFR mutations ($n = 9$; MST after recurrence: 53.4 vs. 20.1 months, $p = 0.0118$; Fig. 3a). On the other hand, no difference was observed in the survival between those with and without EGFR mutations among the patients who were not treated with an EGFR–TKI (Fig. 3b).

Discussion

The current study analyzed the mutations of the EGFR and K-ras genes in resected lung adenocarcinomas. EGFR mutations are detected in the lung adenocarcinomas of Japanese patients more frequently than in Western populations [22]. The frequency of EGFR mutations ranges from 40 to 60 % in Japanese lung adenocarcinomas [8, 23–28]. On the other hand, K-ras mutations are detected in the lung adenocarcinomas of Japanese patients less frequently than in Western populations [29]. The frequency of K-ras mutations ranges from about from 7 to 16 % in all worldwide populations [5, 16, 27, 30]. The frequency of K-ras mutations was 6.4 % in the current study. The rate of mutations in this study was lower than the rates in the previous reports. The rate of stage I disease in females was also higher than that in the previous reports, which might have caused the lower frequency of K-ras mutations.

The presence of an EGFR mutation is closely associated with several clinicopathological factors, such as gender, smoking history and the pathological findings. This is consistent with recent reports that EGFR gene mutations are common in lung cancers in never-smokers, and in females with adenocarcinoma [3, 4, 29]. The present analysis also suggested that the incidence of EGFR



No. of patients at risk						
EGFR-mutation	122	108	96	57	18	1
Kras-mutation	14	11	8	3	0	0
Wild	120	98	88	57	22	1

Fig. 1 The disease-free survival curves of pStage I patients after pulmonary resection. The data are shown for patients with an EGFR mutation, K-ras mutation and for those who were wild-type for both genes

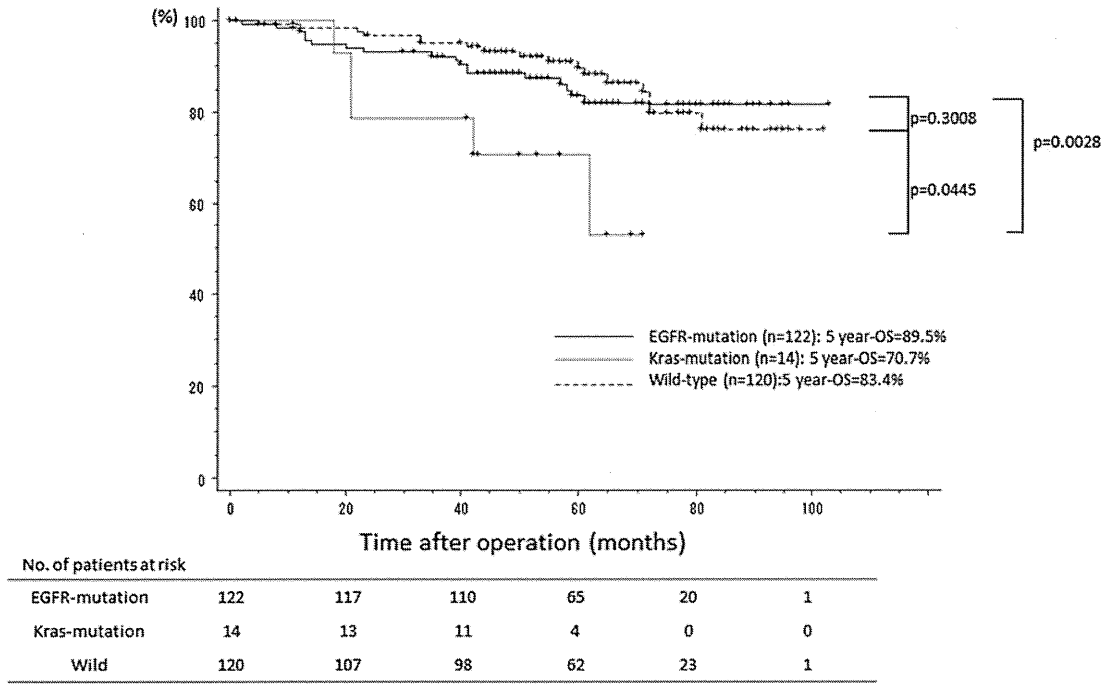


Fig. 2 The overall survival curves of pStage I patients with an EGFR mutation, K-ras mutation or both wild-type genes after pulmonary resection

Table 4 The results of the univariate analysis of the relationships between the survival time after recurrence and the clinical factors

Factor		MST (months)	*p* value
Gender			
Male	18	Not reached	0.1243
Female	23	43.0	
Age			
<70 years	27	54.3	0.3542
≥70 years	14	43.0	
Smoking status			
Never-smoker	20	43.0	0.0665
Smoker	21	Not reached	
pT			
T1	22	51.4	0.3220
T2	19	49.9	
DFI			
<1 year	11	49.8	0.9692
≥1 year	30	55.2	
EGFR			
Mutant	20	54.3	0.3910
Wild-type	21	43.0	
K-ras			
Mutant	4	38.3	0.7236
Wild-type	37	51.4	

DFI; the interval between the time of the last pulmonary resection and the time of the diagnosis of recurrence

MST median survival time, *DFI* disease-free interval, *EGFR* epidermal growth factor receptor

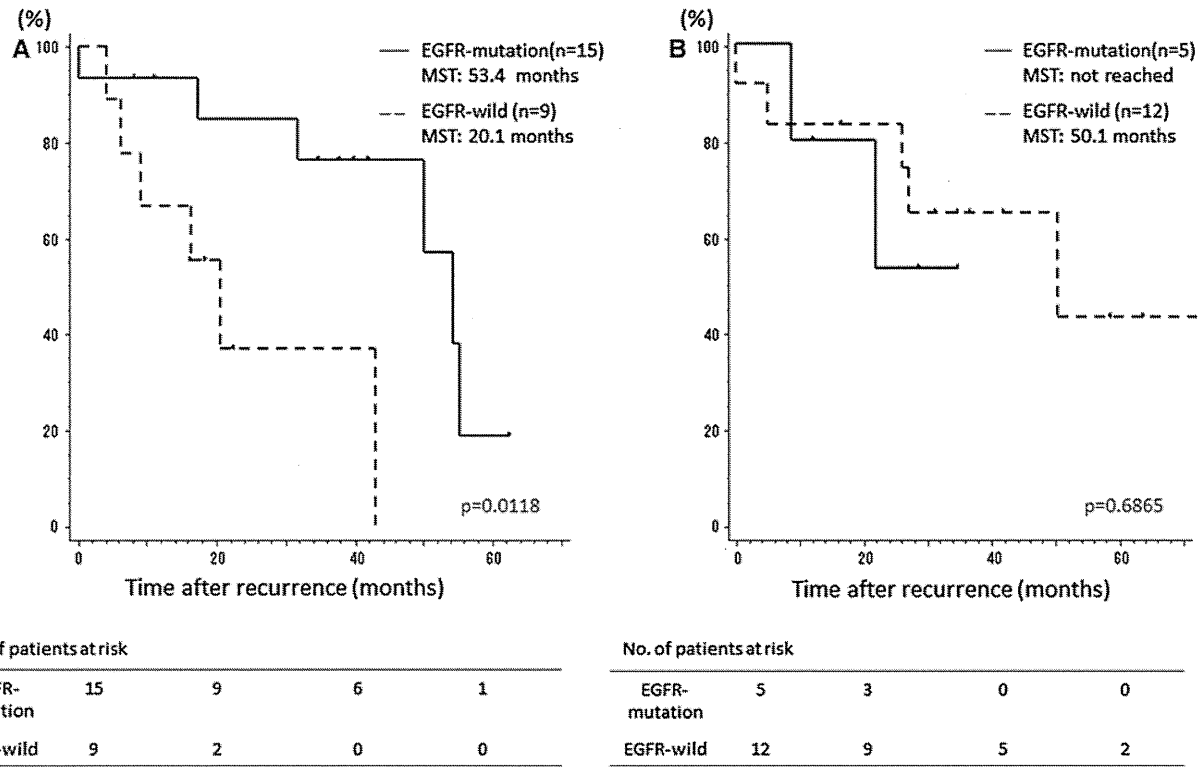


Fig. 3 The overall survival curves after the initial recurrence. **a** Patients treated with EGFR–TKIs. The MST of the patients with an EGFR mutation ($n = 15$) was 53.4 months, and that of those without an EGFR mutation was 20.1 months ($p = 0.0118$). **b** Patients treated without EGFR–TKIs. The MST of the patients with an EGFR mutation ($n = 5$) was not reached, and that of the patients without an EGFR mutation was 50.1 months ($p = 0.6865$)

mutations was significantly higher in females than in males ($p < 0.05$).

Several reports described the relationship between the mutation status of K-ras and clinicopathological factors such as the smoking status, pathological type, and gender [23, 27, 31]. The current series showed a relationship between the mutation status of K-ras and the gender, which was similar to that reported in a previous study [23]. Mucinous bronchioloalveolar carcinoma (BAC)/adenocarcinoma with bronchioloalveolar features is found in 48–76 % of adenocarcinomas with K-ras mutations, and K-ras mutations are found in adenocarcinomas with mucinous BAC, occurring in 28–86 % of the cases [27, 32–36]. Three of the 23 cases with K-ras mutations in the current study (13.0 %) were mucinous BAC/adenocarcinoma with bronchioloalveolar features.

The prognostic role of EGFR mutations in patients with resectable NSCLC has not been established. Kosaka et al. analyzed the survival of Japanese patients who did not receive EGFR–TKI treatment after surgery [23]. A univariate analysis showed that the patients with EGFR mutations had a longer OS period than those without mutations ($p = 0.0046$). However, a multivariate analysis showed that the presence of an EGFR mutation was not an independent prognostic factor. Unfortunately, the DFS after surgery was not analyzed in their article. The current study showed that there was a correlation between EGFR mutations and the DFS after surgery in NSCLC patients. Our findings were further analyzed after the data were restricted to patients with pStage I disease. Therefore, the analyzed patients were oncologically uniform, and this analysis showed the prognostic value of EGFR gene mutations. A univariate analysis showed no significant difference in the DFS between the EGFR-mutant and EGFR-wild-type patients. This result could indicate that the presence of an EGFR mutation is not a prognostic factor after surgery.

On the other hand, K-ras mutations have been demonstrated to be prognostic factors [16, 19, 23, 29, 37]. The presence of K-ras mutations is a significant poor prognostic marker in early stage patients with adenocarcinoma of the lung who undergo curative surgery [16], and this was confirmed by several investigators. Kosaka et al. [23] reported a prognostic analysis of K-ras mutations in 397 resected adenocarcinomas of Japanese patients. The patients with K-ras mutations tended to have a shorter survival period ($p = 0.218$). A meta-analysis of 53 published studies that assessed the prognostic value of

mutations in the K-ras gene was performed in 2005 [19]. This analysis identified K-ras mutations as a negative prognostic factor, with a hazard ratio for death of 1.50 (95 % CI, 1.26–1.80) in lung adenocarcinoma. The findings of the present study were consistent with these results, and the multivariate analysis revealed that K-ras mutations were independent prognostic factors.

There is considerable experimental evidence that the Raf-MEK-ERK cascade is a critical mediator of Ras-induced oncogenesis [20]. In addition, several studies have clearly demonstrated that Ras uses additional effectors to promote tumorigenesis [38]. At least four other effector classes have demonstrated roles in Ras transformation, as assessed in cell culture and mouse models of cancer; these are the p110 catalytic subunits (p110α, β, γ, and δ) of class I phosphatidylinositol 3 kinases (PI3K), the Tiam1 Rac small GTPase-specific GEF, the Ral small GTPase-specific GEFs (RalGDS, Rgl, Rgl2, and Rgl3), and phospholipase C-ε [38, 39]. This is consistent with the current results showing that the presence of a mutation of the K-ras gene was a poor prognostic factor.

Several studies have attempted to investigate the role of K-ras as an independent predictive marker of the benefit of chemotherapy. K-ras has also been perceived as a negative predictive marker of the response to chemotherapy based on retrospective studies. The studies that have investigated K-ras as a predictive marker have included adjuvant chemotherapy, chemotherapy for metastatic disease, or the combination of chemotherapy and radiation [40–43]. Only four patients with K-ras mutations had recurrent disease in the present study. However, the MST of these patients was shorter than that in the patients without K-ras mutations (38.3 vs. 51.4 months). This finding might have affected the results with regard to the findings that the presence of a K-ras mutation was a poor prognostic factor.

About 70–80 % of patients harboring EGFR mutations respond to EGFR–TKIs [21]. Patients with EGFR mutations have a significantly longer survival than those without EGFR mutations when they are treated with EGFR–TKIs [8, 28, 44]. Furthermore, two recent Japanese Phase III trials (NEJ002 and WJTOG3405) that compared gefitinib with platinum-doublet chemotherapy for patients selected according to the presence of EGFR mutations confirmed the predictive impact of these mutations in patients treated with EGFR–TKI. Although the present study size was small because of the restriction to pStage I disease, the presence of an EGFR mutation was a predictive factor for the efficacy of EGFR–TKIs in this study.

In conclusion, the presence of a mutation of the K-ras gene was a poor prognostic factor for recurrence after surgery in patients with stage I adenocarcinoma of the lung who underwent surgery. The presence of a mutation of the EGFR gene was found to be a predictive factor for the response to EGFR–TKI treatment in patients after recurrence, but was not a prognostic factor.

Conflict of interest All authors declare that they have no conflict of interest.

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Anemia Affects the Quality of Life of Japanese Cancer Patients

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The Functional Assessment of Cancer Therapy-Anemia (FACT-An) was developed to measure the effect of anemia on quality of life (QOL) in cancer patients. We have previously validated the Japanese version of the FACT-An in Japanese cancer patients receiving chemotherapy, hormone therapy, or radiation therapy. That analysis was limited to evaluating the relationship between QOL scores and hemoglobin (Hb) levels. In this study, the data were further analyzed in order to identify factors that affect QOL. The mean Hb level of the patients was unchanged over three months. Patient age, Eastern Oncology Group Performance Status (ECOG-PS) score, Hb level, and the type of treatment method received were each predictive factors of a patient's FACT-An score at baseline, while the patient's Hb level at three months and whether the patient had received a blood transfusion were both predictive factors of a patient's FACT-An score at three months. Anemia consistently negatively affected the QOL of cancer patients measured over a three-month period. These results confirm the clinical effectiveness of the FACT-An as a tool to assess anemia-related QOL in Japanese cancer patients.

Key words: anemia, quality of life, FACT-An, cancer, chemotherapy

INTRODUCTION

Toxic responses or the side effects of cancer therapy often affect a patient's quality of life (QOL). However, mild toxic responses that do not interfere with cancer treatment are often neglected. For instance, anemic conditions that do not require blood transfusions are often perceived to be of little clinical importance. Studies have shown that continuous anemia can cause tachycardia, palpitations, fatigue, respiratory disorders, and other symptoms [1]. These symptoms may also affect a patient's QOL. Therefore, anemia management for cancer patients is clinically important even when survival is the primary treatment goal.

The Functional Assessment of Cancer Treatment-Anemia (FACT-An) is a disease-specific scale that has been widely used to measure the effect of anemia on the QOL of cancer patients [2]. The scale has been proven to be reliable and valid in both Western [3] and Japanese populations [4]. Crawford *et al.* [5] reported a non-linear relationship between hemoglobin (Hb) levels and FACT-An scores. Our previous study indicated that this scale is clinically valid for differentiating anemia among patients with a variety of cancers [6]. However, the effects of factors other than anemia on the validity of the scale were not fully examined in the previous study. The current paper reports the findings of an exploratory study to examine the factors that affect QOL in patients with a variety of cancers who received various treatments using the FACT-An.

PATIENTS AND METHODS

From October 2003 to May 2004, cancer patients from nine institutions in Japan were enrolled in this study. The patients were either receiving or about to receive some form of cancer treatment, including chemotherapy, hormone therapy, or radiation therapy. Patients who received surgical treatment alone were

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