Table 1 Clinicopathological characterization underwent robotic surgery

	Lung cancer	Anterior-middle mediastinal disease	Posterior mediastinal disease
Number of cases	60	38	14
Age (range)	64.5 (34–89)	54.1 (18–78)	51 (25–71)
Gender	Male 32	Male 19	Male 5
	Female 28	Female 19	Female 9
Histology	Adeno carcinoma 53	Thymoma 18	Neurogenic tumor 8
	Squamous cell carcinoma 5	Thymic hyperplasia 4	Bronchoesophageal cyst 5
	Small cell carcinoma 1	Thymic cyst 8	Mesenchymal cyst 1
	Neuroendocrine cell carcinoma 1	Pericardial cyst 5	
		Castleman disease 2	
		Teratoma 1	
Complicated disease	–	Myasthenia gravis 9	–
		Autoimmune pancreatitis 1	
Clincal Stage	IA 41	–	–
	IB 13		
	IIA 1		
	IIB 1		
	IIIA 4		
Pathological Stage	IA 37	–	–
	IB 11		
	IIA 4		
	IIB 1		
	IIIA 7		
Operative procedure	Lobectomy 56	Tumor resection 15	Tumor resection 14
	Bronchoplastic lobectomy 1	Thymectomy 23	
	Segmentectomy 3		

and 3 patients died (5.0 %): cancer death in 2 and death from another disease in 1.

Robot-assisted surgery for anterior-middle mediastinal disease

The mean age of the 38 patients with anterior-middle mediastinal disease was 54.1 years, and there were 19 males and females. The histologic type was thymoma in 18 (47 %), accounting for a high rate. As a complication, myasthenia gravis was noted in 9 (24 %). The surgical procedure was tumor excision in 15 and thymectomy in 23. The operative time was 184.3 min, the console time was 112.9 min, and the blood loss was 43.8 mL. One patient bled 740 mL, but the procedure was not converted to thoracotomy, and no blood transfusion was performed in any case. The drainage period was 2.3 days, and postoperative complications developed in 3 (7.9 %): subcutaneous emphysema, median nerve palsy, and chylothorax in one patient each. Chylothorax was conservatively treated, but the drainage period and postoperative hospital stay prolonged to 24 and 27 days, respectively. No 30-day postoperative mortality occurred. The durations of postoperative and total hospital stays were 7.1 and 12.8 days, respectively, and no patient died and no recurrence has occurred in any patient.

Robot-assisted surgery for posterior mediastinal disease

The mean age of the 14 patients with posterior mediastinal disease was 51.0 years, and there were 5 males and 9 females. The histologic type was a neurogenic tumor in 8 (57 %), being the most common. The surgical procedure was tumor resection in all cases. The operative time was 142.6 min, the console time was 68.7 min, and the blood loss was 61.4 mL. The procedure was not converted to thoracotomy in any case, and no patient received blood transfusion. The drainage period was 1.6 days, and no postoperative complication and mortality developed in any patient. The durations of postoperative and total hospital stays were 5.0 and 7.7 days, respectively. No patient died, and no recurrence has occurred in any patient.

Discussion

The recent dissemination of robot-assisted surgery has been marked, but it is performed in only limited institutions in the general thoracic surgery field in Western and Asian countries. The main reasons are problems with national health insurance and the cost, but there are also risk–benefit problems characteristic for the thoracic organs in the general thoracic surgery field: (1) many great vessels with abundant blood flow are present in the thoracic cavity, (2) the target area is wide, (3) the main procedure is resection, and reconstruction procedures are limited, (4) only limited institutions have introduced complete thoracoscopic surgery, and (5) the learning curve is slower than in other fields [1, 2]. We analyzed the initial 112 cases of robotic surgery in Japan.

Robot-assisted surgery was safely introduced with low incidence of postoperative complications and no operation-related mortality. Particularly, 6.5 % of postoperative complication rate in the present study was lower compared to 25.6, 16.9 % of postoperative complication rate with thoracoscopic surgery in Western countries and Japan, respectively [3]. Moreover, Kent et al. [4] recently showed higher, more than 40 % of any complication rate after lung cancer surgery with thoracotomy, thoracoscopic, and robotic surgery in the US national database. On the other hand, the operative time was generally longer [5–8], because this is partially due to the operation being conducted very carefully, and also robot arm setting and the exchange of forceps take time. Dependence on assistants for the use of the vessel sealing device and automatic sutures may be stressful. This may improve along with the learning curve, but the development of devices in the future may also be important. However, considering the merits of robotic surgery, it is expected to be useful to reduce postoperative complications because of the superior operability, and improve the QOL, for lymph node dissection in surgery for lung cancer, as well as surgery in the narrow anterior mediastinum, particularly that for thymic disease [9–11].

No prospective comparative study on robotic and thoracoscopic surgeries has been reported, and the usefulness of robotic surgery has not been proven. Park et al. [12] reported a favorable long-term prognosis observed in a multicenter cooperative study, but only short-term outcomes have been compared in many studies [13–18]. Jang et al. [14] compared 40 cases of robotic lobectomy for lung cancer and 40 initial cases of thoracoscopic surgery, and observed postoperative complications in 4 (10 %) and 13 (32.5 %), respectively, the intraoperative blood losses were 219 and 374 mL, respectively, and the postoperative hospital stays were 6 and 9 days, respectively, showing that the outcomes of robotic surgery were significantly more favorable than those of thoracoscopic surgery. This report is referable with regard to comparison of initial cases, but the superiority of robotic surgery decreases on comparison with the recently advanced thoracoscopic surgery. Louie et al. [15] compared robotic and thoracoscopic surgeries by case–control analysis and observed no marked differences in the perioperative outcome, but analgesics were less used and patients returned to daily living activities earlier when treated with robotic surgery. However, the opposite results were reported by others: Augustin et al. [16] reported that the operative time, postoperative hemoglobin level reflecting intraoperative hemorrhage, and surgical cost were more favorable in thoracoscopic surgery. Therefore, the merits of robotic

Table 2 Perioperative results of robotic surgery

	Lung cancer	Anterior-middle mediastinal disease	Posterior mediastinal disease
Number of cases	60	38	14
Op time, min (range)	284.7 (144–555)	184.3 (62–368)	142.6 (76–270)
Console time, min (range)	206.4 (90–400)	112.9 (15–261)	68.7 (10–132)
Set up time, min (range)	12.2 (2–31)	13.5 (5–32)	12.2 (6–24)
Bleeding amount, mL (range)	129 (0–2069)	43.8 (0–740)	61.4 (3–450)
Blood transfusion [%]	1 [1.7]	0 [0]	0 [0]
Convert [%]	2 [3.3]	0 [0]	0 [0]
Drainage period, day (range)	3.3 (1–27)	2.3 (1–24)	1.6 (1–3)
Hospital stay, day (range)	8.2 (4–37)	7.1 (4–27)	5.0 (4–10)
Postoperative hospital stay, day (range)	10.9 (5–38)	12.8 (5–81)	7.7 (5–13)
Postoperative complication [%]	4 [6.7]	3 [7.9]	0 [0]
Detail of postoperative complication	Prolonged air leak 1	Subcutaneous emphysema 1	–
	Chylothorax 1	Median nerve palsy 1	
	Arrythmia 1	Chylothorax 1	
	Acute cholecystitis 1		
Mortality [%]	0 [0]	0 [0]	0 [0]

1. Verification of advantage
2. Education
3. Training
4. Cost reduction
5. Acquisition of advanced medical care
6. Coverage by health insurance

Fig. 2 List of current problems and future directions of robotic surgery

surgery have yet to be proven. Veronessi [17] investigated robotic surgery including thoracotomy, and stated that, at present, robotic surgery for lung cancer is equivalent to thoracoscopic surgery in terms of curability and safety, and superior in operability and the shortness of the learning curve, but disadvantageous in that usable devices are limited and the operative time is long. Kent et al. [4] compared thoracotomy, thoracoscopic surgery, and robotic surgery in cohorts of a large number of propensity-matched cases using a 2008–2010 database in the US, in which robotic surgery was more favorable than thoracotomy and equivalent to thoracoscopic surgery with regard to the mortality, morbidity, and length of hospital stay.

Regarding thymic disease, Rückert et al. [18] reported that the outcomes of robotic surgery were significantly better than those of thoracoscopic surgery in a retrospective cohort study of the remission rate of myasthenia gravis. Marulli et al. [19] reported that the outcome of robotic surgery for thymoma was equivalent to thoracoscopic surgery with regard to the operative time, postoperative hospital stay, and recurrence rate.

Although no outcomes of robotic surgery surpassing those of thoracoscopic surgery have been reported, robotic surgery has just begun, and all were initial cases. The merits of robotic surgery may be exhibited as skills are acquired and surgical devices are improved. The continuation of comparison and investigation is important. Clinical studies verifying the superiority of robotic surgery over thoracoscopic surgery are required. Advanced medical care starts with deciding on the primary endpoint and submitting a multicenter cooperative study protocol to the Ministry of Health, Labour and Welfare. Robotic surgery protocols for lung cancer and thymic disease have been planned, and comparison with retrospective data on thoracoscopic surgery is important. There is still a long way to go before it is covered by national health insurance, and this depends on the results of clinical studies.

There were several limitations in this study. We have just obtained initial results of robotic surgery with small number. All data were induced by the design of retrospective study with only using questionnaire. So, we can not verify the details of the data including operative cost. Marked differences of surgical method and perioperative results among the institutes were existed, especially the range of mean operative time showed 217–388 min. As Japanese robotic surgeons are still in the learning curve, we can not evaluate it in the present study.

On the other hands, medical insurance system in Japan is very excellent. However, as total medical cost become higher and higher, elimination of the cost is a very important issue in the present time. So, the definitive advantage for patient was required in robotic surgery corresponding with its high cost. Robotic surgeons know meticulous maneuverability in robotic surgery is very attractive, so that we expect to reduce local complications, particularly respiratory postoperative complications as same as other procedures of robotic surgery.

Finally, we described a list of current problems and future directions in Fig. 2. Especially, to be specified as an advanced medical care and covered by national health insurance, it is necessary to accumulate evidence proving the superiority of robot-assisted surgery over thoracoscopic surgery including cost-effectiveness.

Conclusion

The operative time was long but the incidence of postoperative complications was low, and there was no operation-related mortality in the initial results of robotic surgery. The outcomes may improve along with the learning curve, but it is urgently necessary to evaluate the robotic surgical outcomes of lymph node dissection for lung cancer, suture of the bronchus, lung, and esophagus, thymectomy, and nerve conservation, for which robotic surgery is considered useful, by comparison with the outcomes of thoracotomy and thoracoscopic surgery. Preparations for its employment in advanced medical care and coverage by national health insurance are urgent issues.

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Conflict of interest Hiroshige Nakamura and other coauthors have no conflict of interest.

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Clinical usefulness of gefitinib for non-small-cell lung cancer with a double epidermal growth factor receptor mutation

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Abstract. The aim of this study was to investigate whether the pattern of epidermal growth factor receptor (EGFR) gene mutations affects sensitivity to gefitinib treatment. We investigated 44 surgically resected non-small-cell lung cancer (NSCLC) specimens obtained between 2001 and 2012 at the Tokyo Medical University Hospital. The specimens were obtained from patients treated with gefitinib as 1st-, 2nd-, or 3rd-line therapy for postoperative recurrent NSCLC. We detected EGFR mutations using the cycleave PCR technique. In addition, the specimens from non-responders were stained with antibodies against hepatocyte growth factor receptor (HGFR; MET) and hepatocyte growth factor (HGF). We assessed the progression of non-responders over a period of 2 months. Intermediate responders were considered to be patients who responded (exhibiting at least stable disease) to gefitinib therapy for 3-11 months, while long-term responders were defined as those who responded to gefitinib therapy for >12 months. The NSCLCs were histologically classified as 43 adenocarcinomas and one large-cell neuroendocrine carcinoma. One patient had an exon 18 point mutation, 23 an exon 19 deletion, 2 an exon 20 point mutation, 16 an exon 21 point mutation and 2 patients had both exon 20 and 21 point mutations. There were 4 non-responders, including the 2 patients with exon 20 mutation, 25 intermediate responders (including 10 patients under ongoing treatment) and 15 long-term responders (2 of whom are under ongoing treatment), including the 2 patients with both exon 20 and 21 mutations. Of the specimens obtained from non-responders, 3 stained with the anti-MET antibody and 1 stained with the anti-HGF antibody. Therefore, NSCLC with exon 20 mutation may respond to gefitinib treatment in the presence of an additional EGFR mutation.

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Key words: double mutation, T790M, gefitinib, non-small-cell lung cancer

Introduction

Somatic mutations in the tyrosine kinase (TK) domain of epidermal growth factor receptor (EGFR) gene have been reported in patients with non-small-cell lung cancer (NSCLC). Certain mutations in the EGFR gene, such as leucine-to-arginine substitution at amino acid position 858 (L858R) in exon 21 or deletions in exon 19, are highly correlated with sensitivity to EGFR-TK inhibitors (TKIs) (1,2). The EGFR-TKIs gefitinib and erlotinib are effective in the treatment of EGFR-mutant NSCLC; however, there are also cases of EGFR-mutant NSCLCs exhibiting resistance to EGFR-TKI treatment. EGFR-TKIs have been shown to achieve a response in ~80% NSCLC patients with EGFR mutations, indicating that ~20% of NSCLC patients with EGFR mutation are unresponsive to this treatment (3).

A threonine-to-methionine substitution at amino acid position 790 (T790M) in exon 20 was reportedly associated with acquired resistance to EGFR-TKIs (4,5). In addition, hepatocyte growth factor receptor (HGFR; MET) gene amplification was reportedly associated with acquired resistance to EGFR-TKIs (6), while hepatocyte growth factor (HGF)-mediated MET activation was reported as the mechanism underlying EGFR-TKI resistance in lung cancer with EGFR-activating mutations (7). However, these studies were not pertaining to resistance, but rather investigating acquired resistance to EGFR-TKIs.

It was recently reported that pretreatment of NSCLC with T790M shortens the duration of response to EGFR-TKIs (9-12). However, over the last few years, we have observed long progression-free survival (PFS) in patients with T790M.

In this study, we aimed to investigate the pattern of EGFR mutations in NSCLC that affects sensitivity to EGFR-TKIs, determine the cause of shortened EGFR-TKI response duration and determine the correlation between resistance to EGFR-TKIs and phosphorylated MET or HGF expression.

Materials and methods

Patients and specimens. We investigated 44 surgically resected NSCLCs between 2001 and 2012. The specimens were obtained from patients treated with gefitinib as 1st-, 2nd-, or 3rd-line therapy for postoperative recurrent NSCLC.

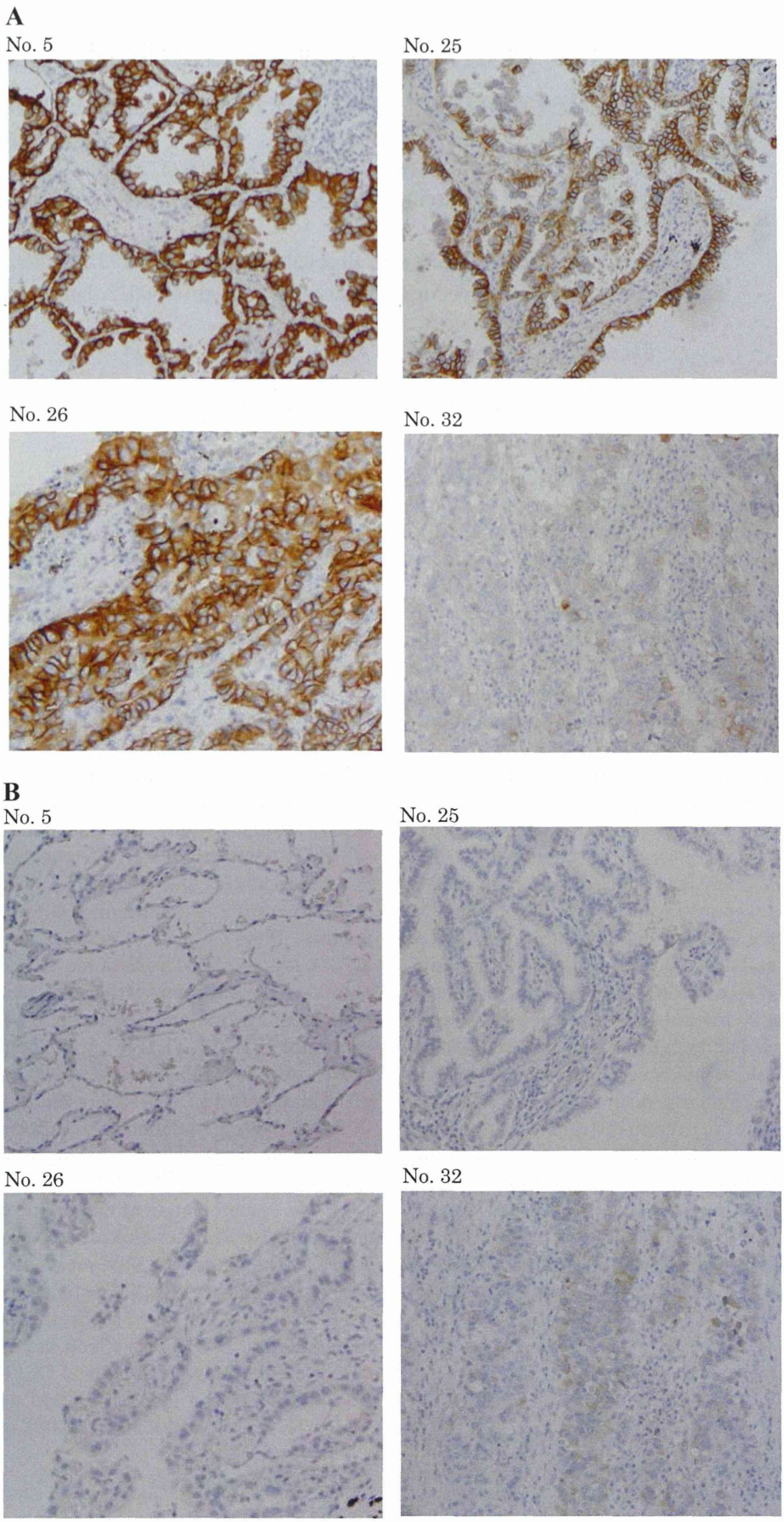

Figure 1. Immunohistochemical staining of non-small-cell lung cancer specimens. (A) The immunohistochemical staining for hepatocyte growth factor receptor (HGFR; MET) exhibited strong reactivity in the cell membranes of specimens no. 5, 25 and 26, whereas there was no reactivity with MET in specimen no. 32. (B) The immunohistochemical staining for HGF exhibited strong reactivity in the cell membranes of specimen no. 32, whereas there was no reactivity with HGF in specimens no. 5, 25, and 26.

Table I. Patient characteristics and response to gefitinib.

Patients	Gender	Age (years)	Histological type	Exon	Lobectomy	Response[a]
1	M	46	AdenoCa	18	Total	2
2	F	73	AdenoCa	19	Total	2
3	F	59	AdenoCa	19	Total	3
4	F	71	AdenoCa	19	Total	3
5	F	54	AdenoCa	19	Total	1
6	M	63	AdenoCa	19	Total	2
7	F	59	AdenoCa	19	Total	2
8	M	78	AdenoCa	19	Partial	2
9	F	68	AdenoCa	19	Partial	2
10	F	71	AdenoCa	19	Total	2
11	F	73	AdenoCa	19	Total	2
12	M	66	AdenoCa	19	Total	2
13	F	51	AdenoCa	19	Total	2
14	M	61	AdenoCa	19	Total	2
15	M	47	AdenoCa	19	Total	2
16	M	60	AdenoCa	19	Total	3
17	F	54	AdenoCa	19	Total	3
18	M	79	AdenoCa	19	Total	2
19	F	27	AdenoCa	19	Total	2
20	M	75	AdenoCa	19	Total	2
21	F	61	AdenoCa	19	Total	3
22	F	77	AdenoCa	19	Total	3
23	F	56	AdenoCa	19	Total	3
24	F	55	AdenoCa	19	Total	3
25	F	55	AdenoCa	20	Total	1
26	M	72	AdenoCa	20	Total	1
27	F	71	AdenoCa	21	Total	2
28	F	66	AdenoCa	21	Total	3
29	M	69	AdenoCa	20,21	Total	3
30	M	64	AdenoCa	20,21	Total	3
31	M	72	AdenoCa	21	Total	3
32	F	60	AdenoCa	21	Total	1
33	F	78	Large-cell Ca	21	Total	2
34	M	57	AdenoCa	21	Total	2
35	M	78	AdenoCa	21	Total	2
36	F	76	AdenoCa	21	Total	2
37	M	65	AdenoCa	21	Total	3
38	F	60	AdenoCa	21	Total	2
39	M	39	AdenoCa	21	Total	2
40	F	57	AdenoCa	21	Total	2
41	M	70	AdenoCa	21	Total	2
42	M	42	AdenoCa	21	Total	3
43	F	62	AdenoCa	21	Total	3
44	F	73	AdenoCa	21	Total	2

[a]1, No response; 2, intermediate response; 3, long-term response. M, male; F, female; Ca, carcinoma.

The NSCLCs were histologically classified as 43 adenocarcinomas and 1 large-cell neuroendocrine carcinoma. The patients included 19 men and 25 women, aged 27-78 years (mean age, 63.0 years).

Immunostaining. We detected EGFR mutations in matching formalin-fixed, paraffin-embedded tissue samples using the cycleave PCR technique (SRL Inc., Tokyo, Japan). We used an anti-MET rabbit monoclonal antibody (clone SP44;

Table II. Type of EGFR mutation and response to gefitinib.

	Type of mutation			
Type of response	Exon 18	Exon 19	Exon 20	Exon 21
Non-responders	0	1	2	1
Intermediate responders	1	14	0	10
Long-term responders	0	8	2[a]	7[a]

[a]Including 2 patients with both exon 20 and 21 mutations. EGFR, epidermal growth factro receptor.

cat no. 518-108830; Ventana Medical Systems, Inc., Tucson, AZ, USA) for MET staining and a goat polyclonal anti-human HGF antibody (cat no. 36073; LifeSpan BioSciences, Inc., Seattle, WA, USA) at a 1:40 dilution for HGF staining. Immunostaining for MET and HGF was performed using the Ventana System (Ventana Medical Systems, Inc, Harvard, MA, USA).

Type of response to gefitinib. We assessed the progression of non-responders to gefitinib treatment over a 2-month period. Intermediate responders included patients who responded (exhibiting at least stable disease) to gefitinib for 3-11 months. Long-term responders included patients who responded to gefitinib therapy for >12 months.

Results

EGFR mutations. The 44 NSCLC specimens included 43 adenocarcinomas and one large-cell neuroendocrine carcinoma. There was 1 patient with an exon 18 point mutation, 23 with an exon 19 deletion, 2 with an exon 20 point mutation, 16 with an exon 21 point mutation and 2 with both exon 20 and 21 point mutations (Table I).

Association of EGFR mutations with response to gefitinib. There were 4 non-responders, including the 2 patients with exon 20 mutation, 25 intermediate responders (including 10 patients under ongoing treatment) and 15 long-term responders (2 of whom are under ongoing treatment), including the 2 patients with both exon 20 and 21 mutations (Table II).

Immunostaining results. We investigated MET and HGF immunostaining in 4 non-responders, 3 of whom were MET-positive and HGF-negative, whereas 1 patient was MET-negative and HGF-positive (Fig. 1).

Discussion

Previous studies reported that the causes of acquired resistance to EGFR-TKIs in patients with EGFR mutations are a second mutation (T790M), MET amplification, or HGF-mediated MET activation. In those studies, ~50% of the cases with resistance to EGFR-TKIs exhibited a second mutation and ~20% were due to MET amplification (8). Our results were similar to those of previous studies, where EGFR-TKI therapy was the initial treatment. However, in our study, patients with NSCLC and exon 20 mutation responded to gefitinib in the presence of an additional EGFR mutation. In particular, 2 cases (29 and 30) in this study were treated with gefitinib for 14 and 21 months, respectively. Our results were better in terms of PFS compared to those previously reported (2-13 months) (9-12).

Inukai *et al* reported that a small fraction of T790M-positive tumor cells at the beginning of treatment may lead to clinical gefitinib resistance as a result of the selective proliferation of T790M mutant cells (9). We therefore considered that the growth speed of T790M-positive cells and the number of T790M cells prior to EGFR-TKI treatment regulation were important for predicting PFS in patients with NSCLC and EGFR mutations. We considered that the T790M cell number was more important, rather than the T790M cell growth speed, as the latter is low (13). However, there is no established clinical method to quantitatively measure the number of T790M cells. Therefore, we must make a prediction based on the sensitivity of EGFR mutation testing in patients with NSCLC. The sensitivity of direct sequencing was previously found to be ~25%, that of cycleave PCR was ~5% and that of Scorpion ARMS was 1% (14).

The PFS of NSCLC patients, as assessed by direct sequencing in a study by Wu *et al* was 2 months (11). However, the PFS of NSCLC patients assessed using cycleave PCR in our study was 17.5 months. We attributed the longer PFS in our study to the detection of fewer T790M cells in our patients using more sensitive cycleave PCR prior to EGFR-TKI treatment.

Consequently, our findings suggest that NSCLC patients may be long-term responders if a double mutation is identified using a highly sensitive method, such as cycleave PCR or Scorpion ARMS.

Our data and previous reports taken together, indicate that NSCLC with exon 20 mutation will respond to gefitinib treatment in the presence of an additional EGFR mutation. However, further investigations are required to determine the mechanism underlying our findings.

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Correlation between whole tumor size and solid component size on high-resolution computed tomography in the prediction of the degree of pathologic malignancy and the prognostic outcome in primary lung adenocarcinoma

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Abstract

Background: The presence of ground glass opacity (GGO) on high-resolution computed tomography (HRCT) is well known to be pathologically closely associated with adenocarcinoma in situ.

Purpose: To determine whether it is more useful to evaluate the whole tumor size or only the solid component size to predict the pathologic high-grade malignancy and the prognostic outcome in lung adenocarcinoma.

Material and Methods: Using HRCT data of 232 patients with adenocarcinoma who underwent curative resection, we retrospectively measured the whole tumor and solid component sizes with lung window setting (WTLW and SCLW) and whole tumor sizes with a mediastinal window setting (WTMW).

Results: There was significant correlation between the WTLW and the measurements of pathological whole tumor (pWT) ($r = 0.792$, $P < 0.0001$). The SCLW and WTLW values significantly correlated with the area of pathological invasive component (pIVS) ($r = 0.762$, $P < 0.0001$ and $r = 0.771$, $P < 0.0001$, respectively). The receiver operating characteristics area under the curve for WTLW, SCLW, and WTMW used to identify lymph node metastasis or lymphatic or vascular invasion were 0.693, 0.817, and 0.824, respectively. Kaplan-Meier curves of disease-free survival (DFS) and overall survival (OS) were better divided according to SCLW and WTMW, compared with WTLW. Multivariate analysis of DFS and OS revealed that WTMW was an independent prognostic factor (HR = 0.72, 95% confidence interval [CI] = 0.58–0.90, $P = 0.004$ and HR = 0.74, 95% CI = 0.57–0.96, $P = 0.022$, respectively).

Conclusion: The predictive values of the solid tumor size visualized on HRCT especially in the mediastinal window for pathologic high-grade malignancy and prognosis in lung adenocarcinoma were greater than those of whole tumor size.

Keywords
Lung adenocarcinoma, prognosis, solid component, ground glass nodule, high-resolution computed tomography

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Introduction

The National Lung Screening Trial demonstrated a significant reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% confidence interval [CI], 6.8–26.7; $P = 0.004$) (1). Recent advances in

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