Impact of the epidermal growth factor receptor mutation status on the prognosis of recurrent adenocarcinoma of the lung after curative surgery

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Abstract

Background: The prognosis of patients with epidermal growth factor receptor (EGFR) mutant adenocarcinoma of the lung (Mt) and EGFR wild-type adenocarcinoma (Wt) after complete resection of the lung differ; however, the mechanisms responsible for these differences remain unclear. The present study examined the post-operative prognosis of recurrent pulmonary adenocarcinoma patients to evaluate the clinicopathological nature of Mt and contribution of EGFR - tyrosine kinase inhibitors (TKI) to the prognosis of patients.

Methods: The subjects were 237 patients with recurrent pulmonary adenocarcinoma who underwent EGFR mutation analysis, and consisted of 108 patients with recurrent Mt and 129 with recurrent Wt. Multivariate analyses were performed to investigate whether the EGFR status is a prognostic factor for relapse-free survival (RFS) and post-relapse survival (PRS).

Results: RFS was significantly better in Mt than in Wt patients; median RFS were 20.2 and 13.3 months, respectively (p < 0.001). The multivariate analysis identified EGFR mutation as an independent prognostic factor for a favorable RFS (hazard ratio = 0.68; 95% confidence interval, 0.52–0.89). Although, no significant differences were observed in PRS between Mt and Wt patients (median PRS were 33.9 and 28.2 months, respectively; p = 0.360), PRS was significantly better in Mt with EGFR - TKI than in Wt and Mt patients without EGFR - TKI (p = 0.008 and p < 0.001, respectively). PRS was also significantly better in Wt than in Mt patients without EGFR - TKI (p < 0.001). The multivariate analysis identified the administration of EGFR - TKI as an independent prognostic factor for PRS (hazard ratio = 0.60; 95% confidence interval, 0.40–0.89).

Conclusions: EGFR mutation tumors were associated with a significantly better RFS for recurrent pulmonary adenocarcinoma after curative resection of the lung, which represented the less aggressive nature of Mt tumors. However, patients with Mt did not have a favorable prognosis after recurrence unless they received EGFR - TKI.

Keywords: Epidermal growth factor receptor mutation, Adenocarcinoma of the lung, Recurrence, Relapse-free survival, Post-relapse survival, Tyrosine kinase inhibitor
Background
The epidermal growth factor receptor (EGFR) mutation status has been identified as a strong predictive factor for the efficacy of EGFR - tyrosine kinase inhibitors (TKI). EGFR - TKI significantly prolong progression-free survival in patients with unresectable EGFR mutant adenocarcinoma of the lung (Mt) over that with chemotherapy [1–3]. Differences in clinicopathological features between Mt and EGFR wild-type adenocarcinoma of the lung (Wt) have recently been examined among resectable lung cancers. Radiologically, Mt has been associated with pure or mixed ground-glass opacities in computed tomography (CT) and also with a longer volume doubling time than Wt, which imply that Mt is a slow-growing tumor [4, 5]. Pathologically, Mt has been associated with a lepidic growth pattern, particularly in early stage lung cancer [6–9]. Although differences in the postoperative prognosis of patients between Mt and Wt remain controversial, most studies have demonstrated that patients with Mt have a significantly better [9–11] or slightly better prognosis than those with Wt [7, 12]. Since Mt is considered to be associated with adenocarcinoma in situ and minimally invasive adenocarcinoma, which rarely recurs after resection of the lung [9], the difference in the prognosis of Mt and Wt patients appears to strongly depend on the frequency of these low-grade adenocarcinomas.

The factors affecting the better postoperative prognosis of patients with Mt than those with Wt have not yet been identified. It currently remains unclear whether the low recurrence rate of Mt after curative surgery, slow progression after the recurrence of Mt, or therapeutic effects after recurrence, particularly EGFR - TKI for Mt patients, results in the better postoperative prognosis of patients with Mt In the present study, the clinicopathological features and postoperative prognosis (relapse-free survival [RFS] and post-relapse survival [PRS]) of Mt were prospectively analyzed and compared with those of Wt.

Methods
Patients and follow-up
Among 1903 patients who underwent complete resection of the lung and lymph node dissection for pathological stage I-III primary lung adenocarcinoma between January 2002 and March 2016, 270 patients (14.2%) developed recurrence. Among the patients with recurrent adenocarcinoma of the lung, 237 (87.8%) underwent an EGFR mutation analysis and they were included in the present study. Patients who received preoperative chemotherapy or radiotherapy were excluded from this study (n=70). Lobectomy was performed for the curative resection of lung cancer localized within a single lobe. Pneumonectomy was also performed if the tumor extended to multiple lobes or the central bronchus. Segmentectomy was performed for high-risk patients who were considered unable to tolerate lobectomy. Patients who underwent wedge resection of the lung were excluded from this study (n=224). Curative surgery was performed without induction therapy for patients with clinical stage III if they had resectable clinical N0–1 (such as clinical T3 N1 and T4 N0–1) or clinical single-station N2 disease. Chemoradiotherapy was performed for patients with clinical multi-station N2 stage III. Systemic mediastinal lymph node dissection or sampling was performed along with resection of the lung. Staging was based on the 7th Edition of the TNM Classification for Lung and Pleural Tumors.

Patients received a chest X-ray and blood examination, including a tumor marker analysis, such as carcinoembryonic antigen and sialyl Lewis-x antigen, regularly every 3–6 months for 1–3 years after surgery and every 6–12 months for 4–5 years after surgery on an outpatient basis. CT was routinely performed 1–2 times for 1 year. Chest X-rays, blood examinations, and CT were performed when patients showed subjective symptoms. When recurrence was suspected, head magnetic resonance imaging, positron emission tomography - CT, or bone scintigraphy was additionally performed in order to identify other recurrent sites. Based on these examinations, patients were diagnosed with recurrence at a joint conference consisting of thoracic surgeons, respiratory physicians, and radiologists. Proposed treatment plans, such as whether patients need to receive EGFR - TKI (e.g. gefitinib, erlotinib, and afatinib), cytotoxic agents, radiation, surgery, or best supportive care, were also decided.

Definition of terms
RFS was defined as the length of time after surgery without any sign of recurrence. New lesions considered to be metachronous multiple lung cancers were not defined as recurrence. PRS was the length of time from recurrence to the last confirmation date or date of death. RFS and PRS were examined for 237 patients with recurrent adenocarcinoma of the lung. The site of recurrence was classified into either locoregional recurrence or systemic recurrence based on initial recurrent sites. Locoregional recurrence was defined as recurrence in the ipsilateral lung, pulmonary hilum, or mediastinal, neck, axillary, or supraclavicular lymph nodes. Systemic recurrence was defined as recurrence other than locoregional recurrence; systemic recurrence included recurrence in the contralateral lung, brain, liver, adrenals, and bone, and pleura dissemination.

EGFR mutation analysis
DNA was extracted from formalin-fixed paraffin-embedded lung cancer tissue from surgical specimens.
The fragment method was performed to detect the EGFR exon 19 deletion mutation, and the Cycleave method was conducted to detect the EGFR exon 18 mutation (G719X), EGFR exon 20 mutation (T790 M), and EGFR exon 21 mutation (L858R and L861Q) [13]. A loop-hybrid mobility shift assay (LH-MSA) was also used to detect the above-described EGFR mutations [14].

Statistical analysis
The clinicopathological backgrounds of Wt and Mt patients were compared using the Student’s t-test for continuous variables and Fisher’s exact tests for categorical variables. RFS and PRS for Wt and Mt patients were analyzed by the Kaplan-Meier method and compared by Log-rank tests. Multivariable analyses for RFS and PRS were performed using Cox’s proportional hazard regression model. A P value< 0.05 was considered to be significant.

Results
The mean age of all 237 patients was 66.3 (38–86) years, and 133 patients (56.1%) were male. Lobectomy was performed on 228 patients (96.2%) (Table 1). The mean observation periods after surgery and relapse were 48.9 (4.2–132.5) months and 25.2 (0–115.3) months, respectively. Systemic recurrence was the common recurrent pattern among all recurrent adenocarcinomas of the lung (165 patients, 69.6%). Among 115 patients with pathological stage III, clinical N0–1 was observed in 97 patients (84.3%) and incidental pathological N2 in 86 (74.8%). Mt was observed in 108 patients (45.5%), and among them, mutations in EGFR exons 18, 19, 20, and 21 were observed in 5 (2.1%), 56 (23.6%), 1 (0.4%), and 46 patients (19.4%), respectively. There were 129 patients (54.4%) with Wt.

The clinicopathological backgrounds of Wt and Mt patients were compared in Table 2. Mt was more common in females (p < 0.001) and non-smokers (p = 0.001). No significant differences were observed in operation procedures (p = 0.958) (Table 2). In comparisons of pathological features, lymph node metastasis was more frequent in Mt than in Wt (p = 0.033), and lymphatic invasion was slightly more frequent in Mt than in Wt (p = 0.077). However, no significant differences were observed in pathological stages or recurrent patterns between Wt and Mt (p = 0.337 and p = 0.280, respectively).

RFS was significantly better in Mt than in Wt patients; median RFS for Mt and Wt patients were 20.2 months and 13.3 months, respectively (p < 0.001, Fig. 1). No significant differences were observed in PRS between Mt and Wt patients; median PRS for Mt and Wt patients were 33.9 months and 28.2 months, respectively (p = 0.360, Fig. 2a). As shown in Fig. 2b, PRS was significantly better in Mt with EGFR - TKI than in Wt and Mt patients without EGFR - TKI (p = 0.008 and p < 0.001, respectively). PRS was also significantly better in Wt than in Mt patients without EGFR - TKI (p < 0.001, Fig. 2b).

Univariate and multivariate analyses for RFS were shown in Table 3. In the univariate analysis, gender, smoking history, pathological T factor, lymphatic invasion, and the EGFR mutation status were identified as prognostic factors. In the multivariate analysis, EGFR mutations (hazard ratio [HR] = 0.68, 95% confidence interval [CI], 0.52–0.89, p = 0.005) and lymphatic invasion (HR = 1.34, 95% CI, 1.03–1.74, p = 0.029) were independent prognostic factors for RFS. Mt patients without lymphatic invasion had significantly better RFS than Mt patients with lymphatic invasion; median RFS were 29.0 (22.8–35.8) months and 15.9 (13.2–19.1) months, respectively (p = 0.020).

Univariate and multivariate analyses for PRS were shown in Table 4. In the univariate analysis, age, smoking history, pathological T factor, the administration of EGFR - TKI, and the recurrence interval were identified as prognostic factors for PRS, whereas the EGFR mutation status was not a prognostic factor for PRS. In the multivariate analysis, age (HR = 1.63, 95% CI, 1.11–2.38, p = 0.012) and the administration of EGFR - TKI (HR = 0.60, 95% CI, 0.40–0.89, p = 0.012) were independent prognostic factors.

Table 1 Clinicopathological features of patients with recurrent adenocarcinoma of the lung

| Total n = 237 |
|--------------|
| Mean age, year (range) | 66.3 (38–86) |
| Male, (%) | 133 (56.1%) |
| Surgical procedure, (%) |
| Pneumonectomy | 5 (2.1%) |
| Lobectomy | 228 (96.2%) |
| Segmentectomy | 4 (1.7%) |
| Pathological stage, (%) |
| I | 60 (25.3%) |
| II | 62 (26.2%) |
| III | 115 (48.5%) |
| Recurrence pattern, (%) |
| Locoregional | 72 (30.4%) |
| Systemic | 165 (69.6%) |
| EGFR status, (%) |
| Mutant | 108 (45.6%) |
| Exon 18 | 5 (2.1%) |
| Exon 19 | 56 (23.6%) |
| Exon 20 | 1 (0.4%) |
| Exon 21 | 46 (19.4%) |
| Wild-type | 129 (54.4%) |

EGFR, epidermal growth factor receptor
In Fig. 3, the prognosis of patients with EGFR exon 21 L858R point mutation (L858R) lung cancer (n = 45) and EGFR exon 19 deletion (19 Del) lung cancer were compared. Patients with L858R lung cancer had significantly poorer RFS than those with 19 Del lung cancer; median RFS were 14.7 months and 28.4 months, respectively (p = 0.001). No significant differences were observed in the frequency of using EGFR-TKI between patients with L858R and 19 Del lung cancer (68.9% vs 80.4%, respectively; p = 0.184). Moreover, there was no significant difference in

Table 2 Comparison of clinicopathological features between patients with Mt and Wt

|                | Mt (n = 108) | Wt (n = 129) | P values\(^a\) |
|----------------|-------------|-------------|----------------|
| Age            | 66.5        | 66.1        | 0.791\(^b\)    |
| Male, (%)      | 48 (44.4)   | 85 (65.9)   | 0.001          |
| Smoking history, (%) | 52 (48.1) | 94 (72.9)  | < 0.001        |
| Surgical procedure, (%) |           |             |                |
| pneumonectomy  | 2 (1.9)     | 3 (2.3)     |                |
| lobectomy      | 104 (96.2)  | 124 (96.1)  |                |
| segmentectomy  | 2 (1.9)     | 2 (1.6)     | 0.958          |
| Pathological tumor size, (mm) | 33.9 (11–100) | 40.0 (11–210) | 0.019\(^b\)    |
| Pathological stage, (%) |            |             |                |
| I              | 24 (22.2)   | 36 (27.9)   |                |
| II             | 26 (24.1)   | 36 (27.9)   |                |
| III            | 58 (53.7)   | 57 (44.2)   | 0.337          |
| Lymphatic invasion, (%) | 61 (56.4) | 58 (45.0)  | 0.077          |
| Vascular invasion, (%) | 68 (63.0)  | 83 (64.3)   | 0.826          |
| Pleural invasion, (%) | 50 (46.3)  | 72 (55.8)   | 0.144          |
| Nodal invasion, (%) | 81 (75.0)  | 80 (62.0)   | 0.033          |
| Recurrence pattern |            |             |                |
| locoregional   | 29 (26.9)   | 43 (33.3)   |                |
| systemic       | 79 (73.1)   | 86 (66.7)   | 0.280          |
| Administration of EGFR - TKI | 81 (75.0) | 7 (5.4)     | < 0.001        |

\(^a\)Fisher’s exact test
\(^b\)Student’s t-test

Mt EGFR mutant, Wt EGFR wild-type, TKI tyrosine kinase inhibitor

In Fig. 3, the prognosis of patients with EGFR exon 21 L858R point mutation (L858R) lung cancer (n = 45) and EGFR exon 19 deletion (19 Del) lung cancer were compared. Patients with L858R lung cancer had significantly poorer RFS than those with 19 Del lung cancer; median RFS were 14.7 months and 28.4 months, respectively (p = 0.001). No significant differences were observed in the frequency of using EGFR - TKI between patients with L858R and 19 Del lung cancer (68.9% vs 80.4%, respectively; p = 0.184). Moreover, there was no significant difference in
PRS between patients with L858R and 19 Del lung cancer; median PRS were 29.5 months and 38.0 months, respectively \((p = 0.525)\).

**Discussion**

Mt patients had better RFS than Wt patients (20.2 vs. 13.3 months, \(p < 0.001\)), and Mt was an independent factor for favorable RFS in the present study (HR = 0.68, \(p = 0.005\)). These results imply that Mt tumors take a longer period to recur after curative surgery and exhibit less aggressive behavior than Wt tumors. No significant differences were observed in PRS; however, Mt patients had slightly better survival than Wt patients (33.9 vs. 28.2 months, \(p = 0.360\)).

![Fig. 2](image)

No significant differences were observed in median PRS between Mt and Wt; median PRS were 33.9 months and 28.2 months, respectively \((p = 0.360, \text{Fig. 2a})\). PRS was significantly better in Mt with EGFR - TKI than in Wt and Mt patients without EGFR - TKI \((p = 0.008 \text{ and } p < 0.001, \text{respectively})\). PRS was also significantly better in Wt than in Mt patients without EGFR - TKI \((p < 0.001, \text{Fig. 2b})\).

**Table 3** Multivariate Cox’s Proportional Hazard Regression Model for RFS

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | \(p\) value         | HR 95% CI \(p\) value |
| Age (> 65)                | 0.809               |                       |
| Gender (Male)             | < 0.001             | 1.09 0.71–1.68 0.687  |
| Smoking history           | < 0.001             | 1.39 0.91–2.13 0.125  |
| Pathological T factor     | < 0.001             | 1.15 0.94–1.42 0.172  |
| Pathological N factor     | 0.353               |                       |
| Pathological stage        | 0.119               |                       |
| Vessel invasion           | 0.314               |                       |
| Lymphatic invasion        | 0.027               | 1.34 1.03–1.74 0.029  |
| Pleural invasion          | 0.231               |                       |
| EGFR mutation (+/-)       | < 0.001             | 0.68 0.52–0.89 0.005  |

**Table 3** Relapse-free survival, EGFR epidermal growth factor receptor, HR Hazards ratio, CI Confidence interval

Previous studies reported that the prognosis of patients with Mt who underwent complete resection of the lung was better than those with Wt; however, the reasons for this difference were unclear [9–11]. In pathological examinations of adenocarcinoma of the lung, the lepidic growth pattern was more frequently observed in Mt than in Wt [6–9], and Mt was associated with adenocarcinoma in situ and minimally invasive adenocarcinoma, which rarely recur [9]. Since the prognosis of Mt may strongly depend on the frequency of adenocarcinoma in situ and minimally invasive adenocarcinoma of the lung, we intended to include recurrent adenocarcinoma of the lung in order to exclude these low-grade adenocarcinomas; none of the tumors in the present study were adenocarcinoma in situ or minimally invasive adenocarcinoma (data not shown) which is defined in WHO classification 2015 and consistent with low-grade adenocarcinoma. The period after curative surgery to recurrence was longer in Mt patients than in Wt patients, and this result implied that Mt tumors had a less aggressive growth nature than Wt tumors among recurrent adenocarcinomas of the lung.

Watanabe et al. previously reported the bimodal distribution of recurrence patterns after curative resection of ...
adenocarcinoma of the lung; the predilection periods of pulmonary adenocarcinoma recurring after curative surgery were 6–14 months and 20–22 months [15]. In the present study, median RFS for Wt and Mt patients were 13.3 months and 20.2, respectively. This difference in RFS between Mt and Wt may result in the bimodal distribution of the recurrence pattern after curative resection for adenocarcinoma of the lung; the early recurrence of Wt and delayed recurrence of Mt. The EGFR mutation status provides thoracic surgeons with useful information on postoperative follow-up strategies for adenocarcinoma of the lung. Nearly 10% of recurrent Mt was observed more than 5 years after curative surgery in this study, and this result implies that patients with Mt need to be followed-up for a longer period than those with Wt.

Lymphatic invasion was another independent prognostic factor for RFS along with the EGFR mutation status. Median RFS for patients with Mt without lymphatic invasion was 29.0 (22.8–35.8) months and these tumors were considered to be less aggressive among Mt. Lymphatic invasion is associated with recurrence and has been identified as a poor prognostic factor for the overall survival of patients with early-stage lung cancer after surgery [16, 17]. In the present study, lymphatic invasion was not a prognostic factor for PRS in patients with recurrent adenocarcinoma of the lung. Lymphatic invasion only affected the RFS of patients with pulmonary adenocarcinoma after surgery.

According to randomized clinical trials on EGFR - TKI for unresectable advanced non-small-cell lung cancer, progression-free survival and overall survival were reported

| Table 4 Multivariate Cox’s Proportional Hazard Regression Model for PRS |
|-----------------------------------------------|
| **Variable**                      | **Univariate analysis** | **Multivariate analysis** |
|-----------------------------------------------|
| **p value** | **HR** | **95% CI** | **p value** |
| Age (> 65) | 0.014 | 1.63 | 1.11–2.38 | 0.012 |
| Gender (Male) | 0.178 | | | |
| Smoking history | 0.008 | 1.38 | 0.93–2.05 | 0.113 |
| Pathological T factor | < 0.001 | 1.07 | 0.80–1.45 | 0.638 |
| Pathological N factor | 0.831 | | | |
| Pathological stage | 0.684 | | | |
| Vessel invasion | 0.722 | | | |
| Lymphatic invasion | 0.787 | | | |
| Pleural invasion | 0.659 | | | |
| Systemic recurrence (vs. locoregional) | 0.072 | | | |
| EGFR mutation (+/-) | 0.360 | | | |
| Administration of EGFR - TKI | < 0.001 | 0.60 | 0.40–0.89 | 0.012 |
| Recurrence interval (24 < vs 24≥) | 0.017 | 1.35 | 0.91–2.01 | 0.142 |

PRS post-relapse survival, EGFR epidermal growth factor receptor, TKI tyrosine kinase inhibitor, HR Hazards ratio, CI Confidence interval

Fig. 3 Median RFS was significantly poorer for lung cancer patients with the Exon 21 L858R point mutation (n = 45) than those with the Exon 19 deletion (n = 56); median RFS were 14.7 months and 28.4 months, respectively (p = 0.001). No significant differences were observed between the two EGFR mutations; median PRS were 29.5 months and 38.0 months, respectively (p = 0.525)
Conclusion

Our study aimed to clarify the recurrence characteristics of each adenocarcinoma of the lung. The longer follow-up of patients with Mt after recurrence is considered necessary, and further studies are needed in order to examine predictive factors that explain the recurrence of adenocarcinoma of the lung after curative surgery.

Abbreviations
- 19 Del: EGFR exon 19 deletion
- CI: confidence interval
- CT: computed tomography
- EGFR: epidermal growth factor receptor
- HR: hazard ratio
- L858R: EGFR point mutation
- Mt: EGFR mutant adenocarcinoma of the lung
- MT: post-relapse survival
- RFS: relapse-free survival
- TKI: tyrosine kinase inhibitors
- Wt: EGFR wild-type adenocarcinoma of the lung

Ethics approval and consent to participate

The present study was approved by the ethics committee of the Kanagawa Cancer Center (EK1-99), and written informed consent was obtained from all patients.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

Authors’ contributions

Study design: TI, HN, HI, and TY. Sample collection: TI, HN, HI, TY, and KY. Data analysis: TI, HN, HI, and TY. Preparation of the manuscript: TI, HN, HI, TY, and MM. Reviewed and commented on the manuscript: HN, HI, TY, and MM. All authors read and approved the manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
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Received: 27 February 2018 Accepted: 24 September 2018
Published online: 05 October 2018

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