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Number of liver metastatic nodules affects treatment options for pulmonary adenocarcinoma patients with liver metastases

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ABSTRACT

Background: In patients with non-small cell lung cancer (NSCLC), the development of liver metastasis (LM) is a poor prognostic factor. Whether systemic treatment combined with local treatment for LM has benefit for NSCLC patients with LM is unknown.
Methods: We retrospectively reviewed and analyzed the clinical data and tumor epidermal growth factor receptor (*EGFR*) mutation status of 673 pulmonary adenocarcinoma patients, including 85 patients who developed LM at any time point in the course of the disease. Radiofrequency ablation (RFA) with real-time ultrasonographic guidance was used for local treatment of LM in these patients, if appropriate.
Results: Patients with an *EGFR* mutation were more prone to having synchronous LM than patients with *EGFR* wild-type (50.0% vs. 23.5%, $P = 0.019$). Fifty-six patients (65.9%) had ≦5 LM nodules. The median overall survival (OS) of patients with ≦5 LM nodules was 7.6 months compared with 2.9 months for those with multiple nodules ($P < 0.001$). The independent prognostic factors after LM were performance status, *EGFR* mutation, synchronous LM and LM numbers. The independent prognostic factors for patients with ≦5 LM nodules were performance status, *EGFR* mutation, LM concomitant with adrenal metastasis and having received RFA. Patients who received RFA treatment ($n = 6$) had longer OS after LM than those without RFA treatment ($n = 42$) (23.1 vs. 7.9 months, $P = 0.035$).
Conclusions: We recommend that patients with a better performance status and ≦5 LM nodules be considered for systemic treatment combined with RFA when LM develops.

1. Introduction

The most common extra-pulmonary sites of distant metastasis in non-small cell lung cancer (NSCLC) patients are the brain, bone, adrenal gland and liver [1]. The incidence of liver metastasis (LM) at the time of initial diagnosis of NSCLC is only 3.8%, and 95% of patients have involvement of more than 1 extra-hepatic organ [2]. The presence of LM is an independent prognostic factor for shorter survival in NSCLC patients; their median overall survival (OS) is only 4.2 months [3–5].

Treatment of NSCLC with chemotherapy has a response rate of about 20–30% [6,7]. Patients with an epidermal growth factor receptor (*EGFR*) somatic mutation had a response rate of over 60% when treated with *EGFR* tyrosine kinase inhibitors (TKIs) [8–10]. Resection of a solitary metastatic lesion in the brain or the adrenal gland is becoming the standard of care and can achieve a significant survival benefit [11–14]. Many published case reports suggest that lung cancer patients with LM may achieve long-term survival after metastatectomy, but determining which patients are likely to benefit from such an intervention is difficult [15–18]. Surgical resection of LM in NSCLC is rare, since the majority of patients are not candidates for operation. Non-surgical alternatives, such as radiofrequency ablation (RFA), are more suitable for these patients because the procedures are generally less invasive, and lead to limited morbidity and speedier recovery [19,20].

Continuation of EGFR-TKI plus local therapy for patients who develop oligometastases during EGFR-TKI treatment was suggested

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recently [21,22]. However, the effect of *EGFR* mutation status and local therapy after LM development is unclear. Therefore, we conducted this retrospective study to examine a large cohort of consecutive patients with LM from pulmonary adenocarcinoma to determine which patients may benefit from combined local therapy for LM lesions and systemic therapy.

2. Methods

2.1. Patients and LM lesions

We reviewed the chart records of 673 pulmonary adenocarcinoma patients who had *EGFR* mutation testing and received treatment at Veterans General Hospital, Taipei (VGH-TPE) from September 2006 to June 2011. Those who had other prior or concurrent malignancies were excluded. Patients who developed LM diagnosed with contrast-enhanced computed tomography (CT) during the disease course were identified. The timing of LM was categorized as synchronous and metachronous. Synchronous LM was defined as LM found at the time of the lung cancer diagnosis, and metachronous LM referred to LM that occurred after the diagnosis of lung cancer. Lung cancer staging was evaluated based on the seventh edition of the tumor-node metastasis staging system for NSCLC [23]. Performance status was assessed according to Eastern Cooperative Oncology Group (ECOG) criteria [24]. The characteristics of the LM lesions (including nodule number, distribution, and maximal size), prior systemic treatment, and extra-hepatic lesions were recorded. Extra-hepatic lesions were considered "active" if the imaging studies revealed new sites of involvement or previous metastatic site progression within 4 weeks of LM. A total of 85 patients with LM entered the final analysis (Supplement Figure 1).

Supplementary Figure 1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2014.09.002.

EGFR mutation analysis was performed with direct nucleotide sequencing. The specimens for analysis were mainly from primary lung lesions ($n = 582$), including the lymph node ($n = 38$), pleural effusion ($n = 31$), and pleural biopsy ($n = 14$), as well as bone ($n = 4$), skin ($n = 2$) and chest wall ($n = 1$). Only 1 specimen was from a LM lesion. In all, 331 patients (49.2%) harbored an *EGFR* mutation (159 had an exon 19 deletion, 162 had L858R and 13 had both mutations).

2.2. Therapeutic efficacy evaluation

RFA was performed with real-time ultrasonography guidance. The radiofrequency electrode was advanced into the tumor and a dynamic CT scan was used to evaluate local therapeutic efficacy 1 month after the procedure. Systemic treatment objective response was classified according to the response evaluation criteria in solid tumors (RECIST) version 1.1 [25]. Progression-free survival (PFS) was measured from the date primary systemic therapy was initiated to documented disease progression or death from any cause. OS was measured from the date of diagnosis of LM until death or last survival follow-up. The last follow-up date was July 30, 2013.

2.3. Statistical analysis

Continuous variables were compared using Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for data that were not normally distributed. Categorical variables were compared using Fisher's exact test and Chi-square, as appropriate. The Kaplan–Meier method was used to analyze OS and PFS, and survival curves were compared using the log-rank test. A Cox proportional hazards method was used to detect multivariate predictors of survival after LM. Only those variables with a P value <0.05 in univariate analysis were included in the multivariate analysis. A 2-sided value of $P < 0.05$ was considered statistically significant. The SPSS version 19 statistical software package (SPSS INC, Chicago, IL, USA) was used for data analysis.

3. Results

3.1. EGFR mutation status and LM nodule characteristics

Eighty-five of the 673 patients who had *EGFR* examined had LM at any point during the disease course. All 85 patients were ethnic Chinese. The median age at LM diagnosis was 62.8 ± 13.6 years. LMs were synchronous with the primary lung cancer diagnosis in 29 (34.1%) patients and metachronous in 56 (65.9%). Synchronous LM was more common in the *EGFR*-mutated patients than in the wild-type patients (50.0% vs. 23.5%, $P = 0.019$). The median time from initial lung cancer diagnosis to the first LM diagnosis among the metachronous LM patients was 10.3 months, which was insignificantly longer than that in the *EGFR*-mutated group (11.2 vs. 10.1 months, $P = 0.184$). Only 3 (3.5%) patients had a solitary LM without active extra-hepatic metastatic disease; 82 (96.5%) had active extra-hepatic metastatic disease and 44 (51.8%) had involvement of more than 2 extra-hepatic organs. The most common extra-hepatic metastatic sites were the contra-lateral lung (78.8%), bone (72.9%) and brain (35.3%). Thirty-three (38.8%) patients had received EGFR-TKI treatment before LM developed, including 14 (16.4%) patients with an *EGFR* mutation (Table 1).

3.2. Prognostic factors associated with survival after development of LM

Seventy-eight (91.8%) patients died before July 30, 2013. The median OS after LM diagnosis was 4.8 months, and was much better for the *EGFR*-mutated patients (6.0 vs. 2.9 months, $P = 0.002$). Twenty-six (30.6%) TKI-naive patients started EGFR-TKI treatment after LM developed, including 17 (20%) who harbored an *EGFR* mutation. The median OS of these 26 patients was 23.6 months in the *EGFR* mutation group and 2.7 months in wild-type group ($P < 0.001$).

Univariate analysis of the 85 patients with LM showed that performance status (PS > 2), no *EGFR* mutation, more than 2 extra-hepatic metastatic organs, metachronous metastasis, brain metastasis, adrenal metastasis and >5 LM nodules were significantly poor prognostic factors for survival after LM. Multivariate analysis showed that poor PS (HR: 10.50, 95% CI: 4.77–23.12, $P < 0.001$), no *EGFR* mutation (HR: 2.26, 95% CI: 1.29–3.97, $P = 0.050$), metachronous metastasis (HR: 1.76, 95% CI: 1.02–3.03, $P = 0.041$) and more LM nodules (HR: 4.48, 95% CI: 1.73–11.65, $P = 0.002$) were independent poor predictive factors for survival after LM (Table 2).

3.3. The impact of numbers of LM on survival

Fifty-six of the 85 patients who had LM had ≦5 LM nodules. The median OS was significantly better for these patients than for the 29 patients who had multiple nodules (7.6 vs. 2.9 months, $P < 0.001$) (Fig. 1). Twenty-one of 34 (61.8%) *EGFR*-mutated patients and 35 of 51 (68.6%) *EGFR* wild-type patients had ≦5 LM nodules ($P = 0.641$). *EGFR* mutation status was not associated with LM nodule number. However, patients with ≦5 LM nodules had significantly less extra-hepatic organ metastasis (2.3 vs. 3.2, $P = 0.003$).

3.4. Systemic treatment for LM patients

Seventy (82.4%) patients received systemic therapy after LM, including 6 patients who also received RFA treatment. Systemic treatment included either EGFR-TKIs ($n = 32$) or chemotherapy