

Unique natural history of an EGFR mutated adenocarcinoma

Unikátní přirozená historie EGFR mutovaného adenokarcinomu

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Summary

Background: Supportive care alone cannot be indicated for cancers for which established standard therapy exists unless there is a specific reason. Due to the refusal of standard therapy by the patient after proper explanation of the therapy, we experienced a long-term follow-up of >10 years with supportive care alone in an epidermal growth factor receptor (EGFR) mutated lung cancer patient. **Case:** A 70-year-old woman was referred due to the right lung with some ground glass opacities (GGOs). One of the GGOs which was resected in another hospital had been confirmed to be EGFR mutation-positive lung adenocarcinoma. Although EGFR-tyrosine kinase inhibitor (TKI) was explained to be the standard therapy, the patient refused receiving the therapy and wished to follow up imaging of the remaining GGOs. During the follow-up period of 13 years, the each GGO showed a gradual increase. The doubling time of the largest GGO and that of serum carcinoembryonic antigen was > 2,000 days, respectively. **Conclusion:** Although very rare, some of EGFR mutated lung adenocarcinoma might have a very slow progression. Clinical course of this patient provides useful information to the clinical practice of future patients who may have similar clinical courses.

Key words

natural history – epidermal growth factor receptor – lung adenocarcinoma – standard therapy – supportive care

Souhrn

Východiska: U nádorů, pro něž je stanovena standardní léčba, nelze indikovat samotnou podpůrnou léčbu, pokud pro to neexistuje zvláštní důvod. Protože pacientka s adenokarcinomem plic a mutací receptoru epidermálního růstového faktoru (epidermal growth factor receptor – EGFR) odmítla standardní terapii, získali jsme zkušenost s dlouhodobým sledováním pacientky pouze na podpůrné léčbě, které trvalo > 10 let. **Případ:** Sedmdesátiletá žena k nám byla odeslána pro výskyt opacit mléčného skla (ground glass opacities – GGO) v pravé plicí. U jedné z GGO, která byla resekována v jiné nemocnici, byl potvrzen EGFR mutovaný adenokarcinom plic. Ačkoli jí bylo vysvětleno, že standardní terapií je EGFR tyrozinkinázový inhibitor (TKI), pacientka tuto terapii odmítla a přála si zbylé GGO sledovat pomocí zobrazovacích technik. Během dlouhodobého sledování, které trvalo 13 let, bylo u každé GGO pozorováno mírné zvětšení. Zdvojnásobení času největší GGO a karcinoembryonálního antigenu v séru byl > 2 000 dní. **Závěr:** I když je to velmi vzácné, některé EGFR mutované adenokarcinomy plic mohou mít velmi pomalou progresi. Klinický průběh u této pacientky poskytuje užitečnou informaci pro klinickou praxi u budoucích pacientů, u kterých může být klinický průběh podobný.

Klíčová slova

přirozená historie – receptor epidermálního růstového faktoru – adenokarcinom plic – standardní terapie – podpůrná léčba

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Introduction

Patients with cancer for which standard therapy has been established rarely receive supportive care alone without standard therapy, unless there might be special reasons. The most common reasons for agonizing the choice of supportive care alone might be impairment of important organs such as the heart, lung, liver and kidneys. This may also apply to patients who refuse standard therapy, even though they have been properly informed and understood the therapy. Many of these patients might not wish to follow up imaging studies. Therefore, it could be difficult to obtain information on the natural history of cancer for which standard treatment have been established.

Epidermal growth factor receptor (EGFR) mutation is the most common driver gene of non-small cell lung cancer (NSCLC) [1]. For patients with this gene mutation, EGFR-tyrosine kinase inhibitor (TKI) treatment is the established stand-

ard therapy [1]. Consented follow-up of clinical status without standard EGFR-TKI therapy appeared to be performed only for selected patients with reasons such as refusal of treatment or serious complications. To our best knowledge, there has been no report of the long-term natural history of EGFR mutated NSCLC patient who had been well informed for standard therapy. We show herein a case with a consented 13-year follow-up observation of EGFR-mutated NSCLC.

Case report

A 69-year-old was referred to a hospital because of some ground glass opacities (GGOs) in the upper lobe of the right lung 7 years ago. These GGOs were incidentally detected by annual mass-screening. The patient had no smoking history. For the purpose of pathological diagnosis, the largest GGO located in the right upper lobe was surgically resected. Pathologically, the tumor cells proliferated while replacing the alveolar struc-

tures without destroying them. Moderate thickening of alveolar septa was accompanied. Pathological diagnosis was well-differentiated lung adenocarcinoma T1bN0M0. Driver gene examination of the resected specimen revealed Exon 21 L858R of epidermal growth factor receptor (EGFR). Eight months after the resection, the patient was referred to our hospital. The patient had no sign and symptom. Physical examination was unremarkable. Serum carcinoembryonic antigen (CEA) level was slightly elevated to 5.2 ng/mL (normal range 0–5.0 ng/mL), although pretreatment CEA level was 3.9 ng/mL. Chest CT scan taken at the time of initial visit revealed two GGOs in the right upper lobe of the lung (Fig. 1A). These GGOs were irregular, heterogeneous size, had a small portion of dense areas. Imaging studies showed no lesions except for lung GGOs. At this time and afterwards, the patient was advised to be treated with EGFR-TKI, however, she refused to have the stand-

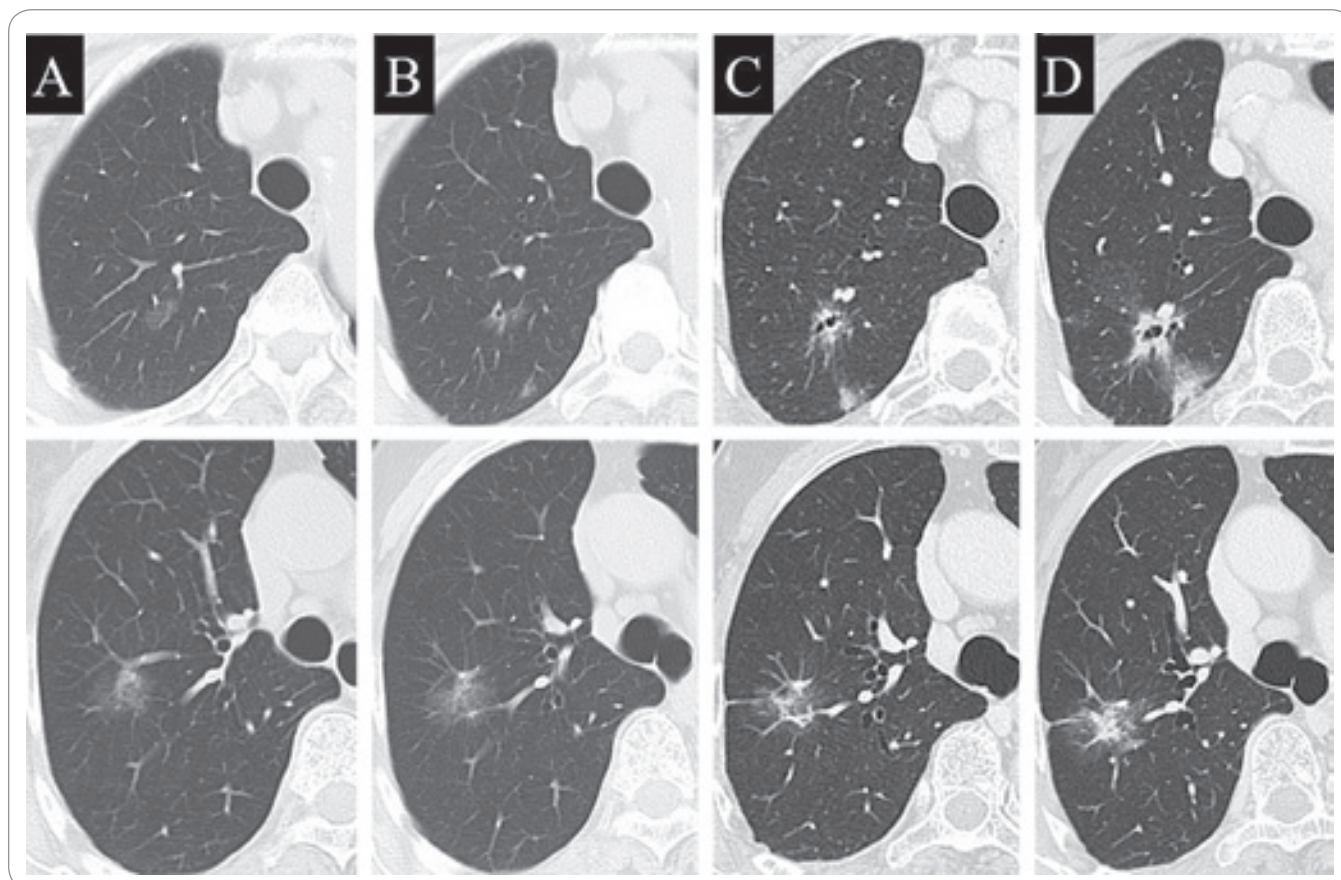
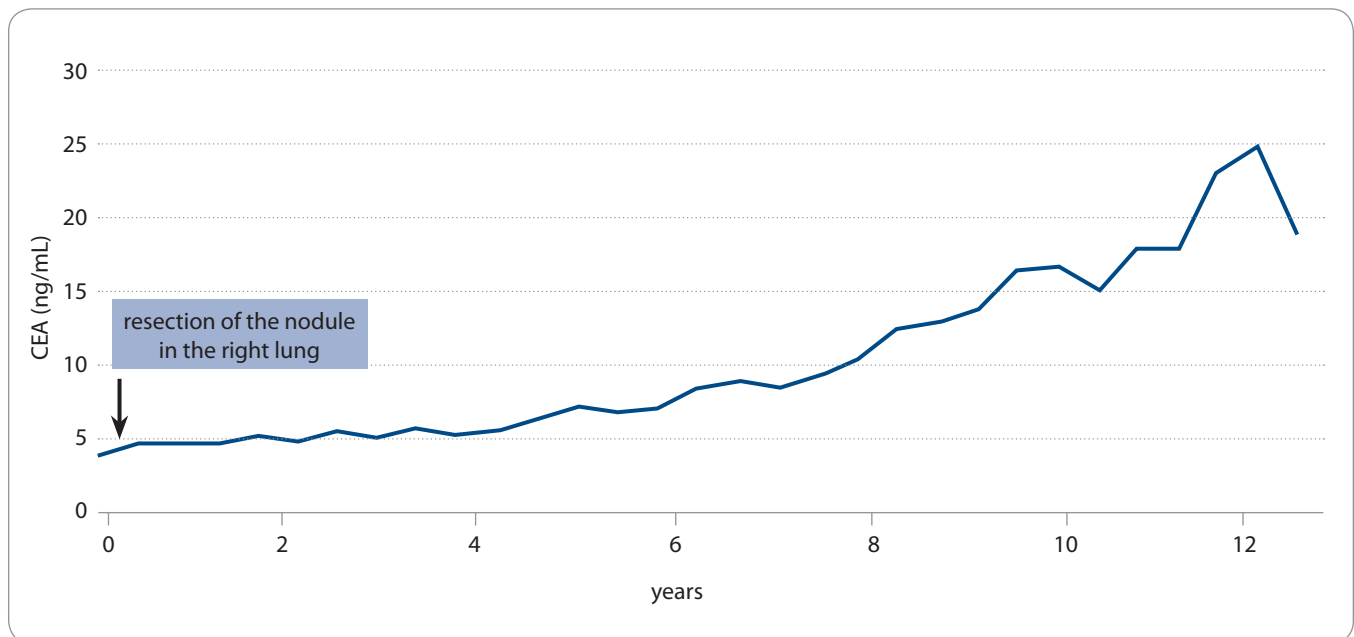


Fig. 1. Chest CT taken 3 months after the largest ground glass opacity (GGO) was resected (A), CT taken at 5 years (B), 10 years (C), and 13 years after the resection (D), showed slowly progression in the remaining GGOs.



Graph 1. Clinical course and serum carcinoembryonic antigen (CEA).

ard therapy based on her own beliefs. In spite of her refusal of taking EGFR-TKI, she agreed to receive follow-up CT scans. Each GGO revealed a gradual increase in the size and proportion of high density areas from year to year (Fig. 1B, C). Regular physical examinations and serum CEA measurements were also performed on a regular basis. There were no physical examination findings suggestive of metastasis. Thirteen years after the initial diagnosis, the maximum diameter of each GGOs was ≥ 30 mm, and the increase in the proportion of high density parts became more remarkable (Fig. 1D). Serum CEA gradually increased up to 25.0 ng/mL (Graph 1), but the patient is fine without any symptoms.

Discussion

EGFR mutation is the most common driver gene of NSCLC [1]. Similar to NSCLC without driver genes, standard treatment has been surgical resection for resectable EGFR mutated NSCLC patients. For those with locally advanced and metastatic EGFR mutated NSCLC, on the other hand, EGFR-TKI has been the standard drug for the last 20 years [1]. Natural history and active surveillance have been reported in some malignant diseases other than EGFR mutated NSCLC [2–4]. To our best knowledge,

however, long-term follow-up EGFR mutated NSCLC has never been reported except for exon 20 insertions, uncommon types for which standard therapy has not been established [5]. From an ethical point of view, long-term follow-up of EGFR mutated NSCLC patients without standard therapy should not be performed without any specific reasons. In our patient, her clinical course has been monitored for 13 years because the patient did not wish to receive EGFR-TKI therapy. Since the patient's consent was obtained for active surveillance, detailed progress could be recorded. This is the first report to describing the natural history of EGFR mutant NSCLC over a decade.

There are some methods to assess the tumor growth. As one of them, assessment of volume doubling time (VDT) on images has been used [6,7]. VDT of the largest GGO in the upper lobe of the right lung was 2,273 days when calculated using Schwartz's formula assessing that it was spherical [6,7]. In our previous study on VDT in 140 patients with lung adenocarcinoma detected in a chest radiograph mass screening program, the mean VDT was 177 days, and 5.0% of these patients had a VDT of > 400 days [8]. In a recent study of 268 lung adenocarcinomas detected on

chest CT scan, Park et al reported that the median VDT was 529 days (interquartile range 278–872 days) for lung adenocarcinomas [9]. Compared to the results of these reports, the VDT of the GGO in our patient was evaluated to be very long. Another method to assess tumor progression is to evaluate serum levels of tumor markers over time. Even in EGFR mutated NSCLC patients, serum CEA has been evaluated to reflect the extent and prognosis of lesions [10–13]. In other words, high CEA levels are generally associated with disease progression and poor prognosis [10–13]. This patient underwent CEA measurements prior to surgical resection, and she had the measurements several times during the 13 years after resection. Serum CEA was within normal limits at diagnosis, but serum CEA did not return to normal after surgical resection and increased levels almost consistently during subsequent follow-up (Graph 1). In this patient, the doubling time of serum CEA was calculated to be 2,109 days. It was a very interesting result; the doubling time of this serum CEA was almost the same as the above-mentioned VDT of the largest GGO in the upper lobe of the right lung.

In general, elevated serum levels of CEA represent „the presence of cancer cells capable of producing CEA“, „in-

creased total number of cancer cells producing CEA", or both. That is, in a cancer cell population with a low ability to produce CEA, there may be an increase in CEA if there is a rapid increase in cancer cells. On the other hand, in a cancer cell population with a high ability to produce CEA, there may be an increase in CEA even if there is a slow increase in cancer cells. Taking the changes of GGOs in imaging studies into consideration, it was speculated that the increase in serum CEA was likely the latter.

An additional point to discuss in this patient was whether the multiple lung nodules were synchronous primary lung adenocarcinomas or multiple lung metastases. At the time of initial presentation, two or more nodules were detected in chest CT scan. It was difficult to determine exactly whether they are simultaneous lung cancers or lung metastases, but it was presumed to be the former, considering the features on the image. Progression of GGO-based inhomogeneous synchronous lung adenocarcinomas seems to be very slow and the prognosis of them to be relatively good among those with lung adenocarcinomas [14,15]. On the other hand, it is known that there is a group of EGFR mutated lung adenocarcinoma patients whose metastases are localized in the lung [16], and it has been reported that the prognosis of these patient groups is relatively good [17]. Whether the lesion might be synchronous lung adenocarcinoma or, unlikely, lung metastases, the course of this patient, whose lesions are long-term confined to the lung, were notable.

It is not possible to discuss all the natural history of EGFR mutant NSCLC by showing the clinical course of this patient. However, we showed the presence of EGFR mutant NSCLC which progresses relatively slowly. The elucidation of the natural history in EGFR mutated NSCLC might contribute to clinical strategies, judgment of treatment efficacy, and prognosis estimation for patients with this type of NSCLC.

Author contributions

SO and HS collected the data. SO and HS analyzed the data and prepared the manuscript. All authors approved the final version of the article.

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Ethics

This study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor, and Welfare of Japan. Written informed consent for a non-interventional retrospective study was obtained from each patient. The analysis of the medical records of patients with lung cancer was approved by the ethics committee of Mito Medical Center—University of Tsukuba Hospital.

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