Osimertinib is remarkablysignificantly effective in treating synchronousthe treatment of simultaneous multiple primary lung cancer with ground-glass nodules and solid nodules: A case report

Abstract:— : With the Following the changes in the disease spectrum of lung cancer spectrum and the wide range of application of spiral computed tomographyCT, the detection rate of simultaneous synchronous multiple primary lung cancer ((sMPLC)) is has increased ing,; but however, many issues related to its the diagnosis and treatment remain unresolvedare still faced with many problems. At pPresently, sMPLC is mainly treated by surgery, and the use of targeted therapy is rare. Here, Wwe report the case of a 70-year-old man with sMPLC who underwent surgical resection of the main lesion of sMPLC in the left lower lung lobe. Genetic testing revealed EGFR a G719A mutation in the EGFR geneprotein. Following treatment with osimertinib, The the ground--glass nodules showed had complete remission and the solid nodules had showed partial remission after treatment with Osimertinib in the right residual lesion in the right lung. This case report showeds that osimertinib, an epidermal growth factor receptor-tyrosine kinase inhibitorEGFR-TKI, has a high has a significant advantage efficacy for treating in the treatment of sMPLCmultiple primary lung cancer and should be deserves further studyied for its potential in treating sMPLC.

Key Wwords: Simultaneous Multiple Primary Lung Cancer;— ; Osimertinib;— ; Targeted tTherapy

Introduction

Osimertinib, an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), is the current recommended standard of care for the first-line treatment of for advanced EGFRepidermal growth factor receptor-positive mutated non-small cell lung cancer (EGFR+ NSCLC)[1], and it is also widely used accepted for as a postoperative adjunctivevant therapy for in stage IB through IIIA EGFR mutation + positive NSCLC

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stages IB-IIIA[2,3], ~~—~~; however, ~~but~~ the efficacy of osimertinib for treating ~~in the treatment of~~ synchronous multiple primary lung cancer (sMPLC) is ~~not~~ unclear. sMPLC involves ~~refers to~~ the simultaneous occurrence of two or more primary lung malignancies in the same patient ~~at the same time,~~; each lesion of sMPLC has independent genetic abnormalities~~changes~~, and most lesions show ground-glass opacities (GGOs)~~changes.~~ [4]. ~~As~~Following the changes in the ~~of~~ disease spectrum of lung cancer and advances in ~~the development of~~ imaginge technology, the number of patients diagnosed to have ~~with S~~sMPLC has ~~is~~ increased~~ing~~. However, it remains a critical challenge to ~~the~~ appropriately diagnose~~is~~ and treat~~ment of~~ s~~S~~MPLC ~~can be challenging~~, particularly because of the controversial ~~especially the~~ treatment strategy ~~remains controversial~~[5]. ~~s~~Surgical resection is the primary treatment option ~~of priority~~, supported ~~assisted~~ by radiofrequency ablation and stereotactic body radiation therapy (SBRT). Targeted therapy ~~is~~ has been rarely reported, and the effects of this therapeutic approach are ~~is~~ unclear. Here, we report the case of a 70-year-old man with sMPLC who underwent surgical resection of the main lesion and was treated with osimertinib.

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Case Report

A 70-year-old man with no history of smoking visited ~~came to~~ our hospital for a physical examination on June 21, 2021. ~~His chest c~~Enhanced computed tomography (CT) of his chest showed multiple lung lesions (lesion 1 was located in the left lower lung lobe, lesion 2 was located in the right middle lung lobe, and lesion 3 was located in the right lower lung lobe (Figure 1)). The patient requested ~~–~~further observation and follow-up. ~~The~~ A chest CT ~~was~~ scan~~ned~~ conducted again on November 06, 2021, revealed an increase in the size of some pulmonary nodules ~~were larger than before, and he~~ The patient then opted for ~~decided to undergo~~ surgical treatment. His medical history included hypertension, diabetes, bronchial asthma, and chronic obstructive pulmonary disease. The ~~L~~lung function test showed severe obstructive ventilatory~~ion~~ dysfunction (forced expiratory volume in 1 s (FEV_1), ~~was~~ 1.01~~,~~; forced vital capacity (FVC), 1.77~~;~~ FEV_1: FVC, ~~was~~ 42.25%). According to the results of ~~P~~preoperative evaluation, ~~showed that~~ the mass in the left lower lung, the ground-glass nodules in the

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right upper lung, and the solid nodules in the right lower lung indicated ~~were all considered as S~~sMPLC. Based on the patient~~'~~s medical condition, we performed a ~~thoracoscopy~~ cuneiform resection of the lesion in the left lower lung through thoracoscopy. Histological examinations confirmed that the mass was ~~showed~~ invasive adenocarcinoma ~~(~~ (~~f~~Figure 2~~)~~)~~,~~. Genetic testing ~~gene detection~~ revealed a point mutation of ~~EGFR~~ G719A~~,~~ in the EGFR ~~gene~~protein. Figure 3 shows ~~T~~the visualized site map of gene mutations ~~is shown in figure 3~~.

Figure 4 shows ~~The~~ the CT image ~~examination~~ of the patient at ~~one~~1 month after surgery ~~was shown (Figure 4)~~. The patient was treated with ~~started~~ oral osimertinib (80 mg QD) from ~~treatment on~~ November 23, 2021. A reexamination with ~~A~~ a CT scan ~~reexamination~~ on March 10, 2022, showed no recurrence of the lesion in ~~that~~ the left lower lung lobe ~~was no recurrence,~~ and a significant reduction in the size of ground-glass nodules in the right middle lung lobe ~~ground glass nodule~~ and ~~the right lower~~ solid nodules in the right lower lung lobe ~~were significantly reduced,~~. ~~and the~~ The treatment efficacy was evaluated as a partial response ~~(~~ (~~f~~Figure 5~~)~~). Based on the treatment outcome~~result~~, the patient continued to take osimertinib. A ~~C~~chest CT scan conducted again ~~reexamination~~ on September 08, 2022, showed that the lesion in the right middle lung lobe ~~was well controlled~~showed no further progression; the treatment ~~with an~~ efficacy was evaluated as complete remission~~response~~ for this lesion and partial remission for the lesion in the right lower lung lobe ~~evaluated as partial response~~ (Figure 5). The report was closed on ~~ends on~~ September 08, 2022. Subsequently, we recommend~~ed~~ ~~that~~ the patient~~s~~ to continue targeted therapy and visit ~~return to~~ the hospital for review every 4 months. If ~~the~~ lesion 3 ~~is in~~ shows remission or ~~has~~ no progression, we will ~~it is~~ recommend~~ed~~ the patient to continue targeted therapy~~;~~. ~~I~~If the disease progresses further, SBRT~~stereotactic radiotherapy~~ or radiofrequency ablation could be considered for treatment~~can be taken。~~.

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Discussion

Multiple primary lung cancer ~~(~~ (MPLC ~~)~~) can be classified ~~divided~~ into

synchronous multiple primary lung cancer (sMPLC) and Mmetachronous multiple primary lung cancer (mMPLC)) according to the time of onset. Previous Sstudies[6-8] have shown found that the detection rate of sMPLCsynchronous multiple primary lung cancer accounts for 2--20% of all lung cancer cases. The main manifestations of sMPLC on a CT scan are GGOsground-glass shadows, with some are solid nodules, and adenocarcinoma is more commonly detected in the pathological examinationy. In the past, In the past, the The diagnosis of MPLC was mainly based on the guidelines first proposedal by of Martini[9] in 1975 and later by the American College of Chest PhysiciansACPP[10] in 2014. MPLC is diagnosed Oonly when each lesion originatesd from carcinoma *in situ* can the diagnosis of multi-primary lung cancer be made. Although surgical treatment is currently has become the main treatment method for mode of MPLC[10,11], many patients cannot accept or tolerate more surgical interventions times after undergoing the second and third stage of surgeriesy,; so hence, there is it is an urgent requirement to develop seek non-surgical treatment approaches. At pPresently, SBRTstereotactic radiotherapy and ablative therapy have become an are important treatment options choice for patients with inoperable early--stage lung cancer, and have been increasingly used for treating sMPLCapplied in the field of synchronous multiple primary lung cancer. Huang[12] and Qu[13] reported that the success rate of microwave ablation for synchronousizing multiple GGOs was 100%, and no severe serious complications were observed. Previous Sstudies have shown favorable survival outcomes, adequate local control, and fewer adverse events in MPLC patients treated with SBRT. However, in some patients, show more than 10 or 20 multiple nodules in both the double lungs are more than ten or twenty,. Dong[14] reported a patient with 28 ground--glass nodules in bothbilateral lungs. These patients are not suitable for treatment with ablation or SBRT treatment,; so hence, clinicians are actively searching for it has become our long-cherished wish to seek effective treatment approaches, even including non-invasive treatments.

Following With the development of next-generation sequencing (NGS) NGStechnology, molecular diagnosis has playeds an important role in the detection of sMPLC. Eunhyang Park conducted second-generation sequencing on 16 patients and

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found ~~showed~~ that ~~multiple~~ synchronous multiple lesions in the same patient showed different mutation~~nt~~ spectra, sometimes within the same mutant gene[15]. The study of Motohiro Izumi's ~~study~~ involving ~~of~~ 34 patients with ~~S~~sMPLC showed that c~~C~~oncomitant EGFR or KRAS mutations in MPLCs were significantly more frequent than the expected probability ~~by chance~~[16]. The ADAURA study[17] showed that d~~D~~isease-free survival (DFS) was significantly improved ~~with~~ by adjunctive~~vant~~ treatment with osimertinib in patients with EGFR L858R and EGFR 19del mutations in NSCLC stages IB-IIIA. However, the DFS benefit was not observed in ~~of~~ patients with other rare sensitive EGFR mutations ~~was not reported~~. In addition to the common EGFR L858R and EGFR~~exon~~ 19del mutations, there are ~~also~~ some rare but ~~still~~ sensitive mutation types~~,~~ such as EGFR G719X, L861Q, and S768I~~, etc~~. Recent studies have shown that specific EGFR-targeted therapy drugs can provide progression-free survival (PFS) and overall survival benefits to ~~for~~ NSCLC patients with these rare mutations~~, Specific EGFR-targeted therapy drugs can bring PFS and OS benefits to patients~~[18,19]. In ~~this~~ our present case, NGS was performed for a tissue sample from the patient's left lower lung ~~tissue was detected by NGS~~, and ~~found to carry~~ a rare mutation of EGFR G719A was detected. According to previous studies, the ~~mutation~~ probability of EGFR G719A mutation in NSCLC patients is approximately ~~about~~ 1–3%[20,21]. T~~k~~KI~~i~~s such as afatinib, daclatinib, and osimertinib ~~have~~ show~~n~~ good binding activity to EGFR with a G719A mutation[22]. In a phase II study, 19 patients with advanced NSCLC harboring EGFR G719X mutation were treated with osimertinib~~,~~; ~~with~~ the patients showed a median PFS of 8.2 months and an overall response rate~~ORR~~ of 53%[19]. In our present~~this~~ case, the initial goal of osimertinib treatment was to provide postoperative adjunctive~~vant~~ therapy for the p~~P~~alliatively resected lesion carrying the ~~with~~ G719A mutation. Unexpectedly, although the type of mutation in the residual lesions of the patient was un~~not~~ clear, the residual ground-glass nodules and solid nodules responded to osimertinib treatment~~,~~. ~~which~~ This might ~~may~~ be because of the presence of the ~~due to the~~ same mutated ~~main driver~~ gene ~~between~~ in both primary and residual ~~the~~ lesions~~,~~; however, ~~but~~ further investigations are required ~~testing is needed~~ to confirm this hypothesis.

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Cheng[23] reported surgical resection of the main lesion of sSMPLC, and treatment of residual ground-glass nodules were treated with first-generation EGFR-TKI; remission was achieved for and some lesions achieved remission. Yu[24] reported the use of sampling first-generation EGFR-TKI to treat multiple ground-glass nodules, and surgical resection of insensitive lesions. Haratake[25] reported a case of mMPLC in which a new lesion developed 8 months after surgery, and the disease was controlled stabilized after treatment with a second-generation EGFR-TKI. Dong[14] reported another case in which osimertinib was effective in treating the treatment of contralateral multiple ground-glass nodules after segmental resection of primary lung adenocarcinoma with EGFR-T790M-mutationsed lung adenocarcinoma. These reports suggest that targeted therapy could be used as an approach may be a way to treat SsMPLC. However, the research of on the use of targeted therapy for treating sMPLC is still in the stage of case reports. A considerable amount of and a large number of data isare required are needed to confirm its the safety and effectiveness of targeted therapy in the future. Moreover, and tfurther research is required to address several other issues such as here are many problems that need further research, such as the indication of targeted therapy, the best time of treatment, the duration of medication, the recurrence after drug withdrawal, and the difference in the therapeutic efficacy effect of different targeted drugs.

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