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Response to crizotinib in advanced intrahepatic cholangiocarcinoma with ZKSCAN1-MET fusion and MET amplification: case reports and literature review

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Abstract

Intrahepatic cholangiocarcinoma (ICC) is the second most prevalent liver cancer after hepatocellular carcinoma and is characterized by high malignancy and poor prognosis. Gemcitabine combined with cisplatin is the standard first-line therapy for metastatic or unresectable ICC. The combination of immunotherapy and targeted therapy represents a promising new direction for ICC treatment. Common genetic mutations in ICC include those in TP53, FGFR2, IDH1/2, and KRAS. MET alterations such as fusions and amplifications are rare in ICC. However, limited research has been conducted on the efficacy of specific MET inhibitors. We present two cases: the first with refractory ICC treated with a combination of immunotherapy and targeted therapy, harboring a ZKSCAN1-MET fusion and the second with a metastatic ICC with MET amplification. Both patients demonstrated a significant clinical response to crizotinib, a MET-specific tyrosine kinase inhibitor.

Keywords *MET* gene, Met mutations, Intrahepatic cholangiocarcinoma, Targeted therapy, Crizotinib

1 Introduction

Intrahepatic cholangiocarcinoma (ICC) accounts for approximately 10% of all primary liver cancers and is the second most common primary hepatic malignancy [1]. The disease onset is insidious and highly aggressive, which often leads to a diagnosis in advanced stages, resulting in lost opportunities for surgical cure. The standard first-line treatment for unresectable advanced ICC is a combination of gemcitabine and cisplatin, as recommended by international guidelines [2]. The standard second-line treatment regimen includes oxaliplatin, leucovorin, and fluorouracil (mFOLFOX) [3]. In recent years, immunotherapy and targeted therapy have undergone rapid advances and have become key areas for exploratory ICC treatment. Although chemotherapy and immunotherapy have improved survival outcomes in patients with advanced ICC, the median overall survival for most patients remains approximately 12 months [4–6].

With advancements in genomics and bioinformatics, comprehensive genomic profiling studies have provided deeper insights into targeted therapies for cholangiocarcinoma (CCA). Therapeutic targets such as vascular endothelial growth factor receptor (VEGFR), isocitrate dehydrogenase, fibroblast growth factor receptor (FGFR), and epidermal growth factor receptor have been investigated in ICC, with some showing potential clinical utility. Some drugs have progressed in the treatment of ICC and have been approved for commercial use [7, 8]. The mesenchymal-epithelial transition factor (c-MET) is a receptor tyrosine kinase that overexpresses in ICC (12–58%) and relates to poor prognosis [9, 10]. MET-directed therapies have shown clinical efficacy in other malignancies, such as non-small cell lung cancer (NSCLC) and esophagogastric cancer, where MET amplifications or fusions are actionable drivers. For instance, crizotinib, a c-MET inhibitor, has demonstrated durable responses in patients with NSCLC and MET alterations, underscoring its therapeutic potential in MET-driven cancers [11]. This supports the rationale for exploring MET inhibition in ICC, particularly in patients with MET genetic aberrations.

Goyal et al. evaluated the efficacy of cabozantinib in chemotherapy-refractory CCA and found no survival benefit in terms of PFS or OS. However, further analysis revealed that one patient with high MET expression (immunohistochemistry analysis of 3+) gained long-term benefits from treatment [12]. In phase I clinical trial, tivantinib (ARQ-197), another c-MET inhibitor, was used in combination with gemcitabine to treat patients with advanced or metastatic solid tumors. The trial included eight patients with CCA, of whom only one showed a partial response [13]. The limited efficacy of MET inhibitors in these studies may stem from the lack of patient selection based on precise molecular biomarkers, such as MET fusions or amplifications, which are critical for successful targeted therapy.

Here, we present two cases: the first involving a patient with refractory ICC treated with a combination of immunotherapy and targeted therapy who carries a ZKSCAN1-MET fusion, and the second regarding a patient with metastatic ICC and MET gene amplification. Both patients demonstrated a significant clinical response to crizotinib.

2 Case reports

2.1 Case 1

2.1.1 Patient story

In August 2021, a 57-year-old woman with no medical history was diagnosed with stage III ICC, and magnetic resonance imaging (MRI) revealed the typical characteristics of ICC (Fig. 1). On August 12, 2021, the patient began first-line treatment with tilelizumab (200 mg intravenously every 3 weeks) and lenvatinib mesylate (8 mg orally, once daily). On August 24, 2021, the patient was admitted to our hospital, where a multidisciplinary consultation recommended a combination with local treatment. However, the patient refused and continued the systemic therapy. In March 2022, the patient returned due to disease progression. The abdominal MRI demonstrated progressive disease, with the largest intrahepatic lesion increasing from 5.3 cm × 5.1 cm to 7.9 cm × 6.5 cm (Fig. 1).

2.1.2 Molecular tumor board

Next-generation sequencing (NGS) was performed using the Illumina NovaSeq 6000 platform. A comprehensive detection panel covering 868 tumor-associated genes was

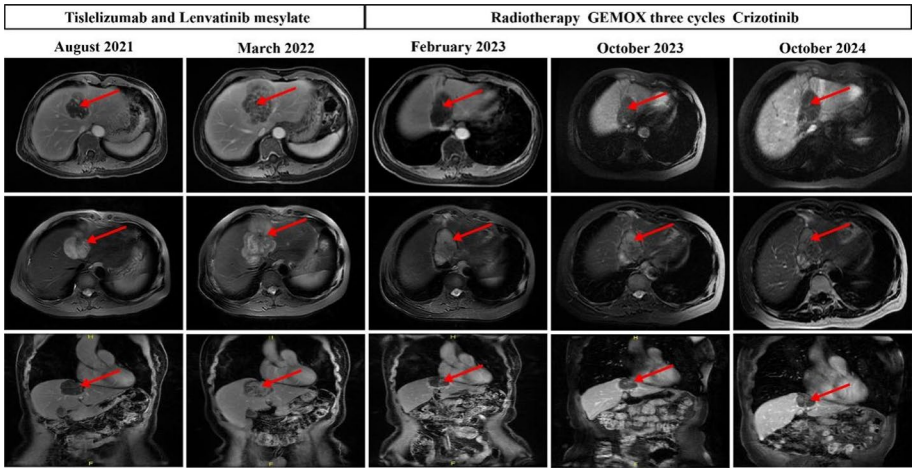

Fig. 1 Enhanced abdominal magnetic resonance imaging (MRI) of liver tumors from August 2021 to October 2024, illustrating tumor progression and treatment response. The patient was diagnosed with intrahepatic cholangiocarcinoma (ICC) in August 2021. Treatment included Tislelizumab and Lenvatinib, with disease progression noted in March 2022, followed by radiotherapy, GEMOX three cycles and crizotinib. Follow-up images show significant tumor shrinkage by February 2023 and stable disease by October 2023. The images include axial T1-weighted enhanced scans (top), axial T2-weighted scans (middle), and coronal T1-weighted enhanced images (bottom). Red arrowheads indicate the tumor lesions to enhance interpretation

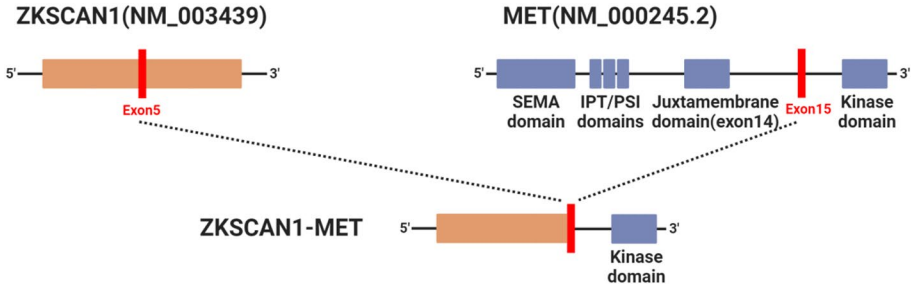

Fig. 2 Schematic schema of ZKSCAN1-MET fusion

used, encompassing point mutations, small insertions/deletions, copy number variations, and gene fusions. High-quality DNA was extracted from FFPE tumor tissues and matched blood samples with an average sequencing depth of 1000×. Genetic analysis of the tumor revealed a fusion between exon 5 of ZKSCAN1 and exon 15 of MET with a fusion allele frequency of 4.4% (Fig. 2). No amplification of the MET copy number was observed. The ZKSCAN1-MET fusion was predicted to result in a chimeric protein retaining the MET kinase domain, which may contribute to the activation of MET signaling pathways. Additionally, NGS results indicated that the patient harbored a low tumor mutation burden (TMB-L, 0 Muts/Mb, 0%) and was microsatellite-stable (MSS).

2.1.3 Patient update

Following discussion within a multidisciplinary team (MDT), the patient received radiotherapy for intrahepatic lesions on March 29, 2022, at a dose of 50 Gy delivered in 10 fractions (DT: 50 Gy/10 fx). Based on the results of genetic testing, it was recommended that the patient consider chemotherapy combined with targeted therapy or targeted therapy alone (crizotinib).

From April 11, 2022, to June 9, 2022, the patient underwent three cycles of GEMOX regimen chemotherapy (gemcitabine 1400 mg/m^{2}d1, oxaliplatin 130 mg/m^{2}d1). On June 9, 2022, the patient was started on targeted therapy with crizotinib capsules (250 mg twice daily orally). Due to gastrointestinal side effects, the dose of crizotinib was subsequently adjusted to 250 mg once daily. The patient's serum tumor markers showed a downward trend, particularly CA19-9 (Fig. 3). Furthermore, follow-up abdominal MRI in February 2023 showed a significant reduction in tumor size compared with that in March 2022, especially evident on T1-weighted enhanced images, suggesting a marked therapeutic effect of crizotinib, although the contribution from prior chemotherapy cannot be excluded. A subsequent follow-up abdominal MRI in October 2023 revealed stable disease (Fig. 1).

2.2 Case 2

2.2.1 Patient story

On March 27, 2021, a 43-year-old male with a history of hepatitis B surface antigen positivity was diagnosed with stage IV ICC, with metastasis to both lungs and multiple lymph nodes, and complaining of abdominal pain. MRI revealed the typical characteristics of ICC (Fig. 4).

2.2.2 Molecular tumor board

Liver rebiopsy was performed to obtain tissue for molecular analysis. Target region capture combined with high-throughput sequencing (Illumina NovaSeq 6000) was performed to accurately identify mutations, amplifications, and fusions. Testing predicted tumor responses to treatments, including targeted therapy, immunotherapy, and chemotherapy, while also evaluating the risk of resistance. Genetic testing of the tumor revealed that the patient had a TP53 mutation, PDGFRA exon 18 mutation, CDK6 amplification, and MET amplification with a copy number of 4, along with MSS. Among potential therapeutic targets, MET is considered an attractive option. Current literature supports

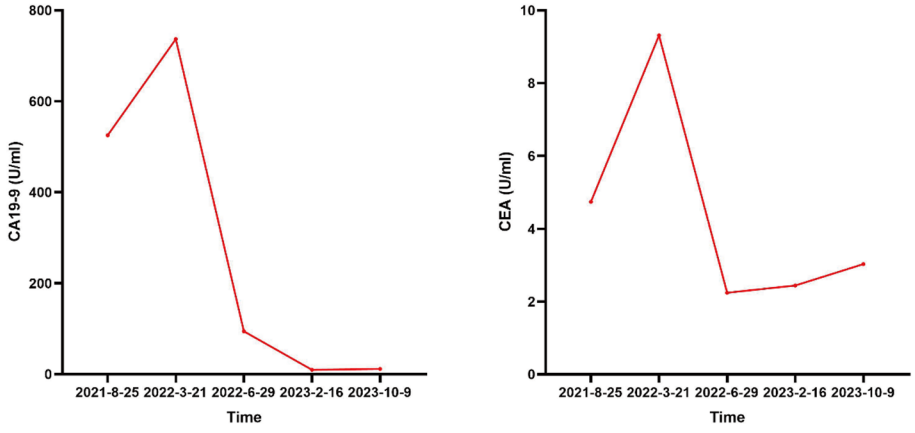

Fig. 3 Serum levels of CA19-9 and CEA over time in Case 1, reflecting the patient's response to treatment. The patient received a treatment regimen that included Tislelizumab, Lenvatinib, radiotherapy, GEMOX chemotherapy, and crizotinib. The time points correspond to key clinical assessments: August 25, 2021 (baseline prior to treatment initiation); March 21, 2022 (post-Tislelizumab and Lenvatinib evaluation); June 29, 2022 (follow-up after radiotherapy, GEMOX chemotherapy, and crizotinib); February 16, 2023 (routine follow-up); and October 9, 2023 (routine follow-up)

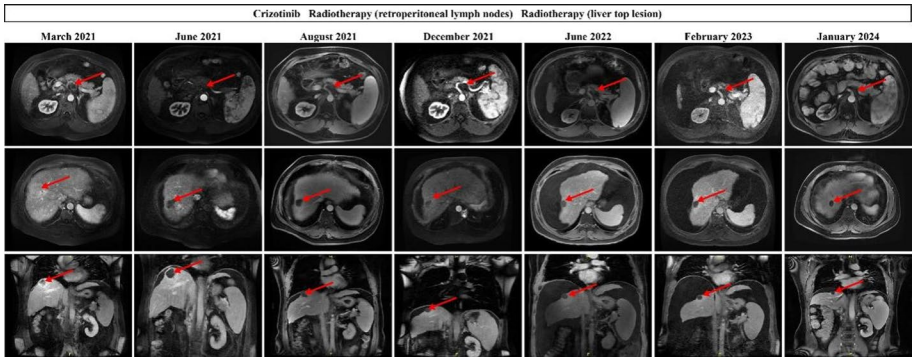

Fig. 4 Enhanced abdominal magnetic resonance imaging (MRI) of liver tumors and retroperitoneal lymph nodes from March 2021 to January 2024, illustrating the treatment response in a patient diagnosed with intrahepatic cholangiocarcinoma (ICC) in March 2021. The treatment regimen included radiotherapy targeting both the retroperitoneal lymph nodes (April 8, 2021) and intrahepatic lesions (June 26, 2021), in conjunction with crizotinib. Follow-up imaging in August 2021 revealed a reduction in the size of both the retroperitoneal lymph nodes and liver lesions. Subsequent assessments in December 2021, June 2022, February 2023, and January 2024 demonstrated stable disease. The images comprise axial T1-weighted enhanced scans of the retroperitoneal lymph nodes (top), axial T1-weighted enhanced scans of the liver lesions (middle), and coronal T1-weighted enhanced images (bottom). Red arrowheads indicate tumor lesions to enhance interpretation

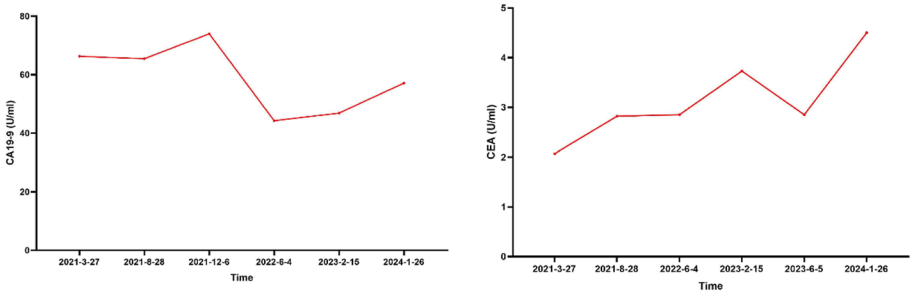

Fig. 5 Trends in serum levels of CA19-9 and CEA over time in Case 2, reflecting the patient's response to treatment. The patient underwent a treatment regimen that included radiotherapy and crizotinib. Key clinical assessments occurred at the following time points: March 27, 2021 (baseline prior to treatment initiation); August 28, 2021 (evaluation after radiotherapy and crizotinib); December 6, 2021 (routine follow-up); June 4, 2022 (routine follow-up); February 15, 2023 (routine follow-up); June 5, 2023 (routine follow-up); and January 26, 2024 (routine follow-up)

the use of tyrosine kinase inhibitors in treating tumors with MET amplification. After discussing the available medications, the patient agreed to undergo crizotinib treatment.

2.2.3 Patient update

After the MDT discussion, the patient began targeted therapy with oral crizotinib capsules (250 mg twice daily) on March 29, 2021. On April 8, 2021, the patient underwent hepatic artery embolization and localized radiotherapy for the retroperitoneal lymph nodes (DT: 45 Gy/9 fx). From June 26 to July 2, 2021, radiotherapy was administered to lesions at the top of the liver (DT: 45 Gy/9 fx). This process proceeded smoothly. The MRI in August 2021 showed a significant reduction in tumor size after the start of treatment. Follow-up abdominal MRIs in December 2021, June 2022, February 2023, and January 2024 indicated stable disease with no clear signs of tumor recurrence or metastasis (Fig. 4). Serum tumor markers (CA19-9 and CEA) showed a downward trend and remained stable during treatment (Fig. 5). These changes in the imaging findings and tumor markers indicate that crizotinib has significant efficacy in controlling the patient's disease. The patient continued oral crizotinib treatment. Due to the complications of

cirrhosis, the patient experienced multiple episodes of gastrointestinal bleeding, which were unresponsive to conservative treatment, and underwent TIPS surgery on July 5, 2023. The surgery was successful, and crizotinib was temporarily discontinued. Once stable, the patient resumed targeted oral therapy with crizotinib capsules (250 mg, twice daily) in September 2023. In January 2024, a follow-up abdominal MRI suggested stable disease (Fig. 4). Imaging assessment was performed by a senior radiologist, and the stable trend of tumor markers further supported the efficacy of crizotinib in controlling the patient's disease.

3 Discussion

Here, we describe the response of patients with ICC, ZKSCAN1-MET fusion, and MET gene amplification to MET-TKI treatment. To date, several case reports have described patients with ICC and MET fusions (including RBPMS-MET, EHBP1-MET, and CAPZA2-MET) who showed sensitivity to the MET inhibitors crizotinib and capmatinib [14–16]. Additionally, other case reports have described patients with ICC and MET gene amplification who were responsive to the MET inhibitors, capmatinib, and savolitinib [17, 18]. In this case report, we describe a patient with ICC and ZKSCAN1-MET fusion and another with MET amplification, both of whom demonstrated a significant therapeutic response to crizotinib. These findings, along with previously reported cases of ICC with MET fusions and amplifications, collectively support crizotinib as a potentially effective treatment option for ICC with MET fusions.

Gemcitabine-based chemotherapy is the main treatment option for advanced ICC but is associated with limited survival benefits, resulting in poor prognosis in this population [4]. A small number of patients with specific genetic mutations may be eligible for targeted therapy [19]. MET alterations are rare in ICC, with only 2% of cases showing MET amplification [20]. A retrospective study by Xu et al. found that only 1.1% of the patients with CCA had MET rearrangements [21]. MET fusions generally result from rearrangements between MET and other genes, forming chimeric proteins that retain intact MET kinase domains. This structure leads to continuous activation of the MET signaling pathway, thereby promoting tumor initiation and progression. For example, in Case 1, a ZKSCAN1-MET fusion was identified. This fusion preserved the MET kinase domain, activating downstream signaling pathways such as MAPK, PI3K, and PLCγ1, thus driving tumor progression [22]. In contrast, MET amplification is characterized by an increased copy number of the MET gene, which typically results in MET protein overexpression and enhanced signaling activity. In Case 2, tumor analysis revealed MET amplification (copy number 4), providing a therapeutic rationale for the use of MET inhibitors. This further supports the possibility that crizotinib may serve as an effective treatment option for patients with ICC patients harboring MET fusions or amplifications.

Currently, the efficacy of MET inhibitors in the treatment of ICC remains controversial. Several clinical trials evaluating MET inhibitors for advanced CCA have yielded unsatisfactory results. This may be because the enrolled patients were not selected based on their molecular status [12, 13, 23]. However, Lefler et al. reported a case of metastatic ICC with high-level *MET* gene amplification that showed a partial response to capmatinib, a selective MET receptor inhibitor [17]. Zhou et al. reported a case of advanced ICC in a patient who was intolerant to chemotherapy. NGS identified MET amplification

(variant allele frequency 5.2), and the patient achieved a partial response after treatment with savolitinib (a MET inhibitor), with a response lasting for 1 year [18]. Additionally, an article by Turpin et al. described a case of ICC with a CAPZA-2-MET fusion that progressed after second-line therapy. Subsequently, the patient received capmatinib and achieved a partial response [16]. These findings suggest that MET inhibitors hold promise for further exploration in the treatment of advanced ICC.

Crizotinib is a small-molecule tyrosine kinase inhibitor that primarily targets ALK, ROS1, and MET receptors [24]. Notably, it has been approved by the Food and Drug Administration for the treatment of ALK-positive locally advanced or metastatic cell lung cancer [25]. In this study, crizotinib demonstrated significant efficacy in both patients, particularly in case 2, who achieved 34 months of local control when combined with radiotherapy. In contrast, capmatinib and savolitinib are selective MET inhibitors that primarily target the MET receptors. According to the literature, capmatinib achieved a partial response and nearly 6 months of improved quality of life in patients with metastatic ICC carrying MET amplification [17]. Similarly, savolitinib resulted in 1 year of partial remission in a patient with ICC and MET amplification [18]. Although these selective inhibitors show good efficacy in certain patients, their therapeutic scope may be more limited than that of crizotinib. The multi-target properties of crizotinib may provide additional therapeutic advantages in complex molecular contexts. Currently, there are no clinical trials specifically targeting c-MET-positive CCA and owing to the limited clinical data, it is challenging to draw definitive conclusions regarding the application of these drugs in CCA. However, as these therapies continue to gain traction, evidence in this field is gradually increasing. For instance, findings from the 2021 AcSé-crizotinib project indicated that c-MET inhibition by crizotinib was effective in MET-amplified esophageal and gastric cancers. In this study, nine patients with chemotherapy-resistant tumors and ≥6 MET copies received crizotinib monotherapy, resulting in an objective response rate of 33.3%, a median progression-free survival of 3.2 months, and an overall survival of 8.1 months [26]. Several reported cases indicate that patients with lung adenocarcinoma harboring MET fusions such as CD47-MET, KIF5B-MET, HLA-DRB1-MET, STARD3NL-MET, MET–ATXN7L1, and MET-UBE2H may respond to crizotinib treatment [27–32]. The studies reported that the duration of response to crizotinib in patients ranges from 4 to 12 months, with a median duration of 8 months. Moreover, Yu et al. described a case of a patient with ICC carrying an EHBP1-MET fusion who achieved an 8-month partial response after treatment with crizotinib [15]. Another patient with ICC and an RBPMS-MET fusion demonstrated significant efficacy with crizotinib treatment [14]. Additionally, a patient with metastatic CCA with novel genetic alterations (Ig-like-III domain FGFR2 alteration [W290_P307 > C), along with CDKN2A/B alterations and a cadherin 1 [CDH1] alteration) achieved notable therapeutic efficacy through a personalized combination therapy regimen including crizotinib after developing resistance to pazopanib [33]. In addition, a pediatric patient with glioma carrying the PTPRZ1-MET fusion exhibited significant tumor shrinkage after 2 months of crizotinib treatment [34]. These findings suggest that crizotinib is a potential therapeutic option for patients with MET fusion tumors. Furthermore, *MET* gene amplification in ICC has demonstrated a good response to the selective MET receptor inhibitors capmatinib and savolitinib. In the first case, the combination of radiotherapy and crizotinib achieved local control for approximately 19 months. In the second case,

the combination of radiotherapy and crizotinib resulted in 34 months of local control. This outcome is notable, and further studies are warranted to explore the therapeutic effects of radiotherapy combined with small-molecule tyrosine kinase inhibitors in patients with advanced ICC.

This study reports two cases of advanced ICC with MET alterations that demonstrated significant responses to crizotinib treatment, further exploring the potential of MET inhibitors in ICC therapy. Although MET alterations are relatively rare in ICC, our findings suggest that crizotinib exhibits considerable efficacy in patients with MET fusions or amplifications, particularly when guided by precise molecular testing. However, this study has several limitations. First, given that only two patients were included, the sample size is too small to comprehensively assess the overall efficacy of MET inhibitors in ICC, thus warranting further validation in larger cohorts. Second, it remains uncertain whether the ZKSCAN1-MET fusion detected in Case 1 represents an acquired resistance mechanism following lenvatinib treatment, as there are no molecular testing data available prior to treatment. The ZKSCAN1-MET fusion was identified when the patient's disease progressed after lenvatinib therapy, suggesting that it could be an acquired resistance mechanism that is potentially linked to the selective pressure of long-term VEGFR/FGFR inhibition. This phenomenon aligns with reports on other cancers in which MET activation serves as a resistance pathway. Furthermore, both patients underwent combination treatment with radiotherapy and crizotinib, making it difficult to attribute tumor response exclusively to radiotherapy, crizotinib, or their combination. In addition, in Case 1, the GEMOX chemotherapy regimen may also have contributed to the reduction in tumor burden and improvement in tumor markers. Therefore, the observed therapeutic effects cannot be fully attributed to crizotinib alone. The combined effects of multiple treatments represent another limitation of this study, and future research is needed to further clarify the role of each therapeutic modality. Nevertheless, clinical experience indicates that combining local radiotherapy with systemic targeted therapy may enhance local control rates and reduce recurrence and metastasis. The stability of tumor markers observed in this study may reflect the synergistic effects of these two treatments. Future large-scale prospective studies and randomized controlled trials are necessary to further validate the efficacy of MET inhibitors in patients with ICC and explore the mechanisms underlying MET fusions or amplifications. Such studies will help clarify the individual and combined effects of these therapies and optimize treatment strategies.

4 Conclusion

ICC is a highly aggressive and heterogeneous malignancy with poor response to chemotherapy, making its treatment challenging. Therefore, it is crucial to refine the genetic landscape and targetprecise therapies in order to extend the survival of patients with advanced ICC. These two cases demonstrate the efficacy of crizotinib in treating advanced ICC with MET alterations, offering an alternative therapy for these patients and underscoring the importance of molecular testing in advanced ICC cases. Further research is needed to confirm whether the combination of radiotherapy and targeted therapy provides greater survival benefits for patients with advanced ICC.

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Author contributions
Jian-Hui Wu, Yu-ze Fan conceived and drafted the manuscript, drew the figures. Jing Sun, and Xue-Zhang Duan discussed the concepts of the manuscript. Jing Sun, and Xue-Zhang Duan provided valuable suggestion. Jing Sun, and Xue-Zhang Duan approved the submission of the manuscript.

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Availability of data and materials
The data used to support the findings of this study have been included in this article. Further inquiries can be directed to the corresponding authors.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and internationally accepted ethical guidelines and was approved by the Institutional Review Board of Beijing 302 Hospital. The patients have consented to the submission of the case reports for submission to the journal.

Consent for publication
Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing interests
The authors declare no competing interests.

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