CASE REPORT
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Application of Immunoenhancing Radiotherapy in Treating Unresectable Intrahepatic Cholangiocarcinoma: A Case Report

Peng Jiang[1,#], Yingqi Zhang[1], Chenxing Shang[1], Jun Lu[1]

[1] Department of Radiation Oncology, Xi'an International Medical Center Hospital, Xi'an 710000, China

Abstract: Unresectable intrahepatic cholangiocarcinoma currently lacks standard treatment methods. This report presents a case where PET/CT scans showed a subcapsular mass in the right posterior lobe of the liver measuring 6.2 cm × 3.7 cm × 3.8 cm, and a soft tissue nodule in the apicoposterior segment of the left upper lung lobe measuring 1.2 cm × 1.3 cm × 1.4 cm, both exhibiting increased glucose metabolism. A biopsy of the liver lesion confirmed well-differentiated cholangiocarcinoma, classified as Stage IV (cT1bN0M1). The patient, supported by their family, declined chemotherapy, surgery, immune checkpoint inhibitor therapy, and targeted therapy. Following a multidisciplinary team discussion, the patient was treated with conformal intensity-modulated radiotherapy aimed at the hepatic lesion, delivering a total dose of 50 Gy in ten sessions (5 Gy per session, once daily, five times per week). This was combined with 300 μg of granulocyte-macrophage colony-stimulating factor (GM-CSF), subcutaneously injected daily from the first to the tenth day of radiotherapy. No subsequent treatments were administered; only follow-up evaluations were performed. MRI assessments at three, twelve-, and twenty-four months post-treatment showed progressive reduction in the size of the hepatic primary lesion, with decreases of 15%, 36%, and 53% from baseline, respectively, and no growth in the pulmonary lesion. This outcome suggests that radiotherapy paired with an immunoadjuvant could be a viable treatment alternative for patients with unresectable intrahepatic cholangiocarcinoma.

Keywords: Intrahepatic cholangiocarcinoma; Radiotherapy; GM-CSF.

Introduction

The primary approach to intrahepatic cholangiocarcinoma is surgical intervention; however, for patients unable to undergo surgery or those who refuse it, there is no consensus on alternative treatments. The combination of radiotherapy and immunotherapy is a rapidly evolving field that shows promise, particularly in enhancing treatment efficacy and minimizing adverse effects[1–3]. Research indicates that GM-CSF used as an immunoadjuvant with radiotherapy is safe and effective. Studies by BC Wang et al. have found that a regimen of radiotherapy combined with GM-CSF (200 μg subcutaneously every other day) is both tolerable and safe[4]. Furthermore, a Phase II clinical trial by Y Kong et al. demonstrated that combining radiotherapy with a PD-1 inhibitor and concurrent GM-CSF (200 μg daily for two weeks) is safe, achieving an objective response rate of 16.7% and a disease control rate of 46.3%[5]. This case report of a patient who refused surgery and chemotherapy but underwent radiotherapy combined with GM-CSF treatment shows a sustained partial response over two years, indicating potential long-term benefits without reaching the end of follow-up.

Correspondence: Peng Jiang. E-mail: 116301859@qq.com. Address: Department of Radiation Therapy, Xi'an International Medical Center Hospital, 777 Xitai Road, Gaoxin District, Xi'an, Shaanxi Province, 710000, China.

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Case Presentation

A 66-year-old male patient was referred to our hospital on December 3, 2020, complaining of right upper abdominal pain for one week, liver mass discovered three days earlier. Starting November 26, 2020, the patient experienced intermittent bloating and pain in the right upper abdomen without apparent cause. There was no fever or jaundice, and the self-administered omeprazole had little effect.

An abdominal CT scan conducted on November 30, 2020, revealed an irregular mass in the right posterior lobe of the liver, measuring approximately 6.5 cm × 4.1 cm, with an elevated liver margin and no apparent dilation of the bile duct. There were no enlarged lymph nodes visible in the abdomen, suggesting liver cancer. A PET/CT scan on December 1, 2020, at our hospital indicated a subcapsular irregular mass in the right posterior lobe of the liver, appearing as multiple merged lesions near the liver margin with a clear border measuring about 6.2 cm × 3.7 cm × 3.8 cm and a mild increase in glucose metabolism, suggesting a malignant liver tumor. A soft tissue nodule in the apicoposterior segment of the left upper lobe of the lung, measuring about 1.2 cm × 1.3 cm × 1.4 cm, also showed mildly increased glucose metabolism. A solid nodule in the posterior segment of the right upper lung lobe measured approximately 0.3 cm in diameter. On December 3, 2020, tumor markers indicated a slightly elevated carcinoembryonic antigen at 5.45 ng/mL; hepatitis B surface antigen was negative; pathology from a liver biopsy of the right lobe indicated well-differentiated cholangiocarcinoma. The lung le-

sion was suggested for a biopsy to further clarify its nature, but the patient refused, and the clinical diagnosis did not exclude metastasis.

On December 11, 2020, the diagnosis was right lobe bile duct carcinoma (well-differentiated cholangiocarcinoma T1bN0M1 Stage IV).

After repeated discussions, the patient and his family firmly decided against local surgical resection or chemotherapy, opting only for radiotherapy. Following multidisciplinary discussions, it was decided to actively control the primary lesion through palliative radiotherapy while combining it with subcutaneous injections of GM-CSF to boost a possible immunoenhancing effect.

With the informed consent of the patient and his family, from December 15 to 28, 2020, the patient underwent conformal radiotherapy combined with GM-CSF treatment for intrahepatic cholangiocarcinoma.

Radiotherapy target area: the tumor target area included the intrahepatic primary lesion, referencing MRI and CT; the planned target area was expanded by 1cm above and below and 0.8 cm anteriorly and laterally. Radiotherapy dose: the planned target area received a dose of 50 Gy in 10 sessions, once daily, 5 Gy per session. Radiotherapy technique: VMAT. 100% of the isodose curve enveloped 95% of the planned target area. The organ at risk doses: liver Dmean = 13.7 Gy, spinal cord Dmax = 17 Gy, stomach Dmax = 10.7 Gy, small intestine Dmax = 4.5 Gy, colon Dmax = 12.2 Gy. Radiotherapy was given concurrently with GM-CSF 300 μg subcutaneously injected once daily for ten times.

The main adverse reactions were hepatic irritation, pain, and sweating, all Grade 1, which improved with symptomatic treatment. Pre-radiotherapy, the largest diameter of the lesion was 6.4 cm. MRI follow-ups at three months, one year, and two years post-treatment showed gradual reduction and stabilization of the lesion, with maximum diameters of 5.4 cm, 4.1 cm, and 3.0 cm, respectively, demonstrating reductions of 15%, 36%, and 53% compared to the original lesion, with the therapeutic effect evaluated as Partial Response (PR) (Fig. 1.).

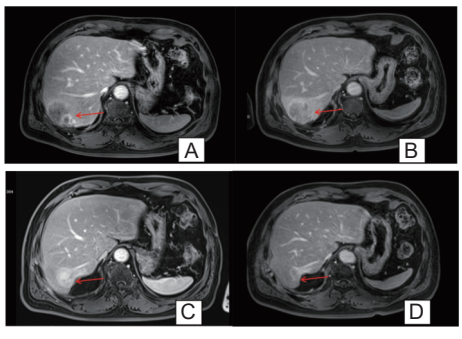

Fig. 1. Changes in Liver Lesions Before and After Radiation Therapy.
A. MRI of liver lesions before radiation therapy.
B. MRI of liver lesions 3 months after radiation therapy.
C. MRI of liver lesions 1 year after radiation therapy.
D. MRI of liver lesions 2 years after radiation therapy.

The pulmonary lesion remained stable during the follow-up period, with no new metastases observed; the last follow-up was on April 8, 2024.

Discussion

Intrahepatic cholangiocarcinoma originates from the epithelium of the secondary bile ducts and their branches within the liver. It has a lower incidence than hepatocellular carcinoma but accounts for 10% to 15% of primary liver cancers[6]. Currently, the first-line chemotherapy regimen for advanced intrahepatic cholangiocarcinoma is gemcitabine combined with cisplatin, with a median survival time of 11.7 months[7]. Recent studies have explored the efficacy of combining other drugs with these two medications. For instance, a Phase III study indicated that the gemcitabine + cisplatin + S-1 regimen had a longer median survival time of 13.5 months compared to 12.6 months[8], suggesting that adding chemotherapy drugs may enhance efficacy. However, many clinical patients refuse chemotherapy, either due to inadequate physical scores to support chemotherapy or due to adverse reactions leading to discontinuation of treatment. This case involved a patient who refused chemotherapy, necessitating a gentler and more acceptable treatment approach.

Compared to chemotherapy, immunotherapy generally has fewer adverse reactions and higher patient acceptability. Whether combined immunotherapy can further improve the efficacy of cholangiocarcinoma treatment remains a question worth studying in the era of immunotherapy. One study found that toripalimab combined with chemotherapy could extend the median overall survival of patients with advanced cholangiocarcinoma to 15.0 months[9]. Another Phase III study's interim analysis showed that the combination of durvalumab with gemcitabine + cisplatin resulted in a median overall survival of 12.8 months for advanced cholangiocarcinoma, which was superior to chemotherapy alone at 11.5 months[10]. The efficacy of chemotherapy combined with immunotherapy has been initially validated. However, some patients still refuse to use it due to concerns about severe immune adverse reactions and financial factors.

The use of GM-CSF as an immunomodulator, although not widely prevalent, offers significant potential in enhancing the immune response when combined with radiotherapy. GM-CSF promotes the maturation and activation of dendritic cells, enhancing antigen presentation and stimulating a robust T-cell response against tumor cells. Additionally, it activates macrophages, increasing their ability to phagocytose tumor cells and present antigens[11]. This mechanism is particularly relevant given the limited literature on the combined use of RT and GM-CSF, highlighting the novelty of our approach.

Some studies have confirmed that radiotherapy combined with immunotherapy, including PD-L1 inhibitors and immune adjuvants, can achieve an excellent synergistic effect[12,13]. In 2015, Golden EB et al. reported that radiotherapy combined with GM-CSF significantly enhanced the abscopal effect of radiotherapy, with patients experiencing an abscopal effect showing a significantly prolonged median survival[14]. This combination could be a feasible option for treating metastatic lesions. After multidisciplinary discussions, we opted for radiotherapy combined with GM-CSF treatment, hoping to address the lung metastases through the immune effect. The unchanged growth of both lung metastases suggested a potential immunotherapeutic impact of the treatment.

Regarding safety, GM-CSF does not have the toxicity associated with chemotherapy, and the typical adverse reactions are

limited to fever or mild bone pain. The patient, concerned about potential adverse reactions from PD-L1 inhibitors, refused them but accepted GM-CSF due to its milder side effects. During use, the patient experienced excessive sweating, which was alleviated with Shengmai drink treatment, demonstrating good tolerability.

A multicenter retrospective study found that stereotactic radiotherapy could extend the median overall survival of cholangiocarcinoma patients to 15 months[15]. Combining these treatment studies, it appears that multi-drug chemotherapy or combined immunotherapy is beneficial for improving efficacy, and radiotherapy can also achieve reasonable local control. For patients with advanced cholangiocarcinoma who refuse surgery, chemotherapy, and PD-L1 inhibitors, the choice of treatment options requires careful consideration.

In this case, after treatment with radiotherapy combined with GM-CSF, the patient's intrahepatic local lesion showed partial remission and remained stable for 24 months, as much as the lung lesions, which was beyond expectations. The main adverse reactions to treatment included fatigue, excessive sweating, and pleural pain, which were mild and well tolerated by the patient. Both the response time to treatment and the mild adverse reactions indicate that radiotherapy combined with GM-CSF treatment achieved significant therapeutic effects. The 24 months of disease control and the mild adverse reactions are highly acceptable to patients.

In summary, for patients with intrahepatic cholangiocarcinoma who are unsuitable for surgery or refuse surgery and chemotherapy, radiotherapy combined with immunotherapy may be a viable option. Future research should further explore the advantages of combined radiotherapy and immunotherapy and find more effective combined treatment regimens to improve cholangiocarcinoma patients' survival rate and quality of life.

Abbreviations

GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; MRI, Magnetic Resonance Imaging; PD-L1, Programmed Death-Ligand 1; PET/CT, Positron Emission Tomography/Computed Tomography.

Ethical approval and consent to participate

Written informed consent was obtained from the patient prior to their inclusion in the study.

Authors' contributions

PJ was responsible for data collection, analysis, and manuscript writing. YQZ handled statistical data. CXS conducted literature review. JL reviewed the manuscript.

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