

Sequential microwave ablation combined with radioactive iodine-125 seed implantation successfully cured multiple metastases of gallbladder cancer: A case report

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Abstract. Advanced tumors are associated with treatment dilemmas. High-risk diffuse metastasis results in increased difficulty in treatment. Furthermore, the deterioration of the patient's physical condition gives rise to an inability to tolerate high-intensity systemic treatment. As a palliative treatment for patients with advanced cancer, interventional therapy is characterized by precise targeting and fewer adverse reactions. Nevertheless, its role is frequently overlooked. Therefore, a female patient who only received local palliative treatment with microwave ablation and radioactive iodine-125 seed implantation for multiple metastatic masses of gallbladder cancer is reported. This intervention achieved complete systemic remission, representing a rare instance of durable systemic remission without chemotherapy throughout the disease course, including the metastatic phase. The present study evaluated its immunological basis as an *in situ* vaccine strategy to benefit chemotherapy-ineligible patients.

Introduction

Gallbladder cancer (GBC) is regarded as the most common biliary malignancy, accounting for 80-95% of all biliary malignancies worldwide (1). The average overall survival of patients with GBC is 6 months, and the 5-year survival rate is 5% (2). Radical resection remains the only curative approach for GBC, with postoperative radiotherapy and chemotherapy routinely given. However, there still exists >1/3 chance of metastasis and recurrence after surgery (3,4). Once GBC recurs, whether it is local recurrence or distant metastasis, the

5-year overall survival rate of patients remains notably low at just 15-20% (5).

For advanced patients with multiple distant metastases, surgical resection does not meet the needs of the patients. Patients with poor general condition are also unable to tolerate chemotherapy (6,7). Minimally invasive interventional therapy is characterized by minimal trauma and accurate positioning, which is suitable for these patients. In several cases, studies have focused on the local efficacy of interventional therapy, but have ignored the systemic immune response caused by interventional therapy (8,9). Only sporadic reports have shown the efficacy of thermal ablation in achieving distant or systemic responses (10-13). Microwave ablation (MWA) can kill tumor cells *in situ*, activate the immune system of the body and exert an immune attack on distant metastases, which is consistent with the concept of the tumor *in situ* vaccine (14). However, it is reported that the immune response induced by it is relatively weak, which is affected by the immunosuppressive microenvironment, and the effect is not sustainable (15). Radioactive particles can change the tumor microenvironment (TME) from an immunosuppressive state to an immune activation state (16,17).

The present study reports a case of a female patient with advanced GBC whose disease course extended >5 years from the initial diagnosis in order to validate the potential of local-only therapy for metastatic GBC and investigate the immune dynamics enabling durable remission. During the disease course time, new metastatic tumors occurred several times, and the patient underwent sequential treatment, including five rounds of ultrasound (US)-guided microwave ablation (MWA) and one occurrence of radioactive iodine-125 (¹²⁵I) seed implantation (RSI).

Case report

Case presentation. In 2018, a 60-year-old woman presented with recurrent epigastric pain for 6 months. US was performed at Zhenjiang Hospital of Chinese Traditional and Western Medicine (Zhenjiang, China) and showed the gallbladder was almost filled with an heterogeneous isoechoic mass, meeting the criteria for high-risk polyp resection. Therefore, although the nature of the mass was not clear, early intervention was

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needed. The patient underwent laparoscopic cholecystectomy, with final pathology showing poorly differentiated adenocarcinoma of the gallbladder, with a size of 1.5x0.8x0.6 cm invading the whole layer, and a small amount of atypical glands at the margin of the bile neck (Fig. 1A). According to tumor, lymph node and metastasis (TNM) staging, it was T3NxMO and belonged to stage IIa, with immunohistochemistry analysis of tissue samples showing cytokeratin (CK; +), CK18 (+; Fig. 1B), Ki-67 (+, 30%) and α -fetoprotein (AFP; -) (Fig. S1A).

For definitive management, the patient was referred to Affiliated Drum Tower Hospital, Medical School of Nanjing University (Nanjing, China). Preoperative MRI demonstrated irregular gallbladder wall thickening with adjacent hepatic infiltration, suggesting residual malignancy (Fig. 1C). Radical cholecystectomy was performed, with pathology confirming residual poorly differentiated adenocarcinoma in the gallbladder bed (Figs. 1D and S1B). After surgery, the patient declined chemoradiotherapy.

In September 2020, the patient presented to the Department of Medical Ultrasound (Affiliated Hospital of Jiangsu University) with the chief complaint of a large mass on their left neck for 3 months. A physical examination revealed an 8x8 cm mass in the left neck, with skin ulcers visible on its surface (Fig. 1E).

To make a definite diagnosis, a core-needle biopsy of the left neck mass was performed. The pathological result indicated malignant epithelial cells (Fig. 1F), possibly originating from the gallbladder, demonstrated using immunohistochemistry analysis of cytokeratin AE1/AE3 (+), vimentin (-), transcription termination factor 1 (TTF-1; -), thyroglobulin (TG; -), CK5/6 (-), CK7 (+), CK20 (+), caudal type homeobox 2 (CDX-2; -), Ki-67 (+, 75%) (Figs. 1G-I and S1C). The Ki-67 proliferative index was quantitatively assessed by a pathologist by visually estimating the percentage of positive tumor nuclei in representative high-power fields, according to standard diagnostic protocols.

The diagnosis of metastatic GBC was solidified by systematically excluding other primary sites. The immunohistochemical profile, notably CK7/CK20 positivity indicating biliary origin, coupled with negative markers for lung (TTF-1), thyroid (TG), colorectal (CDX-2) and squamous carcinomas (CK5/6), provided definitive cellular evidence against alternative primaries. Immunohistochemical staining was performed on 4- μ m-thick formalin-fixed paraffin-embedded sections using standard diagnostic protocols. Antigen retrieval involved citrate buffer incubation, followed by primary antibody incubation (Jiangsu Lanou Biological Material Co., Ltd.), polymer-HRP detection with DAB chromogen and hematoxylin counterstain. This molecular characterization was reinforced by the patient's established history of GBC resection 2 years prior. Regional imaging using physical examination and targeted ultrasonography of the neck/axilla revealed no evidence of new primary lesions. Although comprehensive whole-body PET/CT was not performed due to the palliative treatment focus, the convergence of pathological, clinical and localized radiological findings confirmed metastatic GBC as the sole etiology.

Treatment. After consulting with multidisciplinary experts at the Affiliated Hospital of Jiangsu University, the application of

US-guided MWA for neck mass was considered as a palliative therapy for alleviating the patient's condition. Written informed consent was obtained from the patient before MWA. Fig. 2 shows the specific treatment timelines and details regarding the patient's metastases. Arrows indicate the location of the mass vs. the ablation foci.

In September 2020, the patient underwent US-guided MWA treatment of the left neck masses. Preoperative US showed that the size of the left neck mass was 78x63x57 mm, with a clear boundary and slightly irregular edge. The left common carotid artery and internal jugular vein were notably compressed (Fig. 2A). An ECO-100A1 microwave therapeutic system (Nanjing ECO Medical Technology Co., Ltd.) consisting of a microwave generator, a hollow water-cooled shaft antenna (16 gauge) and a flexible coaxial cable was employed. The whole ablation process was performed under the guidance of US. A total of 10 ml 2% lidocaine was injected at the puncture site for local infiltration anesthesia, followed by 20 ml saline to isolate and protect the surrounding tissue. The needle pin was inserted into the lesion through previously determined path, and ablation was performed using a continuous method, with a power output of 35 W. The ablation continued until the transient hyperechoic zone covered the entire mass. The whole procedure lasted 14 min and 8 sec. The procedure was smooth, and the patient had no obvious abnormal symptoms.

In December 2020, the patient underwent the second MWA treatment for both left neck and left axillary masses. Preoperative US showed that the size of the left axillary mass was 28x25 mm, and the left neck mass had enlarged to 56x50 mm. The intraoperative power output was 35 W. The ablation time for the left axillary mass was 5 min and 47 sec, and for the left neck mass, it was 12 min and 30 sec. The levels of postoperative tumor indicators, measured using electrochemiluminescence immunoassay were: Carcinoembryonic antigen (CEA), 1.62 ng/ml; carbohydrate antigen CA19-9, 15.11 U/ml; and CA72-4, 33.51 IU/ml (Fig. 3A-C).

After 1 week, a follow-up US revealed an ablation focus measuring 22x18 mm in the left axilla and 56x51 mm in the left neck, both with clear margins (Fig. 2B). Contrast-enhanced US (CEUS) demonstrated no enhancement in the early or late phases of enhancement in the axillary and neck masses. A 1-month follow-up US revealed the presence of a newly discovered mass, measuring ~33x35 mm in size, located just superior to the left neck ablation foci.

In January 2021, due to the continuous new occurrence and substantial volume of the metastasis tumors, MWA alone was considered insufficient for inactivation. To achieve further disease control, the patient underwent ¹²⁵I RSI for left neck masses. This decision balanced the lesion's critical location abutting the carotid artery (Fig. 2A), the patient's explicit chemotherapy refusal and the patient's frailty. RSI is not a first-line treatment option for metastatic disease, but it has been shown to be promising for refractory oligometastatic cases in clinical practice (18). Preoperative US identified two hypoechoic masses on the left neck, measuring 54x40 mm and 40x32 mm, with CEUS showing partial necrosis in the larger mass. A total of 58 ¹²⁵I particles (physical dimension, 0.6 mm diameter; activity, 0.5 millicurie per seed) were evenly distributed to the active region of the larger mass, and 72 particles were evenly distributed to the other mass.

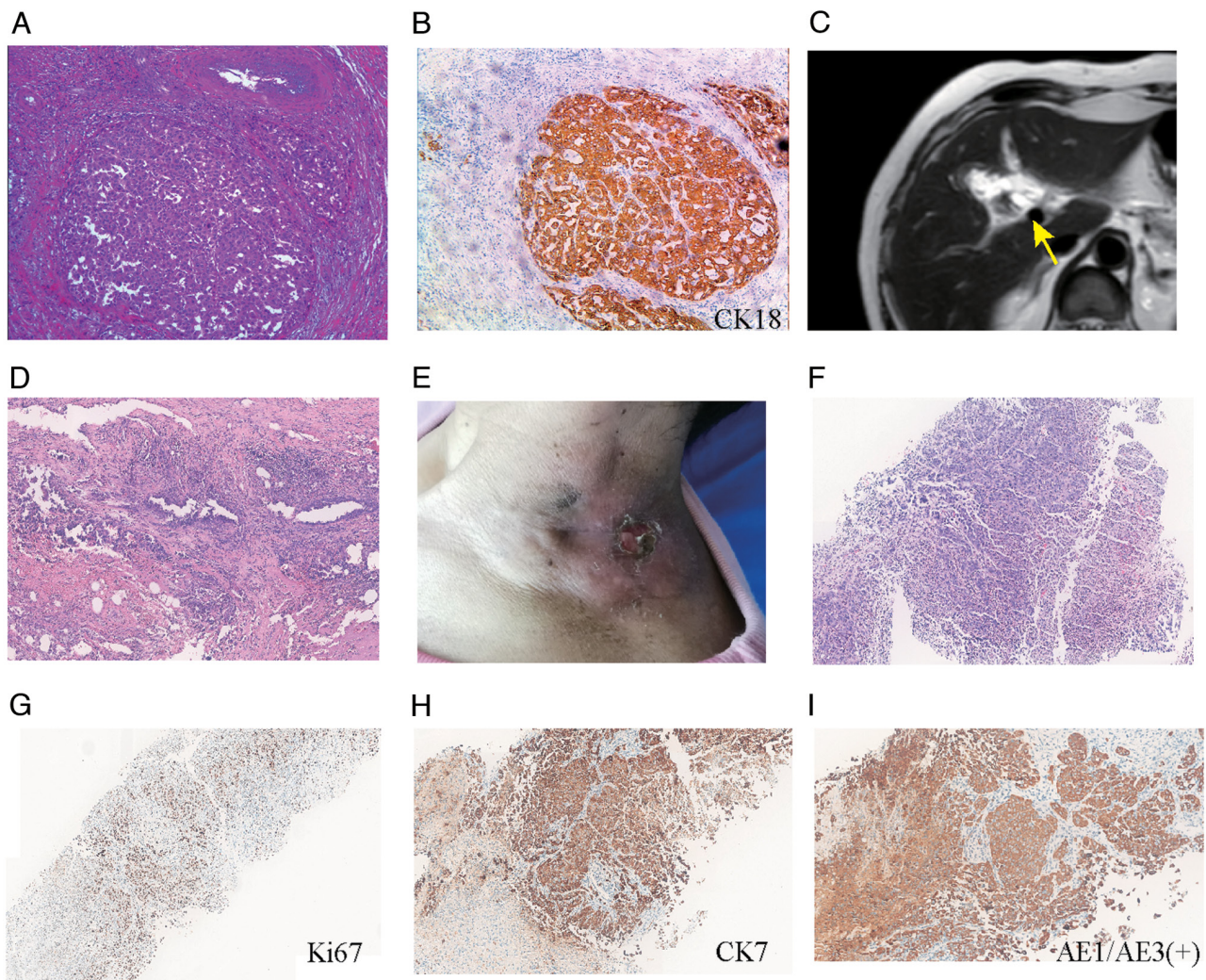


Figure 1. Diagnostic and pathological progression of gallbladder cancer. (A) Laparoscopic cholecystectomy specimen showing poorly differentiated adenocarcinoma (H&E). (B) IHC of primary tumor with positive CK18 confirming epithelial origin. Magnification, x400x. (C) Preoperative MRI showing irregular gallbladder wall thickening (arrow) with adjacent hepatic infiltration, suggesting residual malignancy. (D) Radical resection specimen of residual poorly differentiated adenocarcinoma in gallbladder bed (H&E, 200x magnification). (E) Clinical presentation showing left neck mass (8x8 cm) with surface ulceration prior to treatment. (F) Core-needle biopsy of neck mass demonstrated malignant epithelial cells (H&E), consistent with metastatic carcinoma. IHC of neck metastasis showing (G) Ki-67 (+, 75%) indicative of a high proliferative index, (H) CK7 (+), indicating biliary differentiation and (I) AE1/AE3 (+) indicating pan-cytokeratin confirmation of epithelial lineage. Magnification, x100. IHC, immunohistochemistry; CK, cytokeratin; AE1/AE3, cytokeratin AE1/AE3; H&E, hematoxylin and eosin.

A 1-month follow-up US revealed a reduction in the size of the axillary ablation foci. The two neck masses had decreased in size compared with previous measurements, displaying clear margins and heterogeneous internal echoes with scattered strong echogenic particles (Fig. 2C).

After 3 months, tumor indicators levels were as follows: CEA, 1.55 ng/ml; CA19-9, 7.88 U/ml; and CA72-4, 2.24 IU/ml. All were within the normal range (Fig. 3A-C).

In March, April and June 2021, the patient underwent the third, fourth and fifth sessions of MWA for neck masses, respectively, targeting the residual active areas of the left neck mass and suspicious lymph nodes for repeat ablation.

Outcome and follow-up. Following the last ablation procedure, the patient returned to the hospital for follow-up at 3, 6, 30, 36, 42 and 47 months. The latest examination results were as follows: Physical examination revealed smooth skin without redness or swelling and US indicated the ablation foci

had gradually absorbed and disappeared completely (Fig. 2D). The tumor markers remained within normal ranges. Flow cytometric analysis of T cell subsets indicated that CD3⁺ levels consistently remained high 2 years postoperatively (Fig. 3D).

Discussion

Due to the large number of metastatic tumors and the high tendency for recurrence, traditional surgical treatments struggle to completely eradicate the advanced cancer. This has become a notable challenge in treatment and a leading cause of patient mortality, highlighting the refractory nature of metastatic cancer. Consequently, the focus of treatment and research for advanced metastatic GBC has shifted to systemic therapies. Among these, the GemCis chemotherapy protocol, which combines gemcitabine and cisplatin, has been widely adopted internationally (1). However, a notable number of patients with advanced cancer choose to refrain

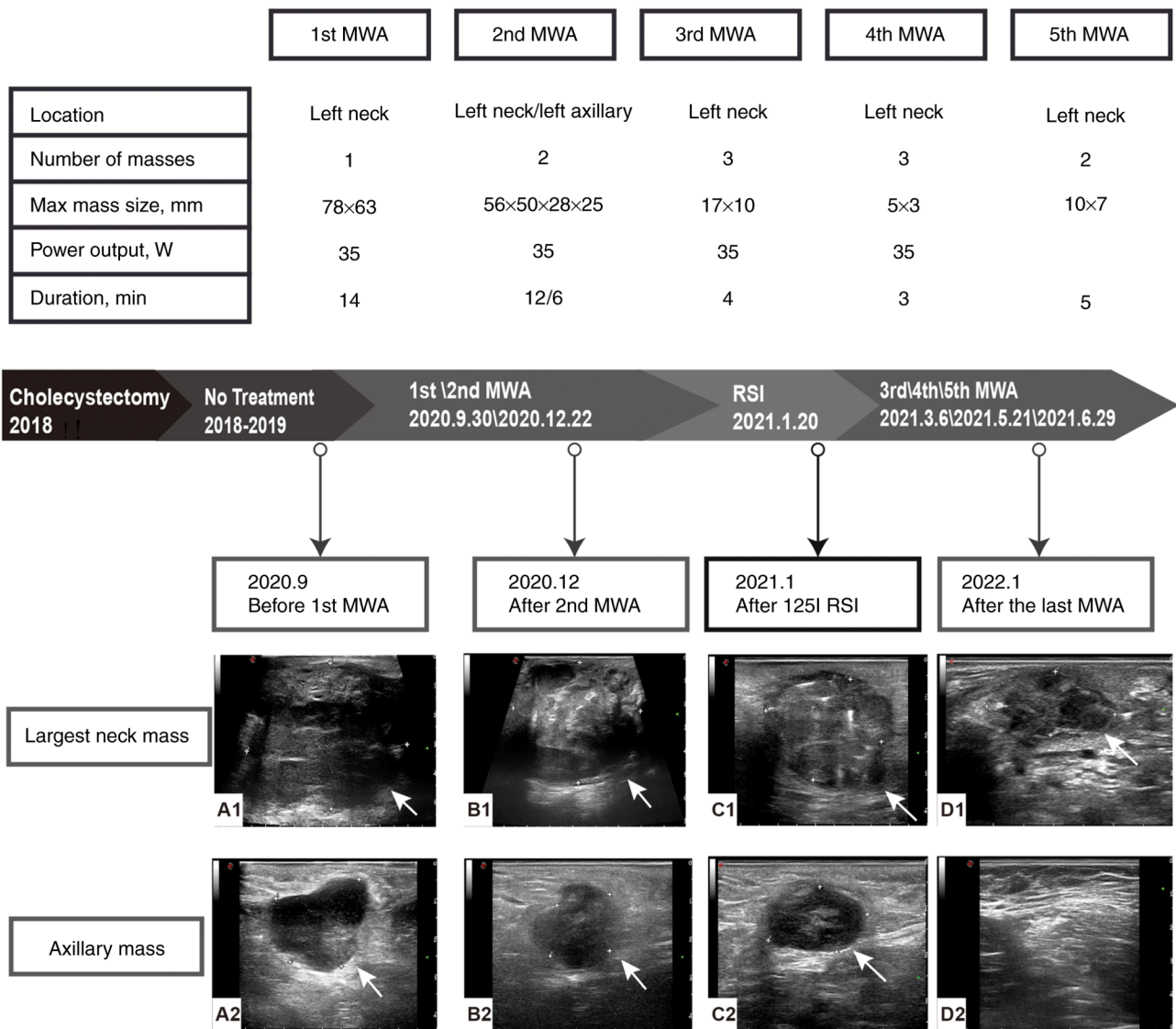


Figure 2. Flow chart of the entire treatment course and disease state. (A1-D1) Serial ultrasonographic images of the largest left neck mass during postoperative follow-up, demonstrating the evolution from pre-ablation to complete resolution. (A2-D2) Serial ultrasonographic images of the left axillary mass during postoperative follow-up, showing the progression from pre-ablation to eventual disappearance. Arrows indicate the location of the mass vs. the ablation foci. MWA, microwave ablation; RSI, radioactive ^{125}I seed implantation.

from chemotherapy in clinical practice due to physical and mental distress, economic pressure and other reasons, instead choosing palliative interventional therapies which are low-cost. In the present case, the patient rejected postoperative adjuvant radiotherapy or chemotherapy, and finally developed distant metastasis. The team offered only local palliative treatment for the metastatic mass of the patient, which unexpectedly achieved long-term systemic remission. Interventional therapy can not only destroy local tumor tissue but also activate the immune system of the body, which in turn has a certain immune attack on the distant metastasis, being consistent with the concept of *in situ* tumor vaccine. Based on a comprehensive literature review (PubMed, Web of Science and EMBASE up to July 2025), no prior case reports or studies have specifically documented the use of sequential MWA combined with ^{125}I -RSI for metastatic GBC.

MWA is a technique that directly utilized thermal energy to kill tumor cells *in situ* (19). Previous research has

demonstrated that thermal ablation can induce abscopal effects (9). This is a rare clinical response that refers to tumor regression or growth at a site distant from ablation or irradiation site. The abscopal response resulting from MWA is seldom reported. However, in the present case, the patient did not receive any systemic therapy prior to metastasis and had a long postoperative follow-up period of 30 months. Thus, the immunological mechanism of the abscopal effect warrants discussion. Natural killer cells, which are effector lymphocytes of the innate immune system and part of the first line of defense against cancer, can be activated by MWA to promote the destruction of tumor cells (20). Subsequently, residual antigens remain in the tumor site (21). These antigens can release inflammatory mediators, damage associated molecular patterns, and immune regulatory factors (such as IL-1, IL-6 and HSP70) (22). Dendritic cells (DCs) phagocytose antigens, present them on major histocompatibility complex molecules and display co-stimulatory factors, thereby stimulating T cells

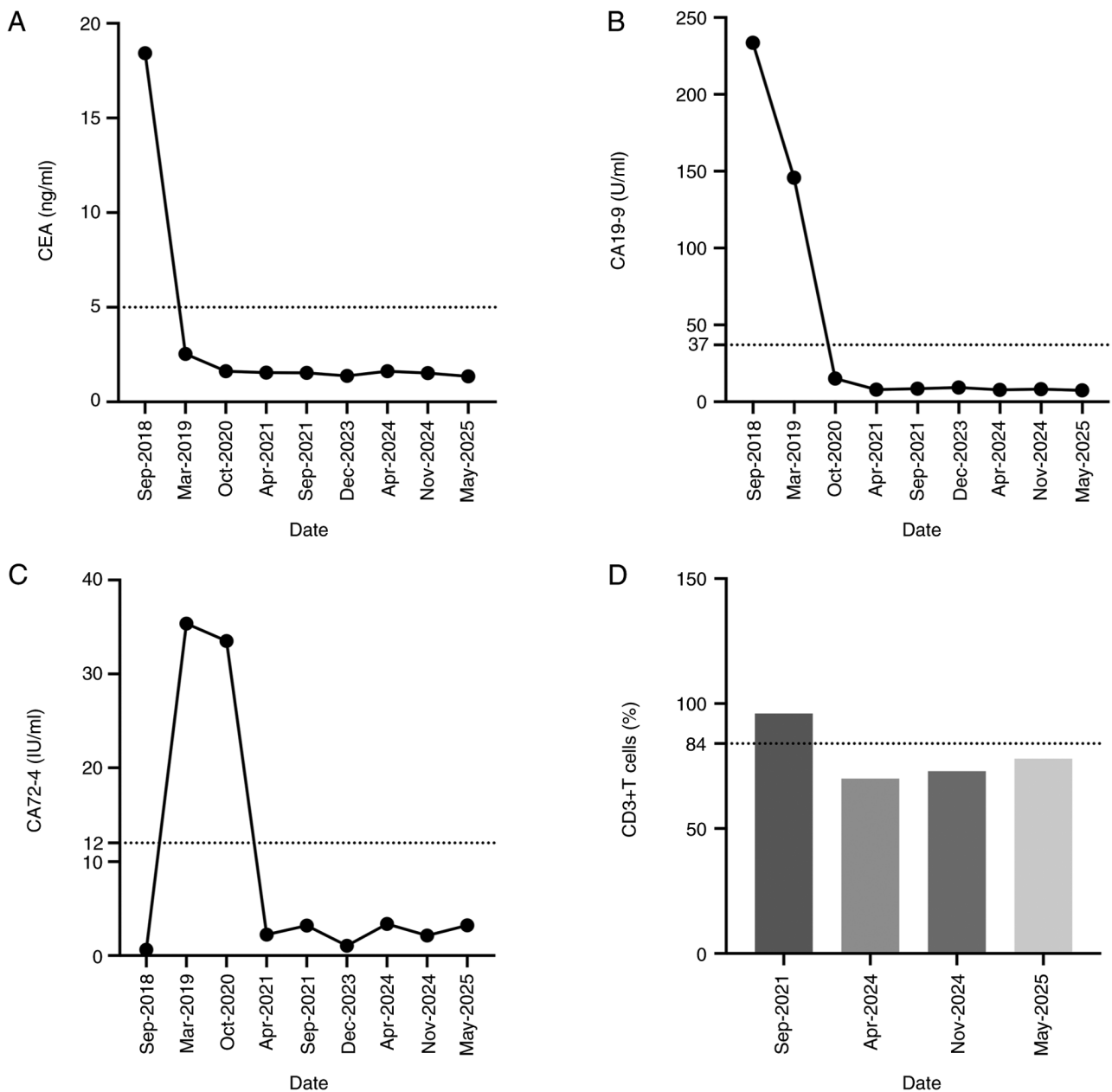


Figure 3. Tumor indicator levels. Levels of (A) CEA (normal, <5 ng/ml), (B) CA19-9, (normal, <37 U/ml) and (C) CA72-4 (normal, <12 IU/ml). (D) Levels of total T cells (CD3⁺)/lymphocytes (normal, 50-84%). CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

to generate adaptive immune responses and change the TME for antitumor effects (9). In the peripheral blood, a previous study reported that B cells are notable antigen-presenting cells in the MWA-induced systemic response (23).

In the present case, the patient was also treated with a single RSI due to the repeated progression of the disease. This treatment approach could create a favorable immune environment for tumor *in situ* vaccines. Radioactive ¹²⁵I seeds are implanted into tumors to emit large doses of γ rays at close range to destroy tumor cells without damaging normal tissues (24,25). RSI is increasingly used in the local treatment of tumors and has been utilized in the treatment of various recurrent and refractory tumors (26-30). RSI can trigger immunogenic tumor cell death. Tumor cells express molecules that promote phagocytosis of cancer cells by surface DCs, such as calreticulin, and release molecules that trigger ingested antigen processing and cross-presentation, such

as high mobility group box 1 protein. This process promotes DC cross-presentation of tumor antigens, altering the TME and generating antitumor immune responses (31). A previous study showed that RT can induce pyroptosis in tumor cells, resulting in the release of cellular contents from tumor cells, causing an inflammatory response and activating the immune system (32). RT can also induce abscopal effects. Siva *et al* (33) reported 10 cases of abscopal effects after radiotherapy, and their median duration was 21 months (range, 3-54 months). While RSI demonstrates notable potential, its physical application faces inherent constraints in metastatic settings. The technique is primarily suited for limited, accessible lesions due to technical challenges in precise seed placement within numerous or sub-centimeter metastases, with risks of migration and adjacent tissue damage (25,28). For cervical applications similar to the present case, radiation damage to adjacent nerves or vessels remains a

concern (27). In the present case, however, US-guided precision prevented such complications, underscoring its importance for high-risk anatomy.

MWA can be utilized as an *in situ* tumor vaccine to a certain extent, but due to the relatively weak response induced by it, it needs to be combined with other treatment methods. In the present case, initial MWA achieved partial control, but disease progression necessitated combined RSI. However, after ¹²⁵I RSI treatment, the notable effect was achieved, and the subsequent ablation effect was greatly enhanced. We hypothesize that the TME was transformed from an immunosuppressive state to an immune activation state after RSI, which provided a favorable immune environment for tumor treatment. While immune checkpoint dynamics (such as programmed cell death protein 1/programmed death-ligand 1) were not assessed in the present study, their role in modulating abscopal responses warrants investigation in future GBC studies (34).

Furthermore, the patient's peripheral blood T cell subsets demonstrated a continuous increase in CD3⁺ levels. Notably, the CD3⁺ T-cell elevation persisted for >30 months, substantially exceeding the typical duration of acute inflammatory responses to cellular debris. Its temporal association with complete clinical remission of all metastatic lesions (47 months) and sustained normalization of tumor markers strongly argues against non-specific inflammation (22), instead supporting a systemic adaptive immune response. These findings align with the paradigm of adaptive immune memory induced by *in situ* vaccination (35,36), whereby localized tumor destruction (via MWA/RSI) releases tumor-associated antigens, reprograms the immunosuppressive microenvironment (16,31) and potentiates sustained immunosurveillance mediated by antigen-experienced T cells. While definitive proof of tumor-specific immunity (such as T cell receptor sequencing or cytotoxic assays) is lacking and remains unavailable due to the retrospective nature of the present study, three concordant observations strongly suggest abscopal immunity mediated by *in situ* vaccination: i) Sustained CD3⁺ lymphocytosis; ii) unprecedented disease control >47 months; and iii) durable normalization of serum tumor markers. This clinical-immunological profile provides compelling evidence consistent with long-term immune memory formation.

The translation importance of the present case is threefold: i) It challenges the therapeutic nihilism for advanced GBC by demonstrating that sequential local interventions alone can achieve durable systemic remission, offering hope for chemotherapy-ineligible patients; ii) it provides the first clinical evidence that combining RSI (radiotherapy) with MWA synergistically overcomes immunosuppression, effectively creating an *in situ* vaccine against metastatic GBC; and iii) It establishes a foundation for minimally invasive strategies to convert palliative care into curative intent, with 47-month disease-free survival exceeding historical medians by >300%. However, as a single-case report, the present study lacks statistical power to establish causal relationships. The exceptional response observed may be influenced by unique patient biology. Comprehensive immune profiling was not available. Future prospective trials are needed to validate the findings.

The patient's entire disease course lasted 5 years and 4 months, during which recurrence and metastasis occurred. Based on the patient's poor condition, a sequential therapy consisting of multiple local interventions was precisely and

appropriately employed, which ultimately resulted in a favorable prognosis. In conclusion, while the present single case cannot confirm efficacy, it provides clinical rationale for exploring combined ablation-RSI as an immune-activating strategy in metastatic GBC. Palliative interventional therapy may induce a systemic effect and can enhance the survival rate of patients with advanced multiple metastatic cancer. The mechanism of the systemic antitumor immune response induced by such local treatments merits further investigation.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

WL made substantial contributions to the conception of the work, analyzed and interpreted the patient data, and drafted the manuscript. YC, SZ and MA contributed to the acquisition and analysis of clinical data. HZ and YC contributed to the study design and methodology. JB and JQ contributed to the data analysis and interpretation. BC conceived and supervised the study, critically revised the manuscript for important intellectual content, and approved the final version to be published. WL and JB confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in the present article.

Competing interests

The authors declare that they have no competing interests.

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