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Case Report

Pulmonary Metastasectomy after Radiofrequency Ablation of Hepatocellular Carcinoma

Takahiro Osuga[a] Shingo Tanaka[a, b] Tomohiro Kubo[a] Kota Hamaguchi[a]
Ryo Ito[a] Akira Sakurada[c] Keidai Ishikawa[d] Koji Miyanishi[a]

[a]Department of Medical Oncology, Sapporo Medical University School of Medicine, Hokkaido, Japan; [b]Department of Infection Control and Laboratory Medicine, Sapporo Medical University School of Medicine, Hokkaido, Japan; [c]Gastroenterology, Otaru Ekisaikai Hospital, Hokkaido, Japan; [d]Thoracic surgery, Otaru Kyokai Hospital, Hokkaido, Japan

Keywords
Hepatocellular carcinoma · Radiofrequency ablation · Pulmonary metastasis

Abstract
Introduction: Single distant metastases after radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) are rare. There are no guidelines for treating patients without liver tumors after resecting lung metastases. ***Case Presentation:*** Here, we report a patient with HCC recurring as a single lung metastasis 14 months after RFA. A 76-year-old woman with primary biliary cholangitis without hepatitis B virus or hepatitis C virus infection had been treated by RFA for a single 16-mm-sized HCC lesion in liver S8. Fourteen months thereafter, despite lack of intrahepatic recurrence, a single new 26-mm-sized mass was found in S10 of the right lung. The patient underwent right lower lobectomy. The histopathological diagnosis was HCC metastasis. Because no residual disease could be found, she was followed up without any additional treatment after surgery. She remains alive with no signs of recurrence 3 years later. ***Conclusion:*** HCC patients who relapse with lung metastases but without intrahepatic recurrence after RFA are extremely rare, especially when RFA is used to treat HCC lesions <30 mm. However, it should be noted that, although rare, HCC may recur in the form of extrahepatic metastases after RFA. Furthermore, it is suggested that, as in the presently-described case, at least some patients without intrahepatic recurrence whose lung metastases are completely resected have a good prognosis even without additional treatment for HCC.

Correspondence to:
Koji Miyanishi, miyako@sapmed.ac.jp

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Introduction

Single distant metastases after radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) are rare. According to the Japanese guidelines for treating recurring HCC, therapy is selected using a treatment algorithm. However, there are no guidelines for treating patients without liver tumors after resecting lung metastases. Here, we report a case in which a lung metastasis that appeared after RFA was resected. The patient remained recurrence-free without additional treatment for 3 years. The CARE Checklist for this case report is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536498.

Case Report

A 76-year-old woman being treated for primary biliary cholangitis, intraductal papillary mucinous neoplasm, and type 2 diabetes mellitus underwent contrast-enhanced CT. She was referred to our department for closer examination and treatment of a liver tumor serendipitously discovered by CT, although she had no liver symptoms. She had no history of alcohol consumption or smoking, and there was no family history of note. Vital signs and abdominal examination findings were normal. Blood was negative for hepatitis B surface antigen and hepatitis C virus antibody. Elevated levels of anti-mitochondrial antibodies M2 and IgM were recorded. Tumor markers alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II (PIVKA-II), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) were all within reference ranges (Table 1). Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced MRI (Gd-EOB-DTPA-MRI; EOB-MRI) showed a 16-mm lesion in hepatic S8 with high signal intensity in the arterial phase, washout from the portal venous phase, low signal in the hepatocellular phase, and high signal on diffusion-weighted images (Fig. 1a–e). CT during arterial portography (CTAP) showed no contrast of the mass (Fig. 1f). CT during hepatic arteriography (CTHA) showed that the mass was entirely contrasted in the early phase and had a coronal-like enhancement in the late phase (Fig. 1g, h). Other than the lesion, there were no findings suggesting HCC. On abdominal ultrasonography, the lesion appeared as a high echoic mass with a marginal hypoechoic zone and was clearly detected. Based on the above imaging findings, a diagnosis of HCC simple nodular type cT1, cN0, cM0, cStage IA (UICC TNM 8th edition) was made. We performed RFA of the lesion. There were no intraoperative or postoperative complications, and the patient was discharged on the seventh postoperative day. EOB-MRI 6 months after surgery showed no evidence of recurrence in the liver. However, although the same imaging 13 months later still showed no intrahepatic recurrence, a 26-mm lesion was observed in the right lower lung (Fig. 2). During the initial stage of imaging, use of a contrast agent revealed that the mass exhibited a prominent and intense signal on diffusion-weighted images (Fig. 3a–d). CT showed a single nodular lesion of 26 mm in S10 of the right lung (Fig. 3e). Bronchoscopy failed to obtain a tumor sample, and it was difficult to distinguish benign from malignant tissue. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) showed no other findings implicating malignancy. Fifteen months after RFA, a thoracoscopic resection of the lower lobe of the right lung was performed. Histopathological findings showed polygonal tumor cells with eosinophilic cytoplasm proliferating in a cord-like to full-blown focal pattern. Immunohistochemically, the tumor cells were negative for thyroid transcription factor-1 (TTF-1), NapsinA, cytokeratin 7, and cytokeratin 20, but weakly AFP-positive. Based on these findings, a diagnosis of pulmonary metastasis of HCC was made. Because there was no residual disease, the patient was followed up without further treatment. More than 3 years have passed since the lung surgery, and the patient has not had any recurrence (Table 2).

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Table 1. Laboratory data on admission

Hematology			*Chemistry*			*Serological tests*		
WBC	5,500	/μL	TP	7.6	g/dL	HBs-Ag	(−)	
RBC	369 × 10^4	/μL	Alb	4.0	g/dL	HBs-Ab	(−)	
Hb	11.5	g/dL	T-Bil	0.7	mg/dL	HBc-Ab	(−)	
Ht	35.0	%	AST	20	U/L	HCV-Ab	(−)	
PLT	20.1 × 10^4	/μL	ALT	16	U/L	AMA-M2	298	U/mL
			LDH	218	U/L	IgM	294	mg/dL
Coagulation			ALP	286	U/L	CRP	<0.10	mg/dL
PT	112.5	%	γ-GTP	29	U/L			
APTT	28.8	s	BUN	14	mg/dL	*Tumor marker*		
ATIII	105	%	CRE	0.68	mg/dL	AFP	4.0	ng/mL
						PIVKA-II	18	mAU/mL
						CEA	1.8	ng/mL
						CA19-9	6.8	U/mL

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; PLT, platelets; PT, prothrombin time, APTT, activated partial thromboplastin time; ATIII, antithrombin III; TP, total protein; Alb, albumin; T-Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; CRE, creatinine; HBs-Ag, hepatitis B surface antigen; HBs-Ab, hepatitis B surface antibody; HBc-Ab, hepatitis B core antibody; HCV-Ab, hepatitis C virus antibody; AMA-M2, anti-mitochondrial antibodies-M2; IgM, immunoglobulin M; CRP, C-reactive protein; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Discussion

Oligometastasis is the localized metastasis seen in certain cancers, for which the usefulness of local treatment such as surgery has been demonstrated (e.g., colorectal cancer and non-small cell lung cancer) [1]. However, systemic therapy remains the standard treatment for distant metastases in HCC, and there is currently insufficient evidence to support a benefit of local treatment such as surgery for oligometastasis. Over the past few years, the efficacy of local treatments such as surgery and RFA for lung metastases and stereotactic body radiotherapy for bone metastases has been reported for HCC, albeit in a small number of cases [1–4]. Propensity score matching analysis has also revealed that local treatment alone or local treatment in combination with systemic therapy can outperform systemic therapy alone in terms of survival benefit [1]. Thus, some patients with HCC oligometastasis may benefit from local therapy. The case presented here can be considered documenting the efficacy of surgical treatment for HCC oligometastasis. Outcomes of surgical resection for pulmonary metastases of HCC such as the present case have previously been reported to yield 5-year survival rates ranging from 12% to 67% (Table 3) [5–19]. As shown in this Table, a long delay between the last treatment for HCC and the finding of lung metastasis (i.e., a long disease-free interval), high AFP level, ≥2 lung metastases, and recurrence at other sites prior to lung metastasectomy have been reported to be poor prognostic factors after pneumonectomy in multiple case reports. It is suggested that surgical resection of HCC lung metastases is effective for patients without those characteristics. The present patient had a disease-free interval of at least 12 months, AFP within the threshold, and a single lung metastasis; these would be considered

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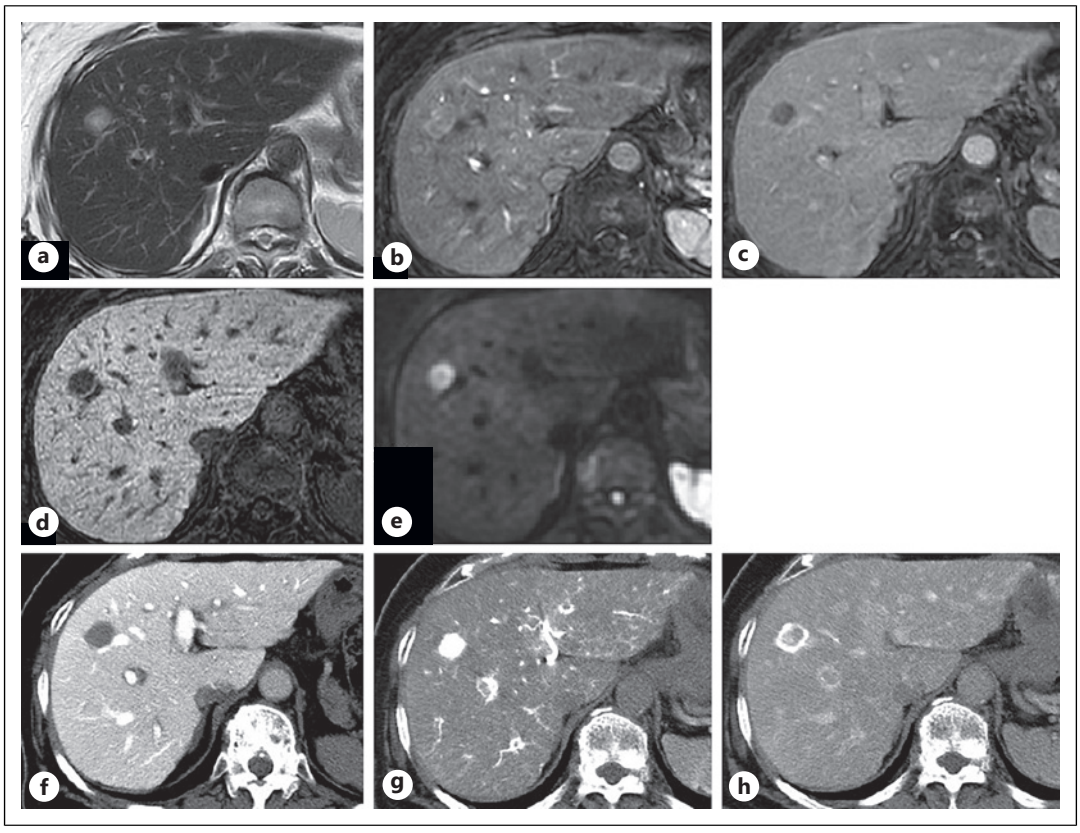

Fig. 1. Imaging liver tumors before RFA. T2-weighted (**a**), arterial phase (**b**), portal phase (**c**), hepatocellular phase (**d**), and diffusion-weighted image (**e**) of Gd-EOB-DTPA-MRI; CT during arterial portography (CTAP) (**f**), CT during hepatic arteriography (CTHA) early phase (**g**), CTHA late phase (**h**).

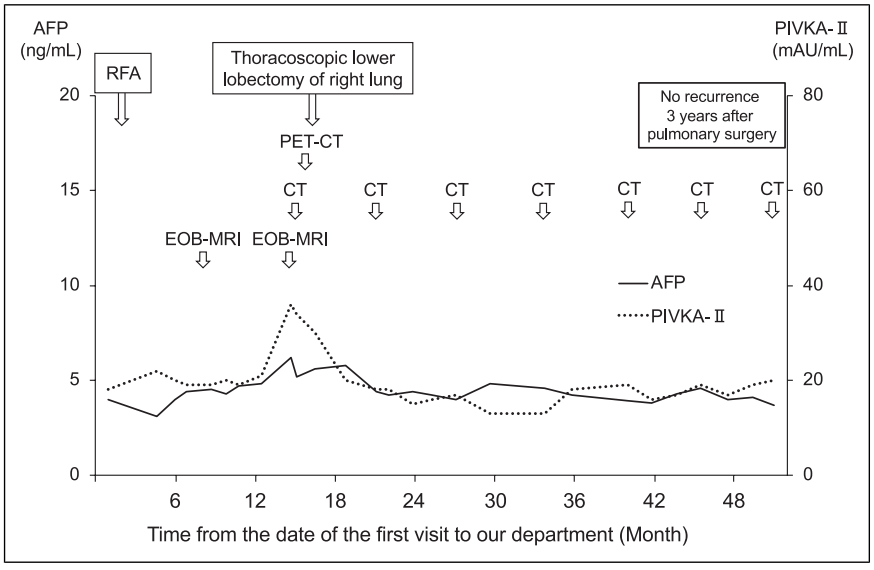

Fig. 2. Progress from the initial visit to our hospital. PIVKA-II tended to be slightly elevated at the time of the appearance of the HCC pulmonary metastasis. FDG-PET/CT showed FDG uptake in the lung tumor, but there were no other findings implicating malignancy. Three years after lung surgery, there was no evidence of recurrence.

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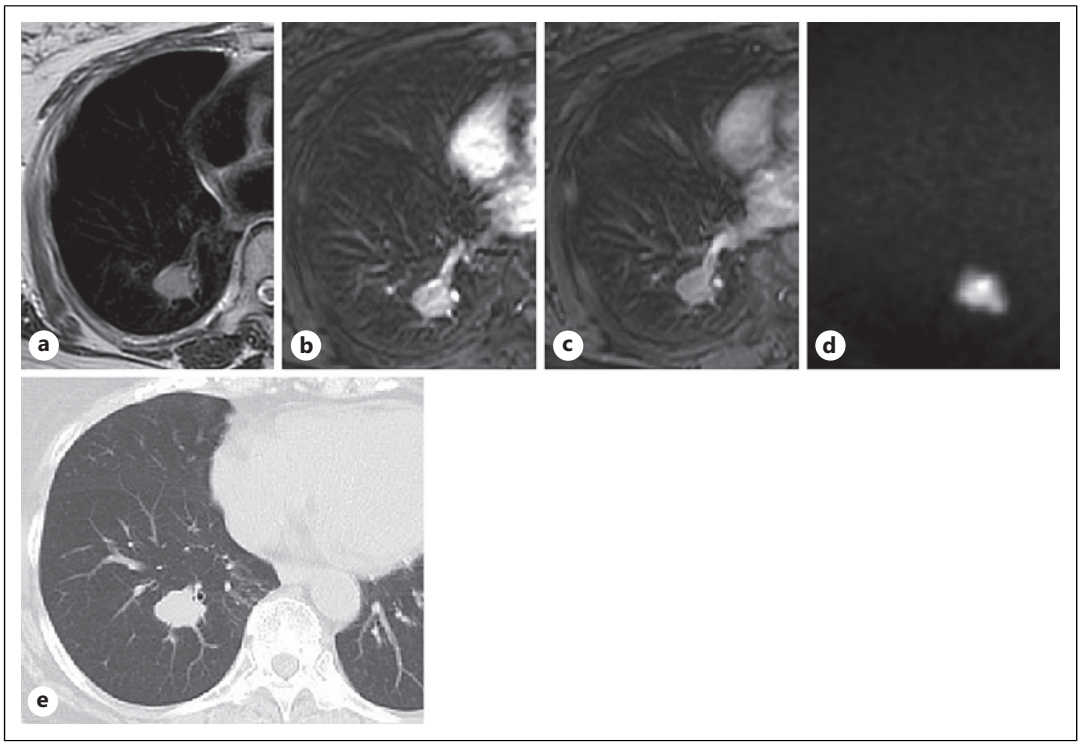

Fig. 3. Imaging of the lung mass appearing 13 months after RFA. T2-weighted (**a**), arterial phase (**b**), portal phase (**c**), and diffusion-weighted image (**d**) of Gd-EOB-DTPA-MRI; plain CT (**e**).

Table 2. Timeline summarizing the main events of this case

Time from the date of the first visit to our department	Event
0 weeks	The patient was referred to our department for closer examination and treatment of a liver tumor serendipitously discovered by CT, although she had no liver symptoms
8 weeks	The patient had been treated by RFA for a single 16-mm-sized HCC lesion in liver S8
62 weeks	The patient had an EOB-MRI scan that showed no evidence of recurrent HCC within the liver, but noted a new lung mass in S10 of the right lung
70 weeks	The patient underwent a right lower lobectomy for a right lung tumor
228 weeks	Date of most recent outpatient visit. Even at this time, there were no findings of recurrent HCC.

RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; EOB-MRI, gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced MRI.

favorable prognostic characteristics for pulmonary resection. If a patient with poor prognostic factors is found to have HCC pulmonary metastasis, resection of the lung lesion should be carefully considered, and possible prior use of systemic therapy should be discussed [20].

In this patient, metastases were incidentally detected in the lung on liver MRI imaging for follow-up 13 months after RFA. Cases of HCC with pulmonary metastasis after RFA are frequent.

Table 3. 5-year survival rate and poor prognostic factors of patients who underwent pulmonary resection for pulmonary metastasis of HCC

Authors	Year	Patients, *n*	5-year survival rate, %	Poor prognostic factors (overall survival)	Ref
Nakagawa et al.	2006	25	36.0	DFI <12 months, AFP ≥500 ng/mL	[5]
Kuo et al.	2007	34	27.5	DFI <12 months, AFP ≥100 ng/mL, <1 cm resection margin	[6]
Koide et al.	2007	14	26.8	≥2 lung metastases	[7]
Kawamura et al.	2008	61	32.2	≥3 lung metastases	[8]
Chen et al.	2008	12	28.9	Lung metastasis size ≥3 cm	[9]
Kwon et al.	2008	16	26.0	Liver transplantation(−), HBV infection, poor differentiation of HCC	[10]
Cho et al.	2010	17	11.8	DFI <24months, AFP ≥100 ng/mL	[11]
Han et al.	2010	41	66.9	Recurrence took place in a distant organ other than the liver or lungs	[12]
Yoon et al.	2010	45	37.0	First recurrence occured in an organ other than the lungs, DFI <12 months, ≥2 lung metastases	[13]
Kitano et al.	2012	45	40.9	Recurrence in other organs before lung metastasis resection, PIVKA-II>40 mAU/mL	[14]
Ohba et al.	2012	20	46.0	AFP ≥500 ng/mL	[15]
Takahashi et al.	2016	93	41.4	DFI <12 months	[16]
Matsuoka et al.	2017	10	46.7	NLR >2.31	[17]
Nakamura et al.	2019	30	33.6	Viral hepatitis, ≥2 lung metastases, other site recurrence before lung metastasectomy	[18]
Wang et al.	2019	103	38.5	Liver recurrence at the time of pulmonary metastasectomy, ≥2 lung metastases	[19]

HCC, hepatocellular carcinoma; DFI, disease-free interval; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; NLR, neutrophil-to-lymphocyte ratio; Ref, reference.

However, most such cases have suffered repeated intrahepatic recurrences before lung metastasis becomes apparent. Patients in whom the first recurrence was only pulmonary metastasis, as in the present case, are extremely rare. A literature search of case reports of lung metastases as the first recurrence after RFA as the initial treatment for HCC over the past 15 years revealed only one instance of solitary lung metastasis [21] and one case with multiple lung metastases and local recurrence in the liver [22] (Table 4). In Japan, surgical resection or RFA is currently recommended for the treatment of a single HCC lesion ≤3 cm in diameter. A randomized comparative study [23] of RFA and surgical resection for HCC reported that the

Table 4. Case reports of lung metastases as first recurrence after RFA as initial treatment for HCC in the past 15 years (2009–2023)

Case	Age	Gender	Diameter of HCC, mm	HCC(s), *n*	Time from RFA to lung metastasis, months	Location of metastases	Treatment of pulmonary metastases	Treatment after resection of pulmonary metastases	Prognosis	Ref
1	87	Male	22	1	24	Pulmonary (solitary)	Surgery	None	Bone metastasis appeared 3 years after pulmonary surgery	[21]
2	83	Male	23	2	2	Pulmonary (multiple), liver (local recurrence)	Systemic therapy (sorafenib)	–	50 months alive	[22]
Our case	76	Female	16	1	13	Pulmonary (solitary)	Surgery	None	Surviving for 3 years without recurrence	

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; Ref, reference.

incidence of distant metastasis was 32% (50 of 156) in patients treated with RFA and 26% (35 of 133) in patients with surgical resection. In that report, pulmonary metastatic recurrence also occurred in 26 (17%) and 17 (13%) patients, respectively. The results of the two treatments were similar, suggesting that there is no significant difference between RFA and hepatic resection in terms of the risk of distant metastatic recurrence. However, that study differs from the Japanese treatment algorithm because the patient selection criteria were based on HCC lesions <5 cm in diameter. In a report by Nishikawa et al. [24], limited to HCC lesions up to 3 cm, 214 of 368 patients developed recurrence, but only 1 patient developed pulmonary metastasis, and that patient also had multiple liver recurrences. In the SURF study [25], a phase III trial comparing surgery and RFA, not a single case of lung metastasis occurred. Therefore, recurrence of distant metastasis, including lung metastasis, is considered extremely rare in HCC lesions <3 cm in size, for which RFA is recommended by the Japanese guidelines. However, as was the case in the present patient, distant metastasis may occur after RFA for HCC lesions <3 cm, even in the absence of intrahepatic recurrence. Therefore, follow-up after RFA should not be limited to intrahepatic lesions but should include extrahepatic sites as well.

There is currently no clinically available adjuvant therapy after resection of HCC metastases. We explained to the patient that there were no obvious residual lesions detectable by contrast-enhanced CT or PET-CT, and after obtaining her consent, we chose to follow up without further treatment. Although no recurrence has been observed in this case, it is assumed that there are probably many similar cases with recurrence. Therefore, it is expected that effective adjuvant treatments will be developed to reduce the recurrence rate by adding systemic drug therapy to local treatments, including surgery. As one example, it has been suggested that the combination of TACE and systemic drug therapy may improve tumor control. However, issues remain regarding patient selection criteria, and the strategy has not yet been firmly established [26]. This is because biological heterogeneity across HCC has been a challenge in the development of effective combined therapy or adjuvant therapy [27]. In fact, for adjuvant therapy, the STORM trial tested sorafenib as an adjuvant drug and found no difference in recurrence-free survival compared to placebo [27]. Multi-targeted

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kinase inhibitors such as sorafenib, traditionally used for HCC, require a clearly defined target and may not be reasonable for use in adjuvant therapy. Recently, however, several promising phase III trials have been conducted using immune checkpoint inhibitors, such as the IMbrave 050 trial [28] comparing atezolizumab plus bevacizumab to observation, the EMERALD-2 trial [29] comparing durvalumab plus bevacizumab to placebo, the CheckMate-9 DX trial [30] comparing nivolumab with placebo, and KEYNOTE-937 [31] comparing pembrolizumab with placebo. Of these, the IMbrave 050 trial reported that the postoperative adjuvant high-risk HCC group had a better recurrence-free survival than the no-treatment follow-up group. Patients with distant metastases resected as in the case reported here are considered to be at high risk for recurrent HCC. If effective adjuvant therapy becomes available for postoperative HCC patients, resection of localized distant metastases with the addition of adjuvant therapy may be an effective treatment strategy.

Conclusions

We report a case of HCC with a single pulmonary metastasis after RFA, which was resected. The patient was followed up without further treatment and suffered no recurrence during the 3-year observation period. This experience may be valuable for deciding treatment strategies for similar cases.

Acknowledgment

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Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Takahiro Osuga and Koji Miyanishi collected and analyzed data, wrote and edited the manuscript, and were involved in the patient's care (mainly radiofrequency ablation). Shingo Tanaka, Tomohiro Kubo, Kota Hamaguchi, and Ryo Ito was involved in the patient's care (mainly radiofrequency ablation) and the acquisition, analysis, and interpretation of data for this case. Akira Sakurada involved in the patient's care (mainly outpatient care) and the

acquisition, analysis, and interpretation of data for this case. Keidai Ishikawa involved in the patient's care (mainly pulmonary surgical therapy) and the acquisition, analysis, and interpretation of data for this case.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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