










Novel strategy to treat lung metastases: Hybrid therapy involving surgery and radiofrequency ablation

Takaaki Hasegawa¹  | Hiroaki Kuroda²  | Noriaki Sakakura² | Yozo Sato¹  |
Shohei Chatani¹  | Shinichi Murata¹  | Hidekazu Yamaura¹  | Takeo Nakada²  |
Yuko Oya³  | Yoshitaka Inaba¹ 

¹Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, Nagoya, Japan

²Department of Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya, Japan

³Department of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Correspondence

Takaaki Hasegawa, Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan.
Email: t-hasegawa@aichi-cc.jp

Abstract

Background: This study was performed to evaluate the clinical outcomes of hybrid treatment involving surgical resection and percutaneous radiofrequency ablation for patients with multiple lung metastases.

Methods: Seventeen patients (6 men, 11 women; median age, 52 years; range, 16–78 years) underwent hybrid treatment involving surgery and radiofrequency ablation to treat multiple lung metastases (median number, 4; range, 2–26) between May 2014 and February 2020. The primary lesions were colorectal carcinoma (n = 9), uterine endometrial carcinoma (n = 3), osteosarcoma (n = 2), renal cell carcinoma (n = 1), glottic carcinoma (n = 1), and fibrolamellar hepatocellular carcinoma (n = 1). Twenty-four sessions each of surgery and radiofrequency ablation were performed. Safety, disease-free survival, and overall survival were evaluated. Safety was assessed according to the Clavien-Dindo Classification.

Results: A grade IVa adverse event of empyema developed in one patient (4%, 1/24) after surgery. A grade IIIa adverse event of pneumothorax and a grade II adverse event of lung abscess occurred in four (17%, 4/24) and one session (4%, 1/24) after radiofrequency ablation, respectively. During the median follow up of 34 months (range, 8–67 months), 10 patients (59%, 10/17) developed new metastases. The 5-year disease-free survival rate was 32%. Four or fewer lung metastases (p = 0.008) and metastases from colorectal carcinoma (p = 0.02) were factors significantly associated with longer disease-free survival. One patient (6%, 1/17) died of tumor progression 29 months after initial treatment. The 5-year overall survival rate was 88%.

Conclusions: The strategy of hybrid treatment involving surgery and radiofrequency ablation may offer good outcomes for patients with multiple lung metastases.

KEYWORDS

colorectal neoplasms, lung, metastasectomy, neoplasm metastasis, radiofrequency ablation

INTRODUCTION

When a patient has metastatic tumors, the malignancy is considered to be showing systemic progression, and the standard treatment in such cases is systemic chemotherapy. On the other hand, locoregional treatment might provide benefit if the apparent lesion is limited and not aggressive.^{1–4}

In fact, recent advancements in effective adjuvant chemotherapy and immunotherapy could lead to survival benefit with local control.^{3,4} The most effective locoregional treatment is surgical resection. Especially for patients with lung metastases, metastasectomy is widely performed because of the advances in video-assisted thoracoscopic surgery (VATS).^{5–10} Nevertheless, resection is sometimes difficult

for patients with multiple lung metastases considering the potential for insufficient remnant pulmonary function.

Recently, the use of radiofrequency ablation (RFA) has also been increasing as another effective locoregional treatment.^{11–17} This treatment has advantages in being less invasive, having a small effect on respiratory function, and tolerance for repeated treatment.^{11–16} However, RFA is effective only for small tumors.^{17,18}

Surgery and RFA each have advantages and disadvantages for the treatment of lung metastases. To compensate for their disadvantages, a strategy to perform both surgical resection and percutaneous RFA is sometimes considered as a hybrid therapy in patients with multiple lung malignancies.^{19,20} By resecting the external or large tumors and performing RFA for internal or small tumors, all lung metastases are treated while maintaining pulmonary function. However, the clinical outcomes of such hybrid therapy have not been well investigated.

In this study, the clinical outcomes of hybrid therapy involving surgery and RFA for patients with multiple lung metastases were retrospectively evaluated.

METHODS

Patients

This retrospective study was approved by our institutional review board. The necessity for informed consent for study inclusion was waived by the institutional review board, but informed consent to perform surgery and RFA was obtained from each patient before each procedure. A multidisciplinary team preoperatively discussed whether to perform surgery, RFA, or radiation therapy. Indication criteria for hybrid therapy are described as follows: (a) all the lung metastases could be treated by surgery and RFA; (b) no extra-lung metastases; (c) the remnant pulmonary function is thought to be low if all the lung metastases were treated by surgery; and (d) the locoregional treatment is recommended for lung metastases as they are considered to be oligometastases^{1,2} or effective systemic chemotherapy regimens are limited. Whether to treat each lesion with surgery or RFA is determined by discussion between surgeons and interventional radiologists. Basically, the possibility of resecting all tumors was pursued first. However, when it was thought that resection of the tumors would severely decrease respiratory function; RFA was planned for the tumors. Exclusion criteria for RFA are as follows: (a) tumors larger than 3 cm; (b) tumors contacting with vessels or bronchi larger than 2 mm; and (c) tumors located in pulmonary apex.

From May 2014 to February 2020, lung metastasectomy was planned for 396 patients at the Department of Thoracic Surgery in our hospital. Treatment of all lung metastases by hybrid therapy involving surgery and RFA was planned for 22 patients, but either surgery or RFA could not be performed in five patients. Therefore, 17 patients (4%, 17/396)

who completed the hybrid therapy were included in this study (Figure 1).

All patients underwent routine physical examinations, laboratory tests, pulmonary function tests (vital capacity [VC] and forced expiratory volume in 1 second [FEV1.0]), and imaging studies including chest radiography and computed tomography (CT) within the 4 weeks preceding treatment (Figure 2(a), (b)). CT was also checked within 4 weeks before each treatment session to prevent starting the next session with complications of previous treatment and development of new metastases. The patients' background and nodule characteristics are summarized in Table 1. There were 6 men and 11 women, with a median age of 52 years (range, 16–78 years). The median nodule number was four (range, 2–26). RFA was chosen to avoid lobectomy for seven nodules, to avoid segmentectomy for 14 nodules, or to prevent from respiratory failure caused by multiple wedge resections for five nodules. Ten of 17 patients (59%, 10/17) had other metastases treated previously, but all lesions were controlled by locoregional treatment. No patients had viable primary tumors or active metastases in an organ other than lung at the time of hybrid therapy.

The order of treatment was determined by thoracic surgeons considering the schedule of elective surgery and the conditions of the patients and their disease. The treatment began with surgery and RFA in seven and 10 patients, respectively. The median interval between initial lung metastases and RFA was 40 days (range, 14–172 days). When performing metastasectomy, all metastases located in one side of the lung were treated in one session. If metastases were present in both sides of the lungs, the surgeries for the right and left lungs were performed in separate sessions. On the other hand, one metastasis was treated in a single session of RFA. However, if several tumors were located in close proximity and could be punctured without withdrawing the needle, they were treated in one session. In total, surgery and RFA were performed in 24 sessions each. The median numbers of sessions of surgery and RFA for each patient were one (range, 1–2) and one (range, 1–4), respectively.

Surgical resection

Pulmonary metastasectomy was generally performed by wedge resection or segmentectomy (Figure 2(c)) under VATS through 1 to 4 ports. Lobectomy was performed for a lobe with a metastasis at the hilum or containing multiple metastases. Thoracotomy was chosen when VATS was thought to be high risk because of postoperative adhesions or comorbid disease.

Radiofrequency ablation

Lung RFA was performed percutaneously with the patient under moderate sedation and local anesthesia on an inpatient basis. Real-time CT fluoroscopy (Aquilion LB; Canon

FIGURE 1 Flowchart of patients who underwent lung metastasectomy in our institution

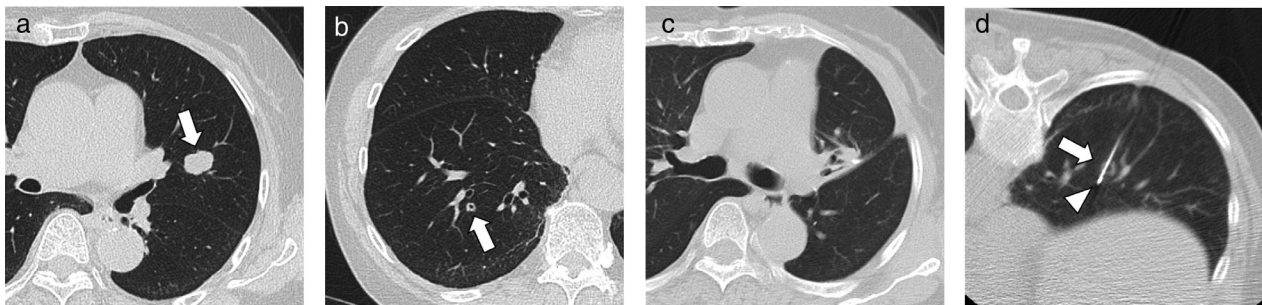
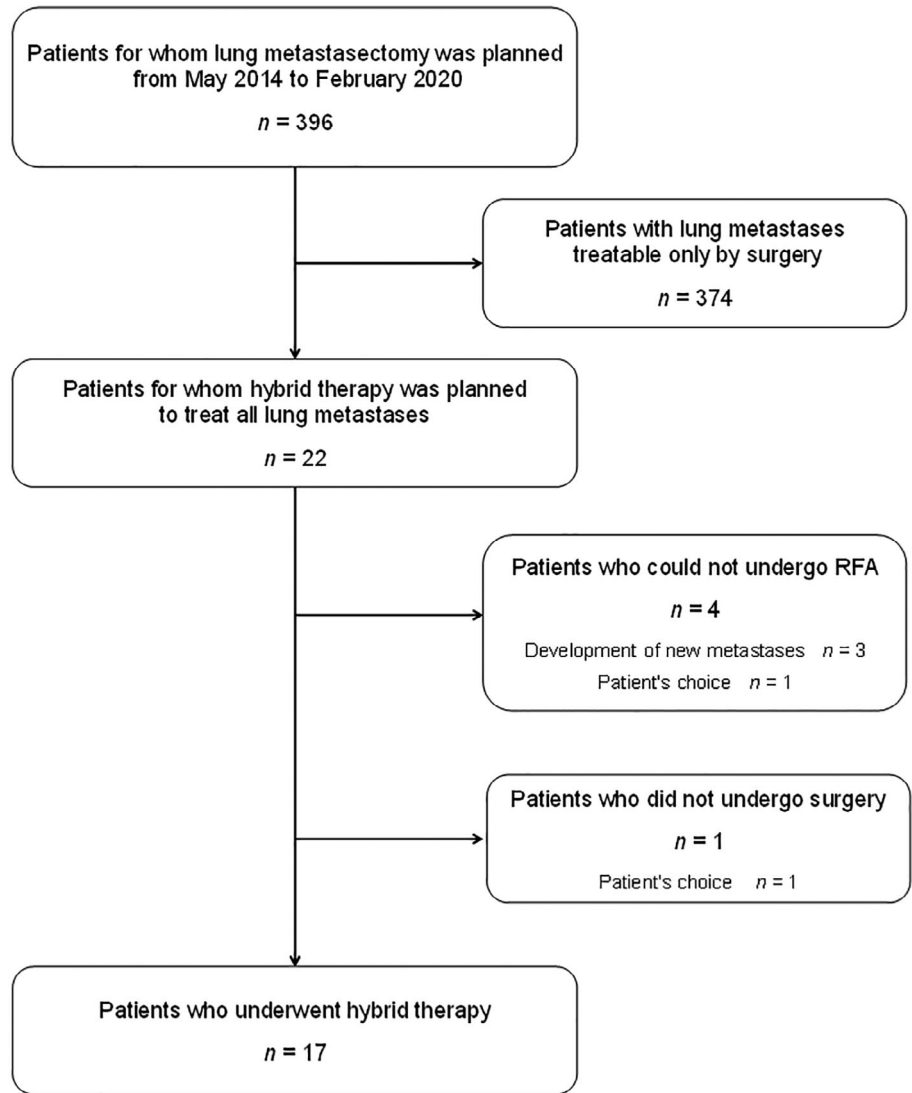


FIGURE 2 CT images of a 78-year-old woman (case 3) who underwent hybrid therapy for lung metastases from rectal cancer. Two lung metastases, (a) a 20-mm nodule (arrow) in the left lingula segment and (b) a 6-mm nodule (arrow) in the right lower lobe, emerged 7 months after resection of the primary tumor. Considering respiratory function and tumor location, surgery and radiofrequency ablation were planned for the left and right lung nodules, respectively. (c) Lingula segmentectomy is performed by video-assisted thoracoscopic surgery. (d) Radiofrequency ablation is performed for right lung metastases (arrow) with a cooled electrode (arrowhead)

Medical Systems Corp.) was used for image guidance (Figure 2(d)). All procedures were performed using an internally cooled electrode (VIVA RF System; STARmed). Radiofrequency energy was applied using an impedance-control

algorithm. Chest CT was performed immediately after RFA, and chest radiography was followed-up at 2 hours and for 2 days after RFA to check for pneumothorax and hemothorax.

TABLE 1 Details of patients and tumors

Case	Sex	Age (y)	Primary lesion	Previous history of metastasis	No of lung metastases	Maximum tumor diameter (mm)	Initial treatment	Surgical procedure	No of tumors treated by surgery	No of tumors treated by RFA	Adjuvant chemotherapy	Recurrence after hybrid therapy	Survival outcome
1	F	40	CRC	Liver	2	7	RFA	vRML	1	1	Yes	Lung	Alive
2	M	47	CRC	None	2	8	RFA	vLUSeg	1	1	Yes	None	Alive
3	F	78	CRC	None	2	20	Surgery	vLingSeg	1	1	No	None	Alive
4	F	39	CRC	None	3	7	Surgery	vRUSeg+LUSeg	2	1	No	LN	Alive
5	F	52	CRC	None	3	13	RFA	vLUp	1	2	No	None	Alive
6	M	64	CRC	Liver	4	14	RFA	vLUp+RLp	3	1	No	None	Alive
7	M	75	CRC	Lung	4	12	Surgery	RMp+RLp	3	1	No	None	Alive
8	F	67	CRC	Liver	5	14	RFA	vRUSeg+LUSeg	2	3	No	Lung	Alive
9	F	49	CRC	Liver	6	14	Surgery	vRMp+RUSeg +RUp+LLp	5	1	Yes	Lung	Alive
10	F	52	Uterine Ca	None	2	7	Surgery	vLingSeg	1	1	No	None	Alive
11	F	40	Uterine Ca	Bone	6	9	RFA	vRUp+RLp	2	4	No	Lung, Liver	Alive
12	F	67	Uterine Ca	Lung	6	12	RFA	RLl	4	2	No	Lung	Alive
13	F	44	Osteosarcoma	Lung	4	10	RFA	vRUSeg+RLp+RUp	3	1	Yes	Lung	Alive
14	F	16	Osteosarcoma	None	13	31	Surgery	vRLL+RUp+LUp+LLp	12	1	Yes	Lung	Dead
15	M	61	RCC	Lung	2	17	RFA	vRML	1	1	Yes	None	Alive
16	M	71	Glottic Ca	Lung, thyroid	3	11	RFA	vRLp+LLp	2	1	No	Lung	Alive
17	M	20	Fibrolamellar HCC	None	26	16	Surgery	vRUp+RMp+RLL+LUp+LLp	23	3	No	LN	Alive

Abbreviations: Ca, carcinoma; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; LingSeg, lingular segmentectomy; LLp, left lower lobe partial resection; LN, lymph node; LUp, left upper lobe partial resection; LUSeg, left upper lobe segmentectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation; RLL, Right lower lobectomy; RLp, right lower lobe partial resection; RML, right middle lobectomy; RMp, right middle lobectomy; RUp, right upper lobe partial resection; RUSeg, right upper lobe segmentectomy; v, video-assisted thoracoscopic surgery.

Follow-up

After completion of hybrid therapy, routine physical examinations, laboratory tests, and CT were performed at 1 month, then every 3–4 months for 2 years, and every 6 months thereafter. Pulmonary function test results were followed up 4–7 months after treatment completion. Data were followed-up until death or March 31, 2021, in surviving patients.

Assessment

Safety, disease-free survival (DFS), and overall survival (OS) after hybrid therapy were evaluated. Safety was assessed on a session basis using the Clavien-Dindo Classification system.²¹ DFS was defined as the time after completion of hybrid therapy to the date of development of new metastases or last follow-up. OS was defined as the time between the completion of hybrid therapy and the date of death or last follow-up.

Cumulative DFS and OS curves were generated by the Kaplan–Meier method. The DFS rates were compared by univariable analysis, using the log-rank test among subgroups categorized by patient background. Differences in pulmonary function between before and after hybrid therapy were compared using the Wilcoxon signed-rank test. A p value <0.05 was considered significant. Statistical analyses were performed using commercially available software (SPSS for Windows, version 24; IBM).

RESULTS

Safety

The median hospital stays after surgery and RFA were 3 days (range, 2–8) and 3 days (range, 2–4), respectively. A grade IVa adverse event (AE) of empyema requiring fenestration developed after one session (4%, 1/24) of surgery. A grade IIIa AE of pneumothorax requiring chest tube placement, a grade II AE of lung abscess, and a grade I AE of pneumothorax developed after 4 (17%, 4/24), 1 (4%, 1/24), and 8 sessions (33%, 8/24) of RFA, respectively. The median VC and FEV 1.0 decreased from 3.0 to 2.6 L ($p = 0.0008$) and 2.5 to 2.1 L ($p = 0.0008$), respectively. No patient complained of respiratory discomfort after completion of hybrid therapy.

DFS and OS after hybrid therapy

There was no local recurrence during the median follow up of 34 months (range, 8–67 months). Ten patients (59%, 10/17) developed new metastases in lungs ($n = 7$), lymph nodes ($n = 2$), and lungs and liver ($n = 1$). The DFS rates were 48% (95% confidence interval [CI], 23–74) at 1 year

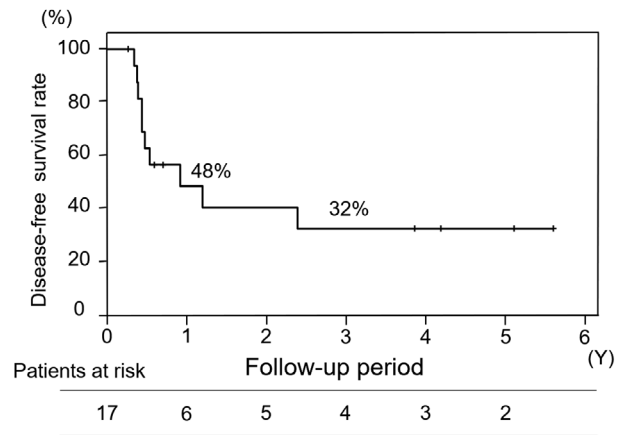


FIGURE 3 The Kaplan–Meier curve of disease-free survival after hybrid therapy for multiple lung metastases. The disease-free survival rates are 48% (95% CI, 23–74) at 1 year and 32% (95% CI, 7–57) at 3 and 5 years after hybrid therapy

and 32% (95% CI, 7–57) at 3 and 5 years (Figure 3). Median DFS was 8 months. Four patients underwent repeat radical treatment by surgery ($n = 1$) and RFA ($n = 3$), and 6 patients started systemic chemotherapy. The DFS rate was significantly better in patients with four or fewer lung metastases ($p = 0.008$) and with primary colorectal carcinoma ($p = 0.02$) (Table 2).

One patient (6%, 1/17) died of tumor progression 29 months after initial lung metastasectomy. The overall survival rates were 100% (95% CI, 100–100) at 1 year and 88% (95% CI, 65–100) at 3 and 5 years (Figure 4).

DISCUSSION

This study showed that hybrid therapy involving surgery and RFA provides good outcomes for patients with multiple lung metastases, with 5-year DFS and OS rates of 32% and 88%, respectively. With this treatment strategy, effective locoregional treatment could be performed while preserving respiratory function.

In performing locoregional treatment for patients with multiple and/or bilateral pulmonary metastases, achieving complete control of all metastases is indispensable, but preservation of pulmonary function is also needed. We could propose hybrid therapy as one solution to overcome this conflict. The small size of the treatable area is one of the drawbacks of RFA, but the effect on surrounding lung parenchyma is also small.²² There is less effect on wound healing after RFA, unlike with radiation therapy, and additional treatment can be performed; therefore, lung RFA is highly compatible with surgery. Moreover, there were no local recurrences in the present study, though the local recurrence rate was previously reported to be 10%–20% after lung RFA.^{17,18,23} Lesions suitable for RFA, such as small lesions or those located apart from large vessels, were selected as RFA targets, and this might contribute to the low local recurrence rate.

TABLE 2 Disease-free survival rate by variable

Variable	No. of patients	DFS rate (%)		p value
		1-year	3-year	
Age (y)				
<60	10	42	28	0.69
≥60	7	57	38	
Sex				
Male	6	60	30	0.75
Female	11	44	33	
Maximum tumor diameter				
≤1 cm	6	33	33	0.79
>1 cm	11	55	33	
Number of lung metastases				
≤4	11	67	53	0.008
≥5	6	17	NA	
Primary tumor				
CRC	9	70	53	0.02
Non-CRC	8	25	13	
Initial treatment				
Surgery	7	57	43	0.31
RFA	10	44	22	
Previous metastases				
No	7	50	50	0.34
Yes	10	50	17	
Adjuvant chemotherapy				
No	11	42	42	0.08
Yes	6	NA	NA	
Total	17	48	32	

Abbreviations: CRC, colorectal carcinoma; DFS, disease-free survival; NA, not applicable; RFA, radiofrequency ablation.

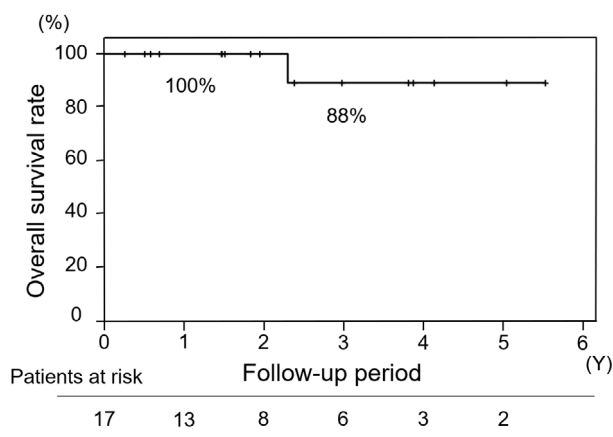


FIGURE 4 The Kaplan–Meier curve of the overall survival rate after hybrid therapy for multiple lung metastases. The overall survival rates are 100% (95% CI, 100–100) at 1 year and 88% (95% CI, 65–100) at 3 and 5 years after hybrid therapy

Nevertheless, complete ablation of small tumors is sometimes difficult to achieve,²⁴ thus it is important to determine the indication for treatment carefully.

During this study period, hybrid therapy was planned for 22 patients but it could not be completed in five patients. In particular, new metastases developed in three patients after initial treatment. Patient selection is, therefore, very important, and multidisciplinary team discussions were held before treatment, but it was not possible to avoid the development of new lesions during the treatment course. However, new lesion development could be checked between treatment sessions, so that it could be said that patients had the opportunity to escape from unnecessary radical and invasive treatment with the hybrid therapy strategy.

This study identified two factors associated with significantly longer DFS. One factor was four or fewer lung metastases. The efficacy of locoregional treatment for oligometastases, defined as metastases limited in number and location, has been reported in the last few decades.^{1–4} Considering that lack of wide spread of the tumor is related to better tumor control, it is reasonable that a smaller number of metastases was a significant factor for longer DFS. The other factor was metastases from colorectal carcinoma; this result corresponded with a previous report that showed better treatment outcomes after metastasectomy of metastases from colorectal carcinoma than of other malignancies.²⁵ In several guidelines for colorectal carcinoma management, resection is recommended when the primary lesion and all metastases are resectable.^{26–28} Therefore, patients with multiple lung metastases from colorectal carcinoma may be good candidates for hybrid therapy.

Hybrid therapy was performed for a 16-year-old woman with 13 metastases from osteosarcoma (case 14) and a 20-year-old man with 26 metastases from fibrolamellar hepatocellular carcinoma (case 17). Surgery or RFA is not usually indicated for such multiple tumors. However, hybrid therapy was performed because there are few effective systemic chemotherapy regimens for such tumors and considering each patient's age.^{29–31} Locoregional treatment plays an important role in such situations, but it was considered difficult to resect all tumors because of the possibility of severely impaired remnant pulmonary function. By treating the inner metastases by RFA, pulmonary function was preserved, and this may have contributed to enabling patients to undergo further treatment if new metastases developed.

The complication rate was higher after RFA than after surgery. Because RFA is a percutaneous procedure, it is difficult to simply compare with surgery, because a chest tube was not usually inserted, and CT showed minor pneumothorax after treatment. However, there were no life-threatening complications after each treatment. Moreover, no patients complained of respiratory discomfort after hybrid therapy. Actually, among 26 tumors treated by RFA in this study, lobectomy or segmentectomy were required to treat 21 nodules if surgery was performed. It has been reported that VC and FEV 1.0 decrease 7.1%–19.2% and 8.7%–21.0% after lobectomy and 4.1%–15.0% and 6.2%–18.4% after segmentectomy,^{32–35} respectively. Moreover, bilateral metastasectomy was reported to impair pulmonary function than unilateral surgery.³⁶ Hybrid therapy may work

to prevent from respiratory failure caused by such pulmonary function impairment.

This study has several limitations. First, because this was a single-center, retrospective study, selection bias could not be avoided. Second, the follow-up period was short, and long-term outcomes were unclear. Third, the inhomogeneous patient sample made it difficult to evaluate treatment outcomes. Fourth, the sample size was too small to conduct multivariate analysis. At last, the quality of life after hybrid therapy was not evaluated, so the effect on less invasiveness with this treatment strategy from the viewpoint of quality of life was unclear. Despite these limitations, the strategy of hybrid therapy involving surgery and RFA may offer good outcomes for patients with multiple lung metastases. In particular, patients with four or fewer lung metastases and those with metastases from colorectal carcinoma appear to be good candidates.

CONFLICT OF INTEREST

Authors declare that they have nothing to disclose.

ORCID

Takaaki Hasegawa  <https://orcid.org/0000-0001-6701-8836>

Hiroaki Kuroda  <https://orcid.org/0000-0001-7292-0293>

Yozo Sato  <https://orcid.org/0000-0001-7605-8434>

Shohei Chatani  <https://orcid.org/0000-0001-5080-2333>

Shinichi Murata  <https://orcid.org/0000-0002-6163-5451>

Hidekazu Yamaura  <https://orcid.org/0000-0003-2076-7017>

Takeo Nakada  <https://orcid.org/0000-0003-1168-0163>

Yuko Oya  <https://orcid.org/0000-0002-3171-6031>

Yoshitaka Inaba  <https://orcid.org/0000-0002-0850-6327>

REFERENCES

- Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995; 13:8–10.
- Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol*. 2011;8:378–82.
- Lo SS, Moffatt-Bruce SD, Dawson LA, Schwarz RE, Teh BS, Mayr NA, et al. The role of local therapy in the management of lung and liver oligometastases. *Nat Rev Clin Oncol*. 2011;8:405–16.
- Reyes DK, Pienta KJ. The biology and treatment of oligometastatic cancer. *Oncotarget*. 2015;6:8491–524.
- Handy JR, Bremner RM, Crocenzi TS, Detterbeck FC, Fernando HC, Fidias PM, et al. Expert consensus document on pulmonary metastasectomy. *Ann Thorac Surg*. 2019;107:631–49.
- Cheung FP, Alam NZ, Wright GM. The past, present and future of pulmonary metastasectomy: a review article. *Ann Thorac Cardiovasc Surg*. 2019;25:129–41.
- van Dorp M, Beck N, Steup WH, Schreurs WH. Surgical treatment of pulmonary metastases in The Netherlands: data from the Dutch lung cancer audit for surgery. *Eur J Cardiothorac Surg*. 2020;58:768–74.
- Sakamaki Y, Ishida D, Tanaka R. Prognosis of patients with recurrence after pulmonary metastasectomy for colorectal cancer. *Gen Thorac Cardiovasc Surg*. 2020;68:1172–8.
- Murakawa T, Sato H, Okumura S, Nakajima J, Horio H, Ozeki Y, et al. Thoracoscopic surgery versus open surgery for lung metastases of colorectal cancer: a multi-institutional retrospective analysis using propensity score adjustment. *Eur J Cardiothorac Surg*. 2017;51: 1157–63.
- Numan RC, Baas P, Klomp HM, Wouters MW. Optimal surgical management of pulmonary metastases: VATS versus thoracotomy. *Respirology*. 2016;21:188–90.
- Hasegawa T, Takaki H, Kodama H, Yamanaka T, Nakatsuka A, Sato Y, et al. Three-year survival rate after radiofrequency ablation for surgically resectable colorectal lung metastases: a prospective multi-center study. *Radiology*. 2020;294:686–95.
- de Baère T, Aupérin A, Deschamps F, Chevallier P, Gaubert Y, Boige V, et al. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. *Ann Oncol*. 2015;26:987–91.
- Lencioni R, Crocetti L, Cioni R, Suh R, Glenn D, Regge D, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol*. 2008;9:621–8.
- Qi H, Fan W. Value of ablation therapy in the treatment of lung metastases. *Thorac Cancer*. 2018;9:199–207.
- Gobara H, Arai Y, Kobayashi T, Yamakado K, Inaba Y, Kodama Y, et al. Percutaneous radiofrequency ablation for patients with malignant lung tumors: a phase II prospective multicenter study (JIVROSG-0702). *Jpn J Radiol*. 2016;34:556–63.
- Hiyoshi Y, Miyamoto Y, Kiyozumi Y, Sawayama H, Eto K, Nagai Y, et al. CT-guided percutaneous radiofrequency ablation for lung metastases from colorectal cancer. *Int J Clin Oncol*. 2019;24:288–95.
- Yan TD, King J, Sjarif A, Glenn D, Steinke K, al-Kindy A, et al. Treatment failure after percutaneous radiofrequency ablation for non-surgical candidates with pulmonary metastases from colorectal carcinoma. *Ann Surg Oncol*. 2007;14:1718–26.
- Fanucchi O, Ambrogi MC, Aprile V, Cioni R, Cappelli C, Melfi F, et al. Long-term results of percutaneous radiofrequency ablation of pulmonary metastases: a single institution experience. *Interact Cardiovasc Thorac Surg*. 2016;23:57–64.
- Sano Y, Kanazawa S, Mimura H, Gobara H, Hiraki T, Fujiwara H, et al. A novel strategy for treatment of metastatic pulmonary tumors: radiofrequency ablation in conjunction with surgery. *J Thorac Oncol*. 2008;3:283–8.
- Tempaku H, Takao M, Shimamoto A, Murashima S, Yamakado K, Nakamura T, et al. Outcome for pulmonary metastases from malignant osteogenic and soft tissue sarcomas. *Kyobu Geka*. 2013;66:311–4.
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–13.
- Miao Y, Ni Y, Bosmans H, Yu J, Vaninbrouckx J, Dymarkowski S, et al. Radiofrequency ablation for eradication of pulmonary tumor in rabbits. *J Surg Res*. 2001;99:265–71.
- Matsui Y, Hiraki T, Gobara H, Iguchi T, Fujiwara H, Nagasaka T, et al. Long-term survival following percutaneous radiofrequency ablation of colorectal lung metastases. *J Vasc Interv Radiol*. 2015;26:303–10.
- Hasegawa T, Sato Y, Kuroda H, Chatani S, Murata S, Yamaura H, et al. Clinical outcomes and techniques for radiofrequency ablation of lung tumors smaller than 1 cm. *Interv Radiol*. 2020;5:94–102.
- Hirai F, Kinoshita I, Matsubara T, Haratake N, Kouzuma Y, Takamori S, et al. Which primary organ is most suitable for performing pulmonary metastasectomy? *Anticancer Res*. 2018;38:1041–5.
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Colon Cancer Version 4. 2020. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf Accessed April 27, 2021.
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Rectal Cancer Version 6. 2020. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf Accessed April 27, 2021.
- van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27:1386–422.
- Denduluri SK, Wang Z, Yan Z, et al. Molecular pathogenesis and therapeutic strategies of human osteosarcoma. *J Biomed Res*. 2015;30:5–18.
- Ramai D, Ofosu A, Lai JK, Gao ZH, Adler DG. Fibrolamellar hepatocellular carcinoma: a population-based observational study. *Dig Dis Sci*. 2021;66:308–14.

31. Lin CC, Yang HM. Fibrolamellar carcinoma: a concise review. *Arch Pathol Lab Med*. 2018;142:1141–5.
32. Gu Z, Wang H, Mao T, Ji C, Xiang Y, Zhu Y, et al. Pulmonary function changes after different extent of pulmonary resection under video-assisted thoracic surgery. *J Thorac Dis*. 2018;10:2331–7.
33. Kobayashi N, Kobayashi K, Kikuchi S, Goto Y, Ichimura H, Endo K, et al. Long-term pulmonary function after surgery for lung cancer. *Interact Cardiovasc Thorac Surg*. 2017;24:727–32.
34. Echavarría MF, Cheng AM, Velez-Cubian FO, Ng EP, Moodie CC, Garrett JR, et al. Comparison of pulmonary function tests and perioperative outcomes after robotic-assisted pulmonary lobectomy vs segmentectomy. *Am J Surg*. 2016;212:1175–82.
35. Kuroda H, Sakata S, Takahashi Y, Nakada T, Oya Y, Sugita Y, et al. Subsegmental resection preserves regional pulmonary function: a focus on thoracoscopy. *Thorac Cancer*. 2021;12:1033–40.
36. Welter S, Cheufou D, Zahin M, Kampe S, Darwiche K, Weinreich G, et al. Short- and mid-term changes in lung function after bilateral pulmonary Metastasectomy. *Thorac Cardiovasc Surg*. 2016;64:139–45.

How to cite this article: Hasegawa T, Kuroda H, Sakakura N, et al. Novel strategy to treat lung metastases: Hybrid therapy involving surgery and radiofrequency ablation. *Thorac Cancer*. 2021;12:2085–2092. <https://doi.org/10.1111/1759-7714.14041>