Original Article | Intervention

https://doi.org/10.3348/kjr.2018.19.1.54
pISSN 1229-6929 · eISSN 2005-8330
Korean J Radiol 2018;19(1):54-62

Korean Journal of Radiology
KJR

Ultrasound-Guided Intraoperative Radiofrequency Ablation and Surgical Resection for Liver Metastasis from Malignant Gastrointestinal Stromal Tumors

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Objective: To evaluate the effectiveness, safety, and feasibility of intraoperative radiofrequency ablation (IORFA) under ultrasound guidance for the treatment of liver metastases from gastrointestinal stromal tumors (GISTs).

Materials and Methods: From August 2009 to February 2017, 24 patients with liver metastases of GISTs underwent IORFA, 14 underwent concurrent IORFA and primary GIST resection, and 10 underwent IORFA to treat hepatic recurrence after previous primary GIST resection. Seventy-six hepatic metastases were treated, of which 47 were surgically resected and 29 underwent IORFA. All included patients received imatinib therapy as standard treatment before and after IORFA or surgical resection. A retrospective medical record review was conducted, and follow-up data were collected. Technical success and effectiveness, overall and GIST-specific survival, and complications were assessed.

Results: The mean follow-up duration was 50.7 ± 34.7 months. The technical success rate of IORFA was 100%. New metastases developed in three of the 24 patients (12.5%) following a complete response 16, 51, and 95 months after IORFA, respectively. The cumulative one-, three-, and five-year overall survival rates were 100, 94.4, and 87.7%, respectively. The one-, three-, and five-year GIST-related survival rates were 100, 94.4, and 94.4%, respectively. Two major complications (biliary stricture and hepatic abscess) were observed.

Conclusion: IORFA appears to be a feasible and safe treatment option for liver metastasis in patients with primary GISTs. In addition, IORFA and surgical resection may be complementary, helping to obtain complete response in cases of otherwise inoperable liver metastases secondary to GISTs.

Keywords: *Intraoperative; Radiofrequency ablation; Hepatic metastasis; Gastrointestinal stromal tumor*

Received March 26, 2017; accepted after revision July 1, 2017.
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2014R1A1A1003475).

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal tumor in the gastrointestinal tract arising from the interstitial cells of Cajal (1). Distant metastasis occurs at rates between 23% and 47%, with 20% to 60% of these cases affecting the liver (2, 3). For treatment of metastatic GISTs, the introduction of imatinib mesylate has resulted in notable improvements in the clinical outcomes for patients (4, 5). Although up to 80% of patients exhibit an initial response to imatinib treatment, secondary resistance eventually develops in most patients

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(6, 7). Therefore, a combination of surgery and imatinib treatment is now widely used in clinical practice for GIST cases, and the treatment protocol is referenced in current practical guidelines on GIST management (8, 9).

Radiofrequency ablation (RFA) has recently been evaluated as an alternative form of treatment in several cases of unresectable GIST with liver metastasis (3, 10-13). RFA may be a useful therapeutic option for patients with metastatic GIST and should be performed at the time of best clinical response, followed by post-procedural imatinib maintenance therapy (14). Among RFA techniques, intraoperative RFA (IORFA), with or without surgical resection, has been reported to yield several advantages when compared with percutaneous RFA, including a broader indication for surgical resection as a treatment for various hepatic metastases (10). By combining IORFA with resection, more patients may become candidates for surgical treatment because the surgeon would be able to resect larger tumors while ablating residual smaller tumors (15, 16). A combination therapy comprising surgical resection and IORFA has yielded potential benefits in certain cases; however, consequent long-term survival rates or broadening of surgical indications have rarely been reported (17).

In this study, we aimed to evaluate the feasibility and safety of IORFA for the complete removal of unresectable hepatic metastases secondary to GIST, with or without combined hepatic resection during continued imatinib therapy.

MATERIALS AND METHODS

The local Institutional Review Board provided study approval and waived the requirement for informed consent because of the retrospective design. Between August 2009 and February 2017, 24 patients with hepatic metastases of GIST that were histologically proven were included in the current study. Firstly, the feasibility and benefit of surgical resection in patients with hepatic metastasis from GIST were considered after a discussion by oncologists and surgeons. Patients with surgically unresectable hepatic metastases (e.g., a daughter tumor in another lobe that would cause hepatic insufficiency if resected) were considered for IORFA.

The inclusion criteria were as follows: 1) complete resectable hepatic tumors by surgical resection with additional IORFA or by IORFA alone after discussion on multidisciplinary team; 2) an unacceptably high risk of hepatic insufficiency after resection alone; 3) tumors in locations unfavorable for surgical resection, such as in the center of liver; and 4) tumors in locations unfavorable for percutaneous RFA, such as in the subcapsular location. The exclusion criteria were as follows: 1) large size (> 3 cm) and number (> 5) of target tumors for IORFA; and 2) target tumors for IORFA were abutting a major structure (e.g., portal vein, hepatic artery, or bile duct). The number, size, and location of liver metastases were assessed to evaluate the feasibility of surgical resection and IORFA, using ultrasound (US), computed tomography (CT), and magnetic resonance image (MRI) one month before surgery.

Background Data of Included Patients

Table 1 lists patients' sex, age, primary tumor characteristics, pre-surgical imatinib administration status, primary and metastatic resection data, and IORFA status. IORFA and/or surgical resection were curatively performed for complete removal of hepatic metastasis. In total, 76 hepatic metastases were treated, of which 47 had been surgically resected (2.4 ± 1.3 per patient; mean size, 2.8 ± 1.6 cm) and 29 had undergone IORFA (1.2 ± 0.5 per patient; mean size, 1.6 ± 0.6 cm). The mean age of the patients was 53.9 ± 12.5 years. The locations of the primary GISTs were the stomach in 10 patients (41.7%), the small intestine in 13 (54.2%), and the large intestine in one (4.2%), and their mean size was 7.1 ± 3.0 cm. Of the 24 patients, 19 (79.2%) received imatinib therapy prior to surgery, whereas five (20.8%) underwent surgical resection before imatinib therapy. All included patients received imatinib therapy as standard treatment after IORFA or surgical resection.

Surgical Resection

At the time of laparotomy, intraoperative hepatic ultrasonography (AVIUS; HITACHI ALOKA Ltd, Tokyo, Japan) was performed to identify, count, and characterize the nature and vascular proximity of the metastatic tumors. The locations of the metastases and their relationships with surrounding vascular and biliary structures dictated whether to perform a formal anatomic resection. In general, the extent of surgery was determined based on the estimated hepatic functional reserve, which was assessed using a combination of preoperative liver biochemistry, distribution of metastatic tumors within the liver, and predicted remnant liver volume after resection. Resection was classified as less than a hemihepatectomy (e.g., wedge or segmentectomy), hemihepatectomy, or extended hepatectomy (≤ 5 liver segments) (18).

Table 1. Patient Characteristics and Treatment Detail

No.	Sex	Age (Years)	Primary GIST		Imatinib before Surgery	Hepatic Resection		Hepatic Metastasis			
								Resection		IORFA	
			Site	Size (cm)		Primary Tumor	Type	Number	Size (cm)	Number	Size (cm)
1	M	66	LI	6.3	+	Me	Wedge	3	3.5	1	1.2
2	F	35	SI	4.3	-	Me	Seg	2	2.1	1	2.0
3	F	73	St	15.0	+	PR	Seg	2	1.8	1	0.8
4	F	43	St	6.2	+	PR	Wedge	1	1.5	2	2.1
5	M	57	SI	4.0	+	PR	Seg	2	1.5	1	1.0
6	F	59	St	5.5	-	Me	Hemi	1	3.9	3	2.0
7	M	38	SI	7.8	+	PR	Hemi	4	5.5	1	2.0
8	F	63	SI	4.0	+	PR	Seg	4	1.7	1	2.7
9	M	75	SI	4.3	-	PR	IORFA*			1	0.5
10	F	67	SI	7.5	+	PR	Seg	5	6.5	1	1.5
11	M	42	St	7.0	+	PR	Hemi	3	2.8	1	2.0
12	F	57	St	4.8	+	PR	IORFA*			1	1.3
13	F	71	St	6.8	-	Me	Seg	1	2.3	2	1.2
14	M	50	SI	3.4	+	PR	Hemi	2	2.5	1	2.9
15	M	36	St	9.0	+	PR	IORFA*			1	1.0
16	F	62	SI	12.5	+	Me	Hemi	1	1.5	1	1.5
17	F	56	SI	3.2	+	Me	Seg	5	4.4	1	1.5
18	M	45	SI	11.2	+	Me	Seg	2	1.3	1	1.2
19	M	66	SI	6.7	+	Me	Seg	1	3.1	1	1.3
20	F	52	SI	10.2	+	Me	Hemi	2	1.2	2	1.2
21	M	43	SI	4.2	-	PR	IORFA*			1	2.1
22	F	57	St	8.2	+	Me	Seg	1	2.1	1	0.8
23	F	36	St	9.0	+	PR	Seg	3	5.2	1	2.3
24	M	44	St	8.2	+	PR	Seg	2	1.3	1	1.2
		53.9 ± 12.5		7.1 ± 3.0				2.4 ± 1.3	2.8 ± 1.6	1.2 ± 0.5	1.6 ± 0.6

F = female, GIST = gastrointestinal stromal tumor, Hemi = hemihepatectomy, IORFA = intraoperative radiofrequency ablation, IORFA* = IORFA only, LI = large intestine, M = male, Me = metasectomy, PR = primary resection, Seg = segmentectomy, SI = small intestine, St = stomach

Following removal of their primary GISTs, 14 patients (58.3%) also underwent hepatic resection during the same procedure. The remaining 10 patients (41.7%) underwent hepatic resection for residual or recurrent hepatic metastases at a mean interval of 27.6 ± 25.6 months following removal of their primary GISTs. Of the total 24 patients, 20 (83.3%) underwent IORFA following hepatic resection and four (16.7%) underwent IORFA alone. In addition, two of the 20 who had IORFA underwent wedge resection (10.0%), 12 underwent segmentectomy (60.0%), and six underwent hemihepatectomy (30.0%) (Table 1).

IORFA

Intraoperative radiofrequency ablation was performed by an interventional radiologist who had 18 years of experience in performing oncological interventions, including RFA under real-time US guidance with a 7-MHz convex probe (AVIUS; HITACHI ALOKA Ltd). Before the surgical resection of possible metastatic liver tumors, an intraoperative US evaluation was performed to identify the liver metastatic tumors; these findings were compared with preoperative CT or MRI findings. After the surgical resection was done for the surgically resectable tumors, a single 17-gauge internally cooled electrode (Proteus; STARmed Co., Goyang, Korea) was inserted in the center of the tumors under real-time US guidance (Fig. 1). If the tumor was ovoid in shape, insertion of the electrode along the longer side was attempted. The electrode was then connected to a 480-kHz electric current generator (VIVA RF system; STARmed Co.) that delivered a maximum output of 200 W. Correct positioning was confirmed by US before applying radiofrequency energy for 12 minutes in the

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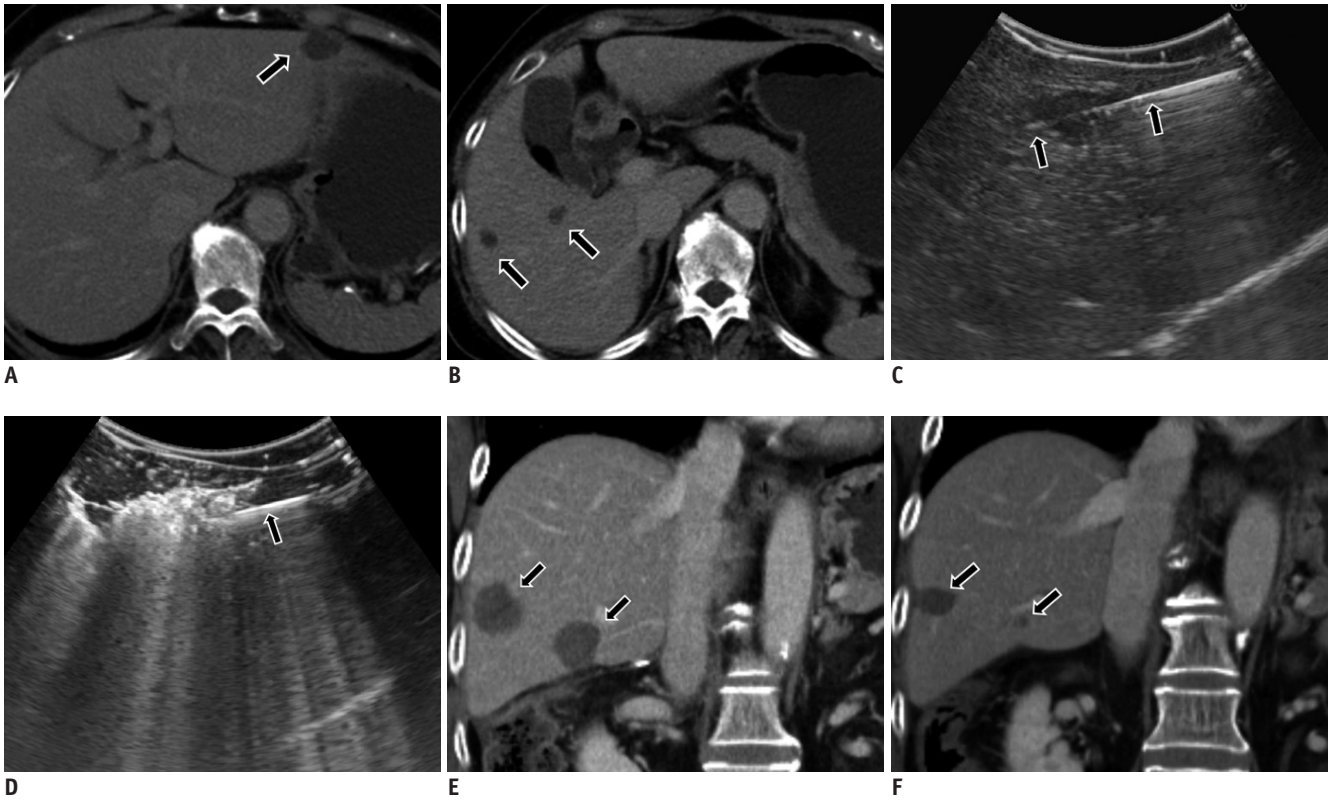

Fig. 1. 71-year-old female patient (No. 13) presented with three liver metastases.
A. Metastatic tumor in left lateral segment (arrow on axial CT) was surgically resected. **B.** Two tumors (arrows) in right lobe were ablated because of suspected hepatic failure after extensive hepatectomy. **C.** Radiofrequency electrode (arrows) was placed in hepatic tumor under intraoperative ultrasound guidance. **D.** Echogenic bubble was noted at tip of electrode (arrow) during ablation. **E.** Coronal CT image obtained seven days after IORFA shows two ablated zones (arrows) with complete coverage. **F.** Coronal CT image obtained 13 months after IORFA shows no evidence of local tumor progression. Ablation zones (arrows) indicate considerable decrease in size. CT = computed tomography, IORFA = intraoperative radiofrequency ablation

automatic impedance mode. Post-ablation intraoperative US images were evaluated immediately after the procedure. The endpoint of IORFA was confirming the tumors inside the echogenic ablated zone with more than 5 mm-circumferential margins.

Follow-Up, Definitions and Evaluation of Data

Contrast-enhanced CT, MRI, and/or positron emission tomography were used to evaluate the target tumor or recurrence at one, three, six, and 12 months, and annually thereafter.

The reporting standards of the Society of Interventional Radiology were used to define success, outcomes, and complications (19). Technical success was achieved when a treated tumor was ablated with sufficient margin (more than 5 mm) at the time of the procedure. Technical effectiveness was defined as complete tumor ablation shown on imaging follow-up 1–3 months after IORFA. As the lesions commonly appear hypoattenuating before and after ablation, full coverage of the index tumor by the non-enhancing ablation zone was regarded as complete ablation (3). The overall and cancer specific patient survival period were defined as the interval, in months, between the initial IORFA and the patient's death from any cause or from cancer, respectively.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Overall and GIST-specific survival rates were calculated using the Kaplan-Meier method.

RESULTS

Therapeutic Response and Complications

The mean follow-up duration was 50.7 ± 34.7 months. Each tumor was subjected to a single IORFA procedure, 100% of which were technically successful and effective for the treated metastases. Two patients (8.3%) had major complications, namely biliary stricture and hepatic abscess. These complications were attributed to either the surgical

Table 2. Treatment Results and Clinical Outcomes after IORFA

No.	Response of IORFA	Major Complication	Recurrence	Imatinib after IORFA	Follow-Up Period (Months)	Alive/Death	Cause of Death
1	Complete	-	-	+	40	Death	Pulmonary emphysema
2	Complete	-	-	+	85	Alive	
3	Complete	-	-	+	77	Alive	
4	Complete	-	+*	+	102	Alive	
5	Complete	-	-	+	88	Alive	
6	Complete	-	-	+	101	Alive	
7	Complete	-	+†	+	24	Death	Tumor progression
8	Complete	-	+‡	+	87	Alive	
9	Complete	-	-	+	86	Alive	
10	Complete	-	-	+	68	Alive	
11	Complete	-	-	+	90	Alive	
12	Complete	-	-	+	71	Alive	
13	Complete	-	-	+	65	Alive	
14	Complete	-	-	+	65	Alive	
15	Complete	-	-	+	43	Alive	
16	Complete	-	-	+	34	Alive	
17	Complete	Biliary stricture	-	+	24	Alive	
18	Complete	-	-	+	10	Alive	
19	Complete	Abscess	-	+	9	Alive	
20	Complete	-	-	+	6	Alive	
21	Complete	-	-	+	3	Alive	
22	Complete	-	-	+	29	Alive	
23	Complete	-	-	+	6	Alive	
24	Complete	-	-	+	3	Alive	
					50.7 ± 34.7		

*Gastric recurrence after 95 months, †Hepatic and peritoneal GIST recurrence after 16 months, ‡Hepatic recurrence after 51 months

resection or the IORFA procedure. Patient 17 underwent IORFA for a 1.5-cm-sized perihilar tumor and presented with symptomatic biliary stenosis at the 15-month follow-up, which was successfully treated with endoscopic drainage. Patient 19 had a hepatic abscess following surgical resection, which was successfully treated with percutaneous drainage and antibiotic administration. Two patients (8.3%) had persistent pain as a minor complication that improved with conservative treatment. Imatinib therapy was resumed postoperatively in all included patients (Table 2).

Three patients (12.5%) developed recurrent tumors during the follow-up period. Patient 7 recurred with multiple distant tumors in the liver and peritoneum 16 months after a technically successful IORFA (Fig. 2). The primary tumor had been a 7.8 cm GIST in the small intestine, and their metastatic tumors were completely removed by lobar resection (n = 4) or IORFA (n = 1) at initial. The patient also received imatinib therapy before and after IORFA. Despite continued imatinib therapy plus cisplatin-based transarterial chemoembolization for the relapsed hepatic metastasis, the patient died 24 months after IORFA. Patient 8 had a marginal recurrent tumor around the ablated zone in the liver 51 months after an effective IORFA procedure. Patient 4, who had presented with a gastric GIST with hepatic metastasis, developed a gastric recurrence 95 months after IORFA. We concluded that patients 4 and 8 were resistant to imatinib and therefore changed their chemotherapy regimens. No other patient developed intrahepatic or extrahepatic recurrence or metastasis during the follow-up period.

Survival

Two patients (1 and 7) died, and 13 remained alive without residual tumors at the time of the last imaging follow-up. Patient 7 (mentioned above) died from tumor progression 24 months after IORFA. Patient 1 died from

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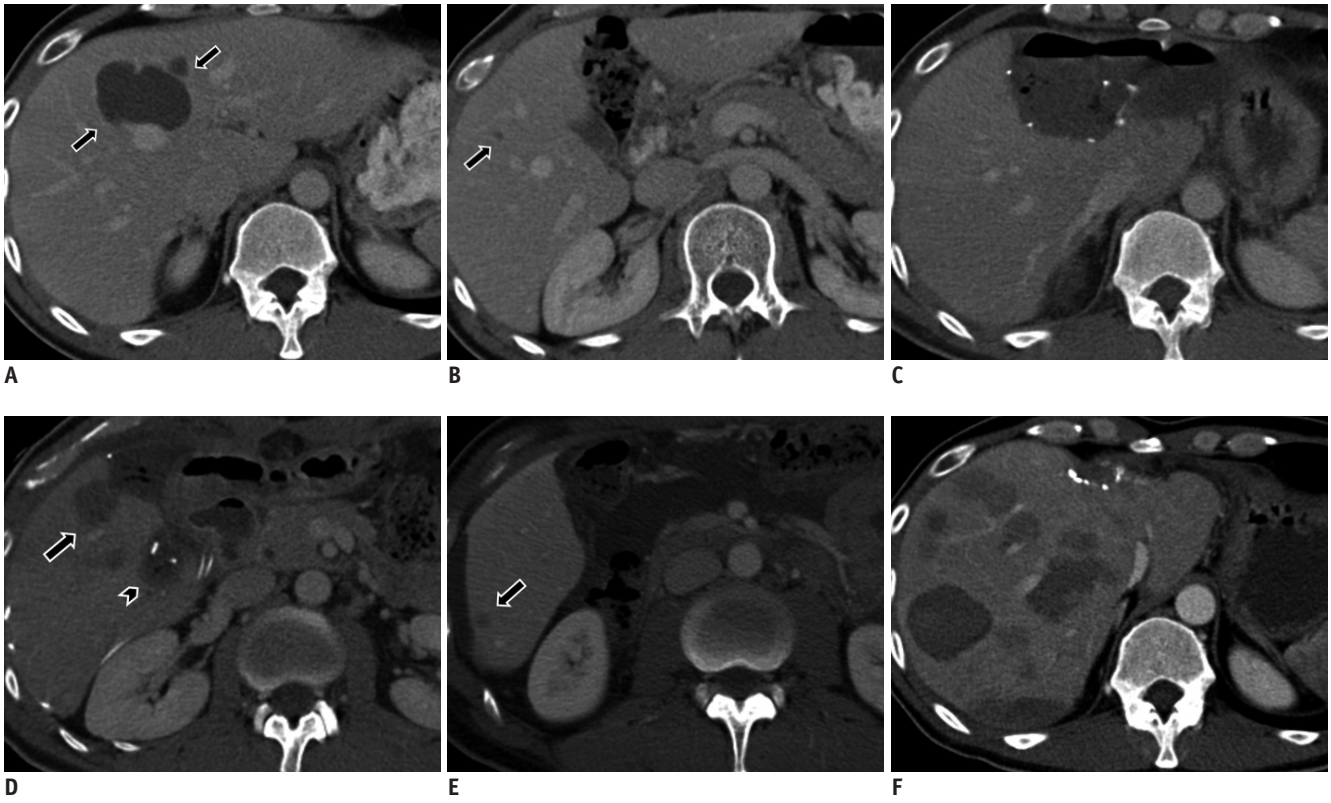

Fig. 2. 38-year-old male (Patient 7) presented with five liver metastases.
A. Metastatic tumors in segment 4 (arrows, axial CT) were surgically resected with sub-capsular metastatic tumors. **B.** Tumor (arrow) in right lobe could not be removed surgically because of risk of hepatic failure after extensive hepatectomy. **C.** Left lobectomy was performed to remove bulk of main metastases. **D.** IORFA (arrow) was performed for tumor located deep in right lobe. Partial hepatectomy (arrowhead) for sub-capsular tumor is visible. **E.** Axial CT image obtained five months after IORFA shows single recurrence (arrow) in right lobe. **F.** Axial CT image obtained 10 months after IORFA shows progression of multiple tumors and recurrence in remaining liver.

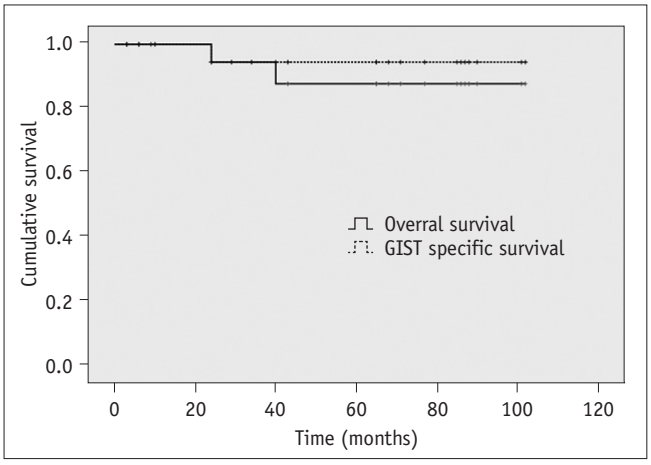

Fig. 3. Survival curves for overall and GIST-specific survival after IORFA. Five-year overall and GIST-specific survival rate was 87.7% and 94.4%, respectively. GIST = gastrointestinal stromal tumor

aggravated pulmonary emphysema 40 months after IORFA, and had no evidence of GIST recurrence at any point during follow-up.

The cumulative overall survival rates were 100, 94.4, and 87.7% at one, three, and five years, respectively. The GIST-specific survival rates were 100, 94.4, and 94.4% at one, three, and five years, respectively (Fig. 3). The median survival time was not calculated because the survival curve did not decrease to 50%.

DISCUSSION

Managing hepatic metastasis from GISTs remains a challenging clinical problem. Liver resection, which may be curative, is the preferred treatment when the indications for complete resection are met (20, 21). However, a large tumor burden or multiple tumor locations in the hepatic parenchyma may contraindicate resection because of the risk of leaving insufficient liver tissue that can result in postoperative liver failure (22). In the current study, in which we aimed to treat metastases that would otherwise be considered unresectable because of the risk of hepatic insufficiency, IORFA was applied either alone (n = 4) or with resection (n = 20). This combination approach allowed

surgery in patients who had unresectable tumors, because the surgeon can resect larger tumors and ablate smaller ones. IORFA was used alone in the following situations: patients had tumors in unfavorable locations for surgical resection; when there was an unacceptably high risk of hepatic insufficiency after resection; or if the patient could not tolerate a major parenchymal resection.

The introduction of tyrosine kinase inhibitors (TKIs) revolutionized the treatment of metastatic GISTs; these agents target specific molecular abnormalities that are crucial to tumor physiology (23, 24). Although the exact role of surgical resection remains unclear, it is generally recommended either for responders within six months of initiating TKI therapy (to minimize the risk of acquiring secondary mutations responsible for TKI resistance) or for patients who demonstrate early signs of TKI resistance on CT (e.g., slowed or halted tumor shrinkage) (25, 26). Disease relapse during imatinib therapy has mainly been attributed to tumor resistance caused by the development of secondary mutations. An increase in the dose of imatinib mesylate, or changing to another targeting agent (e.g., sunitinib, nilotinib, or sorafenib), could improve the outcomes and stabilize the disease for some patients (27). However, TKI treatment appears to be critical for achieving long-term survival when there is recurrent or metastatic GIST. Given that the combination of TKI therapy and surgery seems to prolong survival, it is vital that measures are developed to prevent acquired resistance (28, 29).

If surgical resection is not feasible, the administration of multiple TKIs or TKI therapy in a neoadjuvant setting might improve the survival of a patient with unresectable liver metastases (20, 29). However, the authors of the current study attempted to administer IORFA with surgical hepatic resection to broaden the indications of surgical resection, and thus include patients with apparently unresectable liver metastases. Pawlik et al. (15) also administered IORFA for unresectable hepatic metastases of GIST either in combination with surgical resection or alone. These authors reported that patients who were treated with IORFA either alone (84.6%) or in combination with surgical resection (88.9%) had a significantly higher rate of recurrence, compared with patients who underwent resection alone (57.1%). Pawlik et al. (15) further reported a median overall survival duration of 47.2 months, with one-, three-, and five-year actual overall survival rates of 91.2, 65.4, and 27.1%, respectively.

In the current study, we achieved a therapeutic response of 100% and a tumor recurrence rate of 6.7%. The GIST-related survival rates were 100, 94.4, and 94.4% at one, three, and five years, respectively. Note, however, the median survival duration was not calculated because the survival curve did not decrease to 50%.

There are three main explanations for the low tumor recurrence and high survival rates in this study. First, the combination of RFA and imatinib may be responsible because 73.3% and 100% of our patients received imatinib before and after surgery, respectively. By contrast, in the study by Pawlik et al. (15), only 39.5% and 39.4% received imatinib before and after surgery, respectively. Second, the sizes of the metastatic tumors may be important. In the current study, the mean maximum sizes of the resected and ablated tumors were 3.0 ± 0.6 cm and 1.6 ± 0.7 cm, respectively, whereas Pawlik et al. (15) reported a median size of 3.9 cm for all included tumors. During planning for our study, metastatic tumors > 3 cm were not indicated for IORFA, which might explain the improved results. Third, US guidance during IORFA may have played a role, because an interventional radiologist performed IORFA under real-time US guidance. This method yields a more accurate and precise ablation zone compared with palpation alone, especially for cases involving deeply located metastatic tumors. Finally, complete removal by IORFA and/or surgical resection may have been important. In the current study, a surgeon, an oncologist, and an interventional radiologist reported that all included patients achieved non-detectable GIST on radiographic images after surgery.

In the current study, a multidisciplinary team initially planned IORFA prior to the surgical procedures for complete removal of the hepatic tumors. Generally, compared with percutaneous RFA, IORFA has some advantages and disadvantages. Advantages include good patient tolerance due to the use of general anesthesia and the ease and accuracy of targeting due to the intraoperative US guidance. Disadvantages include unavailability of US fusion imaging and change of orientation of the tumor location due to the surgical mobilization of tissue outside the tumor site.

The major limitations of this study are its retrospective design, small sample size, and the lack of a control group. A prospective randomized study with a larger sample should be performed to confirm our findings. Another important limitation is that the inclusion and exclusion criteria were vague. When the decision to resect hepatic metastases was made, it was hard to give an exact prediction of residual hepatic function after hepatic surgery. To overcome

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this limitation, the multidisciplinary team, including an oncologist, surgeon, and interventional radiologist, discussed the tumor resectability and potential for clinical benefit to patients before making their final decisions. Moreover, the inclusion and exclusion criteria for IORFA were otherwise clear in terms of the size, number, and location of hepatic tumors considered suitable for treatment.

In conclusion, the present study indicates that IORFA produces acceptable outcomes in appropriately selected patients with unresectable hepatic metastases from GISTs. Assuming a well-designed multidisciplinary intervention, IORFA with or without surgical resection might be helpful in providing effective local tumor control and longer disease-free survival in patients with unresectable hepatic metastases from GISTs or who exhibit partial response to imatinib.

REFERENCES

1. Correa-Cote J, Morales-Uribe C, Sanabria A. Laparoscopic management of gastric gastrointestinal stromal tumors. *World J Gastrointest Endosc* 2014;6:296-303
2. Yamanaka T, Takaki H, Nakatsuka A, Uraki J, Fujimori M, Hasegawa T, et al. Radiofrequency ablation for liver metastasis from gastrointestinal stromal tumor. *J Vasc Interv Radiol* 2013;24:341-346
3. Jung JH, Won HJ, Shin YM, Kim PN. Safety and efficacy of radiofrequency ablation for hepatic metastases from gastrointestinal stromal tumor. *J Vasc Interv Radiol* 2015;26:1797-1802
4. Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001;344:1052-1056
5. Park SJ, Ryu MH, Ryoo BY, Park YS, Sohn BS, Kim HJ, et al. The role of surgical resection following imatinib treatment in patients with recurrent or metastatic gastrointestinal stromal tumors: results of propensity score analyses. *Ann Surg Oncol* 2014;21:4211-4217
6. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004;364:1127-1134
7. An HJ, Ryu MH, Ryoo BY, Sohn BS, Kim KH, Oh ST, et al. The effects of surgical cytoreduction prior to imatinib therapy on the prognosis of patients with advanced GIST. *Ann Surg Oncol* 2013;20:4212-4218
8. Kang YK, Kang HJ, Kim KM, Sohn T, Choi D, Ryu MH, et al. Clinical practice guideline for accurate diagnosis and effective treatment of gastrointestinal stromal tumor in Korea. *Cancer Res Treat* 2012;44:85-96
9. ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23 Suppl 7:vii92-vii99
10. Tepel J, Hinz S, Klomp HJ, Kapischke M, Kremer B. Intraoperative radiofrequency ablation (RFA) for irresectable liver malignancies. *Eur J Surg Oncol* 2004;30:551-555
11. Eisele RM, Zhukowa J, Chopra S, Schmidt SC, Neumann U, Pratschke J, et al. Results of liver resection in combination with radiofrequency ablation for hepatic malignancies. *Eur J Surg Oncol* 2010;36:269-274
12. Park SI, Kim IJ, Lee SJ, Shin MW, Shin WS, Chung YE, et al. Angled cool-tip electrode for radiofrequency ablation of small superficial subcapsular tumors in the liver: a feasibility study. *Korean J Radiol* 2016;17:742-749
13. Wang X, Hu Y, Ren M, Lu X, Lu G, He S. Efficacy and safety of radiofrequency ablation combined with transcatheter arterial chemoembolization for hepatocellular carcinomas compared with radiofrequency ablation alone: a time-to-event meta-analysis. *Korean J Radiol* 2016;17:93-102
14. Hakimé A, Le Cesne A, Deschamps F, Farouil G, Boudabous S, Aupérin A, et al. A role for adjuvant RFA in managing hepatic metastases from gastrointestinal stromal tumors (GIST) after treatment with targeted systemic therapy using kinase inhibitors. *Cardiovasc Intervent Radiol* 2014;37:132-139
15. Pawlik TM, Vauthey JN, Abdalla EK, Pollock RE, Ellis LM, Curley SA. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. *Arch Surg* 2006;141:537-543; discussion 543-544
16. Ishikawa A, Teratani T, Ono S, Ochiai T, Kakinoki N, Kishimoto Y, et al. [A case of gastrointestinal stromal tumor with liver and bone metastases effectively treated with radiofrequency ablation and imatinib mesylate]. *Nihon Shokakibyo Gakkai Zasshi* 2006;103:1274-1279
17. Jones RL, McCall J, Adam A, O'Donnell D, Ashley S, Al-Muderis O, et al. Radiofrequency ablation is a feasible therapeutic option in the multi modality management of sarcoma. *Eur J Surg Oncol* 2010;36:477-482
18. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 2005;12:351-355
19. Ahmed M, Solbiati L, Brace CL, Breen DJ, Callstrom MR, Charboneau JW, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. *J Vasc Interv Radiol* 2014;25:1691-1705.e4
20. Vassos N, Agaimy A, Hohenberger W, Croner RS. Management of liver metastases of gastrointestinal stromal tumors (GIST). *Ann Hepatol* 2015;14:531-539
21. Ye YJ, Gao ZD, Poston GJ, Wang S. Diagnosis and multi-disciplinary management of hepatic metastases from gastrointestinal stromal tumour (GIST). *Eur J Surg Oncol* 2009;35:787-792
22. Sato T, Ohyama S, Kokudo N, Suenaga M, Yamamoto J, Yamaguchi T, et al. The repeated hepatectomy for frequent recurrence of hepatic metastasis from gastrointestinal stromal

tumor of the stomach. *Hepatogastroenterology* 2004;51:181-183
23. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002;347:472-480
24. Zhu J, Yang Y, Zhou L, Jiang M, Hou M. A long-term follow-up of the imatinib mesylate treatment for the patients with recurrent gastrointestinal stromal tumor (GIST): the liver metastasis and the outcome. *BMC Cancer* 2010;10:199
25. DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg* 2007;245:347-352
26. Haller F, Detken S, Schulten HJ, Happel N, Gunawan B, Kuhlgatz J, et al. Surgical management after neoadjuvant imatinib therapy in gastrointestinal stromal tumours (GISTs) with respect to imatinib resistance caused by secondary KIT mutations. *Ann Surg Oncol* 2007;14:526-532
27. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006;368:1329-1338
28. Zalinski S, Palavecino M, Abdalla EK. Hepatic resection for gastrointestinal stromal tumor liver metastases. *Hematol Oncol Clin North Am* 2009;23:115-127
29. Rutkowski P, Nyckowski P, Grzesiakowska U, Nowecki ZI, Nasierowska-Guttmejer A, Pienkowski A, et al. The clinical characteristics and the role of surgery and imatinib treatment in patients with liver metastases from c-Kit positive gastrointestinal stromal tumors (GIST). *Neoplasma* 2003;50:438-442